

# THE PREVALENCE OF VITAMIN B<sub>12</sub> DEFICIENCY IN HEMODIALYSIS PATIENTS



Alaa H. A. Alkrush<sup>a</sup> Sarhad Ahmed Mahmood<sup>b</sup>

Submitted: 23/12/2022; Accepted: 25/3/2023; Published: 21/12/2023

## ABSTRACT

### *Background*

Vitamin B<sub>12</sub> is a water-soluble vitamin in several normal cellular functions. Low vitamin B<sub>12</sub> has been associated with high concentrations of homocysteine and can lead to health complications. In addition to metabolic alteration and restricted food products allowable in renal failure patients, vitamin B<sub>12</sub> is actively removed by hemodialysis with high flux membranes.

### *Objective*

To detect the prevalence of vitamin B<sub>12</sub> levels in hemodialysis patients and its relation to the duration of dialysis and daily protein intake.

### *Method*

This cross-section observational multicenter study was conducted on 169 hemodialysis patients in four Sulaimani Governorate centres. A questionnaire used to gather data included patient, dialysis, diet, and medication information. Blood investigation was taken to detect the vitamin B<sub>12</sub> level and mean corpuscular volume.

### *Results*

Twenty-nine patients (17.1 %) had vitamin B<sub>12</sub> deficiency. High flux filter hemodialysis was not used in all the centres included in this study. No cases with four hours of dialysis sessions had vitamin B<sub>12</sub> deficiency. All the patients were on sub-optimum protein diet restriction. No cases of vitamin B<sub>12</sub> deficiency were present in patients receiving protein of 0.6-0.7 gm/kg/day. All our patients had normochromic normocytic anaemia.

### *Conclusion*

Our patients have an average percentage of vitamin B<sub>12</sub> deficiency compared to other centres worldwide. The main causes of vitamin B<sub>12</sub> deficiency in our patients were the sub-optimum restriction of protein diet and the sub-optimum dialysis.

**Keywords:** *Vitamin B 12 deficiency, hemodialysis.*

---

<sup>a</sup> College of Medicine, University of Sulaimani, Kurdistan Region, Iraq.

<sup>b</sup> Dialysis Department, Ministry of Health< Sulaimani, Kurdistan Region, Iraq.

Correspondence: [alaa.awn@univsul.edu.iq](mailto:alaa.awn@univsul.edu.iq)

## INTRODUCTION

Vitamin B12 (cobalamin) is a water-soluble vitamin involved in several normal cellular functions<sup>(1)</sup>. Vitamin B12 is required for the development, myelination, and function of the central nervous system; healthy red blood cell formation; and DNA synthesis<sup>(2-4)</sup>. Low levels of vitamin B12 have been associated with high concentrations of homocysteine (Hcy) and can lead to health complications<sup>(5)</sup>. Hyperhomocysteinemia is an important risk factor for cardiovascular disease<sup>(6)</sup>. Vitamin B12 and other B vitamins are involved in homocysteine metabolism, and researchers have hypothesized that supplementation with these micronutrients can reduce the risk of cardiovascular disease by lowering homocysteine levels<sup>(7,8)</sup>. Vitamin B12 deficiency is one of the causes of Macrocytic anaemia with increased mean corpuscular volume (MCV), defined as more than 100 fL, which is the hallmark of megaloblastic anaemia<sup>(9)</sup>.

Intake recommendations for vitamin B12 and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the National Academies of Sciences, Engineering, and Medicine<sup>(2)</sup>. Vitamin B12 is naturally present in foods of animal origin, including fish, meat, poultry, eggs, and dairy products<sup>(10)</sup>.

Different foods have different amounts of protein. Animal origin or high biological value (HBV) foods such as meat, fish, and poultry have 7.0 grams of protein per 30 gm of that food (nearly 25% of the net weight), milk has 4 grams per half-cup, 6 gm per egg. Grains such as pasta, breads, and cereals like rice = (2.0 grams) of protein per serving, vegetables (1.0 grams) per serving. While Fruits (trace)<sup>(11-13)</sup>.

The recommended dietary allowance (RDA) for vitamin B<sub>12</sub> is 2.4 mcg/d for adult males and females, including dialysis patients. Deficiencies occur mainly because of inadequate absorption caused by atrophic gastritis (lack of hydrochloric acid) or a lack of intrinsic factors (pernicious anaemia). Inadequate absorption may be caused by drug interactions such as those taken during chemotherapy, salicylates (aspirin and antacids), oral contraceptives, Anticonvulsants, chemotherapy agents, colchicine, bile acid sequestrates, H<sub>2</sub> blockers, metformin, and proton pump inhibitors may reduce the levels of vitamin B<sub>12</sub><sup>(14)</sup>.

Dialysis patients usually have poor nutritional intake, predisposing them to B12 deficiency.

Moreover, food sources of vitamin B12 contain high concentrations of electrolytes, which are dangerous for dialysis patients, and they are limited to foods with low vitamin B12 content<sup>(15,16)</sup>.

Plasma total homocysteine (tHcy) concentration is noticeably increased in end-stage renal disease (ESRD)<sup>(17)</sup>.

Furthermore, compared to patients with normal renal function, the prevalence of hyperhomocysteinemia and the resulting death caused by atherosclerotic vascular disease are substantially greater in ESRD patients<sup>(18)</sup>.

Therefore, the pathophysiological chain of mechanisms that include vitamin prescription-homocysteine lowering-reduction in cardiovascular events has to be fully validated with more and bigger randomized controlled studies. In dialysis patients, especially those who are *Helicobacter Pylori* positive, a functional resistance in vitamin B<sub>12</sub> therapy has been recognized; the implementation necessitates supra-physiologic doses and serum levels to achieve the desired effects<sup>(19,20)</sup>.

Solute removal from the body was evaluated differently for each treatment modality. Solute clearance during dialysis-hemofiltration (DHF) therapy was assumed to be proportional to the ultrafiltration rate; the convective permeability factor was the solute sieving coefficient. The solute sieving coefficients during DHF for most calculations in a study were based on reported in vitro measurements conducted with either bovine or human plasma with a protein concentration of 6 mg/dl<sup>(21)</sup>.

Vitamin B12 is typically present in the serum at a concentration of about 250-900 pg/mL. At a molecular weight of 1,355, vitamin B12 is not easily dialyzable with low-flux dialysis. However, removing a significant amount of vitamin B12 with high-flux dialyzers is possible under certain conditions. The authors concluded that it is important for dialysis patients to take renal vitamins (which are mainly B complex vitamins) while on dialysis. The water-soluble vitamins are not routinely added to the dialysate<sup>(22)</sup>.

So, in addition to restricted food products allowable in renal failure patients, vitamin B12 is actively removed by hemodialysis with high flux membranes<sup>(23)</sup>.

In both chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients, several metabolic alterations, including acidosis, systemic inflammation, and hormonal dysregulation, together with

## *The Prevalence of Vitamin B12 Deficiency in Hemodialysis Patients*

comorbidities and multi-drug therapies, can lead to malnutrition with subsequent vitamin B12 deficiency. In addition, anorexia, gastroparesis, slow intestinal transit or diarrhoea, increased gut mucosal permeability, and gut microbiota impairment may represent worsening factors<sup>(24-26)</sup>.

The cutoff between regular vitamin B12 levels and deficiency varies by method and laboratory, but most laboratories define subnormal serum or plasma values as those lower than 200 pg/mL<sup>(27)</sup>. The rate of protein intake of 1 to 1.2 g/kg/day indicates optimal nutritional intake in dialysis patients, while rates below 0.8 g/kg/day indicate possible malnutrition<sup>(28)</sup>.

### **Aim of the study**

To detect the prevalence of vitamin B12 levels in HD patients, to know the correlation between the vitamin B12 deficiency in those patients and the duration and the frequency of the sessions of dialysis., and to know the correlation between the vitamin B12 deficiency in those patients and the amount of the daily protein intake.

### **METHOD AND PATIENTS**

This cross-section observational multi-centre study was done from November 22, 2021, to April 5, 2022, among Chronic Hemodialysis patients visiting four hemodialysis centres in Sulaimani governorate in Iraq /Kurdistan region. History and examinations were done, and blood samples were drawn from each patient for laboratory analysis.

### **The exclusion criteria**

Patients with recent renal transplantation, patients who are taking sulpham drugs, methotrexate, anticonvulsants, chemotherapy agents, colchicine, bile acid sequestrates, H<sub>2</sub> blockers, metformin, and proton pump inhibitors, patients on dialysis for less than three months.

### **Inclusion criteria**

chronic hemodialysis patients for more than three months.

### **Study Instrument**

A questionnaire used to gather data included the following questions;

Patient information (age, gender), dialysis information, diet information focused on a healthy lifestyle and

protein intake, and medication information for administering B12 by tablet or ampule.

To calculate the amount of protein in the diet that the patient was taking every day, we asked the patient the average weight of food taken per week. Then, as described in the introduction, different foods have different amounts of protein<sup>(11,12)</sup>.

Then we calculate the total protein taken per week, then per day, and divide the amount over the patient's weight to have the results of the amount of protein taken by the patient in gm/kg/day.

### **Specimen procedure and Research protocol:**

Laboratory rotational testing for B12 measurement, complete blood count including mean corpuscular volume (MCV).

Blood samples were obtained for laboratory investigation. Each participant provided around 1-2 mL of blood, which was split into Ethylenediaminetetraacetic acid (EDTA) tubes (2 mL) and processed by an automated counter for haemoglobin (Hb) content and other whole blood component concentrations. They were screening for serum vitamin B12 concentrations, adding (3-4) ml and Methylmalonic acid (MMA) levels in the blood. Specimens were placed in centrifuge tubes and spun for 10 minutes at > 10,000 relative centrifugal force before being examined for the presence of fibrin, red blood cells (RBCs), or other particulate material. Cobas e411 and the Swilab alfa machine were used for accurate diagnostics.

### **Statistical Analysis**

Statistical investigation for data input and analysis, the Statistical Package for the Social Sciences (SPSS) version 24.0 was used. The data had been coded, tabulated, and presented descriptively. The statistical procedure that was applied to determine the results of the present study included Descriptive statistics (Frequency, percentage, Mean, and standard deviation), Chi-Square Test ( $\chi^2$ -test), Independent samples T-test, and One-way ANOVA (F-test). P < 0.05 was determined statistically significant.

### **RESULTS**

The total number of patients involved in the study was 169 cases from Sulaimani City, and they are as follows: Shar Hospital, 53 patients; Qirga HD Center, 60 patients; Rania HD Center, 43 patients; Halabja HD

Center, 13 patients. They include 50 males (53.3%) and 79 females (46.7%), as shown in Tables (1, 3).

Twenty-nine patients (17.1 %) had vitamin B12 deficiency. The lowest number of patients was in Shar centres (1.89%), while the highest was in Qirga and Ranya centres (31.6 and 18.6 %). Even 9.4 % of cases (5 patients) in Shar Center had high vitamin B12 levels. No patients had 4-hour dialysis sessions in all centres apart from Shar centre (50.9%) (Table 1 , 2).

High flux filter hemodialysis was not used in all the centres included in this study. No cases with four hours of dialysis sessions had vitamin B12 deficiency (Table 3). Even the mean vitamin B12 in those patients was higher than those patients with 3 hours of session of dialysis with statistically significant value (Table 5).

All the patients were on sub-optimum protein diet restriction. If we divide them into three groups, severe (0.1-0.3 gm/kg/day), moderate (0.4-0.59 gm/kg/day),

and mild (0.6- 0.7 gm/kg/day) sub-optimum protein restriction, we found that no cases with vitamin B 12 deficiency present in patients receiving protein of 0.6-0.7 gm/kg/day (Table 2.3). Also, the mean vitamin B12 in those patients was higher than the patients in the other groups with statistically significant values (Table 5).

However, none of our patients with vitamin B12 deficiency had Macrocytic anaemia (MCV>100). However, the mean MCV in those patients was higher than those without vitamin B12 deficiency, with a statistically significant value (Table 4).

All the cases that had anaemia presented with the normochromic normocytic type of anaemia.

The level of vitamin B12 was not related to the age, gender, and weight of the patients (Table 5).

**Table 1. Distribution of the vitamin B12 of patients in hospitals.**

Hospitals	Shar		Qirga		Ranya		Halabja		Total		P-value
	Fr.	%	Fr.	%	Fr.	%	Fr.	%	Fr.	%	
<b>Vitamin B12</b>											
Low	1	1.89	19	31.67	8	18.60	1	7.69	29	17.16	P=0.001
Normal	47	88.68	39	65.00	35	81.40	12	92.31	133	78.70	
High	5	9.43	2	3.33	0	0	0	0.00	7	4.14	
Total	53	100	60	100	43	100	13	100	169	100	
<b>Duration of each session of dialysis in hours</b>											
3 hours	26	49.06	60	100	43	100	13	100.00	142	84.02	P=0.000
4 hours	27	50.94	0	0	0	0	0	0.00	27	15.98	
Total	53	100	60	100	43	100	13	100	169	100	
<b>No. of dialysis/week</b>											
1	1	1.89	1	1.67	4	9.30	0	0.00	6	3.55	P=0.000
2	46	86.79	16	26.67	22	51.16	6	46.15	30	17.75	
3	6	11.32	43	71.67	17	39.53	7	53.85	73	43.20	
Total	53	100	60	100	43	100	13	100	169	100	

The Prevalence of Vitamin B12 Deficiency in Hemodialysis Patients

Table 2. Distribution of the vitamin B12 of patients in hospitals.

Hospitals	Shar		Qirga		Ranya		Halabja		Total		P-value
	Fr.	%	Fr.	%	Fr.	%	Fr.	%	Fr.	%	
<b>Vitamin B12</b>											
Low	1	1.9	19	31.7	8	18.6	1	7.7	29	17.2	P=0.001
Other (normal or high)	52	98.1	41	68.3	35	81.4	12	92.3	140	82.8	
Total	53	100	60	100	43	100	13	100	169	100	
<b>Duration of each session of dialysis in hours</b>											
3 hours	26	49.06	60	100	43	100	13	100.00	142	84.02	P=0.000
4 hours	27	50.94	0	0	0	0	0	0.00	27	15.98	
Total	53	100	60	100	43	100	13	100	169	100	
<b>No. of dialysis/week</b>											
1	1	1.89	1	1.67	4	9.30	0	0.00	6	3.55	P=0.000
2	46	86.79	16	26.67	22	51.16	6	46.15	30	17.75	
3	6	11.32	43	71.67	17	39.53	7	53.85	73	43.20	
Total	53	100	60	100	43	100	13	100	169	100	

Table 3. Distribution of the socio-demographic characteristics according to vitamin B12 deficiency patients.

Socio-demographic	Low		Other (normal or high)		Total	
	Fr.	%	Fr.	%	Fr.	%
<b>Age (years)</b>						
< 30	4	13.8	13	9.3	17	10.1
30 – 60	16	55.2	66	47.1	82	48.5
> 60	9	31.0	61	43.6	70	41.4
<b>Sex</b>						
Male	20	69.0	70	50.0	90	53.3
Female	9	31.0	70	50.0	79	46.7
<b>Weight (kg.)</b>						
< 50	2	6.9	9	6.4	11	6.5
50 – 75	17	58.6	89	63.6	106	62.7
> 75	10	34.5	42	30.0	52	30.8
<b>Duration of each session of dialysis in hours</b>						
3 hours	29	100.0	113	80.7	142	84.0
4 hours	0	0.0	27	19.3	27	16.0
<b>Protein diet gm/kg/day</b>						
(0.1-0.3)	16	55.2	48	34.3	64	37.9
(0.4-0.59)	13	44.8	73	52.1	86	50.9
(0.6- 0.7)	0	0.0	19	13.6	19	11.2
<b>Medication of vitamin B12</b>						
Yes	0	0.0	2	1.4	2	1.2
No	29	100.0	138	98.6	167	98.8
Total	29	100.0	140	100.0	169	100.0

Table 4. Compare mean score of laboratory investigations with vitamin B12 deficiency patients.

laboratory investigations	Vitamin B12	No.	Mean	Std. Deviation	T-test	P-value
<b>Hb (gm/dl)</b>	Low	29	9.4828	2.09797	0.532	0.595
	Other (normal or high)	140	9.2857	1.75182		
<b>MCV</b>	Low	29	88.4138	10.91041	2.057	0.041
	Other (normal or high)	140	84.9071	7.74123		
<b>MCHC</b>	Low	29	32.1034	1.47224	-0.913	0.363
	Other (normal or high)	140	32.3500	1.29151		

Table 5. Compare mean score of vitamin B12 in socio-demographic of patients.

Socio-demographic	Vitamin B12			
		Mean	S.D	P-value
<b>Age (years)</b>	< 30	404.2	271.9	0.7
	30 – 60	424.7	357.9	
	> 60	462.4	293.7	
<b>Sex</b>	Male	431.6	360.9	0.778
	Female	445.8	276.9	
<b>Weight (Kg.)</b>	< 50	441.7	302.4	0.22
	50 – 75	406.6	292.3	
	> 75	502.0	380.4	
<b>Duration of each session of dialysis in hours</b>	3 hours	388.5	235.0	0.000
	4 hours	699.7	540.8	
<b>Protein diet gm/kg/day</b>	(0.1-0.3)	363.3	184.6	0.001
	(0.4-0.59)	444.2	318.9	
	(0.6- 0.7)	663.9	551.0	

## DISCUSSION

While (17.1%) of our patients had vitamin B12 deficiency, in some other hemodialysis centres, the prevalence of vitamin B12 deficiency was 60 % among hemodialysis patients. This deficiency is caused by inadequate nutrition and loss through the high flux-hemodialysis procedure. In our study, the high-flux hemodialysis was not used <sup>(29)</sup>. Seven (9.4%) of the 169 patients have high levels of vitamin B12. This was also seen in other studies in Swaziland, as 6.9% of their patients have high levels of vitamin B12 <sup>(31)</sup>. Low serum B12 levels occur in high-flux hemodialysis patients and losses during dialysis and dietary deficiency may be contributing factors <sup>(30)</sup>.

The prevalence of vitamin B12 deficiency was 2.5 % in other centres because dieticians followed the patients, and they had the optimum daily protein intake. In our study, none of our patients were seen or followed by any dietician, and vitamin B12 deficiency was among those with severe protein diet malnutrition <sup>(31)</sup>. Also, this explains why there was no vitamin B12 deficiency among hemodialysis patients in other studies <sup>(32)</sup>.

Other studies show that macrocytosis was observed in 38% of the patients on maintenance hemodialysis and in 44% of the patients with combined hemodialysis and hemofiltration treatment; this was mostly because of efficient dialysis (with high flux- -hemodialysis) in patients with vitamin B12 deficiency <sup>(33)</sup>. In our patients, all the cases with anaemia had a normochromic

normocytic type. The duration of dialysis may play a role in explaining this point.

No cases of vitamin B12 deficiency are present in our patients who were on a 4-hour dialysis session. We are not using high flux- hemodialysis in our patients because those patients had better general conditions and appetite. Moreover, better dialysis gives us better intestinal absorption of vitamins and better metabolism. We have fewer cases of vitamin B12 deficiency in Shar Hospital because 50.9 % of the cases were on four-hour dialysis sessions, post-graduated nephrology doctors supervised the patients, and they had less restricted protein diets.

In conclusion, our patients have an average percentage of vitamin B12 deficiency compared to other centres worldwide. The main causes of this problem in our study were the sub-optimum restriction of protein diet and the sub-optimum dialysis.

### **Recommendations**

All patients should be examined, followed by a dietician, and reassessed every six months. Cover the patients with the optimum sessions of dialysis. All hemodialysis patients must regularly follow up for vitamin B12 and treat them.

### **REFERENCES**

1. Kang S, Wong P, Malinow M. Hyperhomocyst(e) inemia as a risk factor for occlusive vascular disease. *Annu. Rev. Nutr.* 1992;12: 279–298.
2. Dietary Reference Intakes: Thiamin R, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Institute of Medicine. Food and Nutrition Board.
3. Allen LH. Vitamin B-12. *Adv Nutr* 2012; 3:54-5.
4. Stabler SP, Marriott BP, Birt DF, Stallings VA. *Present Knowledge in Nutrition*. 11th ed. Washington, DC: Elsevier. 2020;257–71.
5. Barnabé A, Aléssio AC, Bittar LF, de Moraes Mazetto B. Folate, vitamin B12 and Homocysteine status in the post-folic acid fortification era in different subgroups of the Brazilian population attended to at a public health care centre. *Nutr J.* 2015 Feb 19; 14:19.
6. Ross AC, Caballero B, Cousins RJ, Tucker KL. *Modern nutrition in health and disease*. Jones & Bartlett Learning; 2020 July 10.
7. Debrececi B, Debrececi L. The role of homocysteine-lowering B-vitamins in the primary prevention of cardiovascular disease. *Cardiovasc Ther.* 2014; 32:130-8.
8. Djuric D, Jakovljevic V, Zivkovic V, Srejovic I. Homocysteine and homocysteine-related compounds: An overview of the roles in the pathology of the cardiovascular and nervous systems. *Can J Physiol Pharmacol.* 2018; 96:991-1003.
9. Socha DS, DeSouza SI, Flagg A, Sekeres M, Rogers HJ. Severe megaloblastic anaemia: Vitamin deficiency and other causes. *Cleveland clinic journal of medicine.* 2020 Mar 1;87(3):153-64.
10. Stabler SP. Vitamin B12. In: Marriott BP, Birt DF, Stallings VA, Yates AA, eds. *Present Knowledge in Nutrition*. 11th ed. Washington, DC: Elsevier; 2020:257-71
11. Gupta E, Mishra P. Functional food with some health benefits, so-called superfood: a review. *Current Nutrition & Food Science.* 2021 Feb 1;17(2):144-66.
12. Lonnie M, Hooker E, Brunstrom JM, Corfe BM, Green MA, Watson AW, Williams EA, Stevenson EJ, Penson S, Johnstone AM. Protein for life: Review of optimal protein intake, sustainable dietary sources and the effect on appetite in ageing adults. *Nutrients.* 2018 Mar 16;10(3):360.
13. Barabási AL, Menichetti G, Loscalzo J. The unmapped chemical complexity of our diet. *Nature Food.* 2020 Jan;1(1):33-7.
14. Boeschoten EW, Schrijver J, Krediet RT, Schreurs WH, Arisz L. Deficiencies of vitamins in CAPD patients: the effect of supplementation. *Nephrology Dialysis Transplantation.* 1988 Jan 1;3(2):187-93.
15. Iqbal N, Azar D, Yun YM, Ghausi O, Ix J, Fitzgerald RL. Serum methylmalonic acid and holotranscobalamin-II as markers for vitamin B12 deficiency in end-stage renal disease patients. *Annals of Clinical & Laboratory Science.* 2013 Jun 20;43(3):243-9.
16. Chen Y, Smith-Norowitz TA, Joks R. Levels of Salivary Melatonin (AM and PM) in Adults with Allergic Respiratory Disease. *Annals of Clinical & Laboratory Science.* 2022 May 1;52(3):507-9.

17. Dierkes J, Domröse U, Ambrosch A, Schneede J, Guttormsen AB, Neumann KH, Luley C. Supplementation with vitamin B12 decreases homocysteine and methylmalonic acid but also serum folate in patients with end-stage renal disease. *Metabolism*. 1999 May 1;48(5):631-5.
18. Hyndman ME., Manns BJ, Snyder FF, Bridge PJ, Scott-Douglas NW, Fung E, Parsons HG. Vitamin B12 decreases but does not normalize, homocysteine and methylmalonic acid in end-stage renal disease: a link with glycine metabolism and a possible explanation of hyperhomocysteinemia in end-stage renal disease. *Metabolism*. 2003 Feb 1;52(2):168-72.
19. Su VC, Shalansky K, Jastrzebski J, Martyn A, Li G, Yeung CK, Snyder F, Zalunardo N. Parenteral vitamin B12 in macrocytic hemodialysis patients reduced MMA levels but did not change mean red cell volume or haemoglobin. *Clinical nephrology*. 2011 Apr 1;75(4):336-45.
20. Trimarchi H, Forrester M, Schropp J, Pereyra H, Freixas EA. Low initial vitamin B12 levels in *Helicobacter pylori*-positive patients on chronic hemodialysis. *Nephron Clinical Practice*. 2004;96(1):c28-32
21. Leypoldt JK, Jaber BL, Lysaght MJ, McCarthy JT, Moran J. Kinetics and dosing predictions for daily haemofiltration. *Nephrology Dialysis Transplantation*. 2003 Apr 1;18(4):769-76.
22. Chandna SM, Tattersall JE, Nevett G, Tew CJ, O'Sullivan J, Greenwood RN, Farrington K. Low serum vitamin B12 levels in chronic high-flux hemodialysis patients. *Nephron*. 1997;75(3):259-63.
23. Saifan C, Samarneh M, Shtaynberg N, Nasr R, El-Charabaty E, El-Sayegh S. Treatment of confirmed B12 deficiency in hemodialysis patients improves Epogen® requirements. *International journal of nephrology and renovascular disease*. 2013 Jun 5:89-93.
24. Van Guldener C, Kulik W, Berger R, Dijkstra DA, Jakobs C, Reijngoud DJ, Donker AJ, Stehouwer CD, De Meer K. Homocysteine and methionine metabolism in ESRD: a stable isotope study. *Kidney international*. 1999 Sep 1;56(3):1064-71.
25. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, Tuohy K. Gut microbiota functions metabolism of nutrients and other food components. *European journal of nutrition*. 2018 Feb;57:1-24.
26. Kosmadakis G, Da Costa Correia E, Carceles O, Somda F, Aguilera D. Vitamins in dialysis: who, when and how much? *Renal failure*. 2014 May 1;36(4):638-50.
27. O'Leary F, Samman S. Vitamin B12 in health and disease. *Nutrients*. 2010 Mar;2(3):299-316.
28. Sutton D, Higgins B, Stevens JM. Continuous ambulatory peritoneal dialysis patients cannot increase dietary intake to recommended levels. *J Renal Nutr*. 2007;17(5):329-335.
29. Vani K, Arshi M, Jaya N. A Study of Vitamin B12 Levels In Chronic Kidney Disease Patients In Tertiary Care Hospital. *IOSR Journal of Dental and Medical Sciences*. 2019 Sep;18(9): 10-14
30. Chandna S, M, Tattersall J, E, Nevett G, Tew C, J, O'Sullivan J, Greenwood R, N, Farrington K: Low Serum Vitamin B Levels in Chronic High-Flux Haemodialysis Patients. *Nephron* 1997; 75:259-263.
31. Descombes E, Hanck AB, Fellay G. Water-soluble vitamins in chronic hemodialysis patients and need for supplementation. *Kidney international*. 1993 Jun 30;43(6):1319-28.
32. Ramirez G, Chen M, Jwr HW, Fuller SM, Ganguly R, Brueggemeyer CD, Butcher DE. Longitudinal follow-up of chronic hemodialysis patients without vitamin supplementation. *Kidney international*. 1986 Jul 1;30(1):99-106.
33. Minar E, Zazgornik J, Bayer PM, Lanschützer H, Mengele K, Marosi L. Hematologic changes in patients under long-term hemodialysis and hemofiltration treatment with particular reference to serum concentrations of folic acid and vitamin B 12). *Schweiz Med Wochenschr*. 1984 Jan 14;114(2):48-53.