

Original Research Article

Study of vitamin B12 deficiency in chronic kidney disease

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a growing health burden and important cause of mortality and morbidity worldwide as well as India. Anaemia a feature of CKD, is multifactorial, one of the most important factor responsible for the development of left ventricular hypertrophy, diastolic and later systolic dysfunction and cardiovascular disease, which is the single most important contributor to the mortality in CKD. Severe Chronic Kidney Disease has an adverse effect on haematopoiesis. Lack of erythropoietin, Iron deficiency anaemia and shortened red cell life span, Nutritional deficiency or deranged metabolism of vitamins is the major factors contributing to anaemia in CRF. Patients with CKD show megaloblastosis on examination of the bone marrow. Suggestive of Vitamin B12 and folic acid deficiency might Be Additional Factors Contributing to inadequate Haematopoiesis in uremia. Patients with CKD are at higher risk for nutritional deficiencies due to medication interactions, dietary restrictions and malnutrition. The dialysis procedure itself may cause loss of vitamin B12, Folic acid and there deficiency.

Methods: Sample size of 80 cases of CKD patients aged between 18-80 year admitted in SMIMER Hospital were included in study. Serum vitamin B12 Level was checked, correlation B12 deficiency with duration of CKD was observed.

Results: It was observed that, 47 cases of CKD had vitamin B12 deficiency. The mean duration of CKD is more in B12deficient group as compared to Normal Group and also finds the higher proportion of vitamin B12 deficiency in CKD patients.

Conclusions: Serum vitamin B12 level testing should be recommended routinely in patients with CKD and All the treating Nephrologists should anticipate the deficiency of vitamin B12 in CKD patients.

Keywords: Chronic kidney disease, Erythropoietin, Serum vitamin B12, Uraemia

INTRODUCTION

Patients affected by CKD have a shorter life expectancy than those with normal renal function, primarily due to the dramatic increase in cardiovascular mortality. Chronic Haemodialysis treatment is associated with a 10-50-fold higher risk of premature death than in the general population, and cardiovascular disease (CVD) represents the leading cause of death in haemodialysis patients.

Nevertheless, such increased cardiovascular risk is present since earlier stages of CKD.

Hypertension, dyslipidemia and diabetes mellitus have been proven to be poor predictors of cardiovascular risk in this population. Therefore, there has been growing attention on non-traditional cardiovascular risk factors, in particular oxidative stress, endothelial dysfunction, chronic inflammation, vascular calcification, Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) and hyperhomocysteinemia.¹ Furthermore, the high

prevalence of hyperhomocysteinemia in patients with CKD has increased interest in speculating the role for hyperhomocysteinemia as a risk factor for the progression of CKD.² The role of folic acid and vitamin B12 role is well recognized, as they are not only essential cofactors for homocysteine metabolism, but their homeostasis disruption may be related directly to cardiovascular risk and CKD progression. A serum B12 above 300pg/mL is interpreted as normal. Patient's with B12 levels between 200 and 300pg/mL are considered borderline. Patients with B12 levels below 200pg/mL are considered deficient. However; a low serum B12 level does not determine the etiology of the deficiency. If the etiology is uncertain, further testing should be done to investigate.³

Patients with CKD have been shown to have higher homocysteine blood levels compared to the general population. It has been hypothesized that hyperhomocysteinemia in these patients may be induced by the abnormality of homocysteine metabolism in the kidneys rather than by reduced glomerular filtration rate. Infact, although free homocysteine can pass the ultra filtration barrier due to its low molecular weight, it circulates in the blood stream mostly (about 90%) in the protein-bound form. In particular, trans sulfuration and remethylation pathways occurring in the kidney may be affected by renal disease. Stable isotope studies in Non-diabetic and diabetic patients with CKD have shown impaired metabolic clearance of homocysteine determined by dysfunction in both pathways.⁴

In patients of CKD, several metabolic alterations, including acidosis, systemic inflammation and hormonal dysregulation, together with co morbidities and multidrug therapies, can lead to malnutrition with subsequent folic acid and vitamin B12 deficiency. In addition, anorexia, gastroparesis, slow intestinal transit or diarrhoea, increased gut mucosal permeability and gutmicrobioes impairment may represent worsening factors.

Vitamin B12 in the blood is primarily protein-bound. Approximately 20% of circulating B12 is bound to transcobalamin; this is the biologically active form that can be taken up into cells. Although CKD patients display increased transcobalamin levels, they show an impaired vitamin uptake of B12. Moreover, in uremic patients a functional vitamin B12 deficiency can be observed because of increased transcobalamin losses in the urine and reduced absorption in the proximal tubule. This can lead to a "paradoxical" increase in cellular homocysteine levels despite normal total B12.⁵

On the other hand, potentially overdosage-related vitamin B12 toxicity could result exacerbated in individuals with CKD. Cyanocobalamin, the most commonly used form of B12s supplementation therapy, is indeed metabolized to active methylcobalamin, releasing small amounts of cyanide whose clearance is reduced in CKD. Under normal conditions, methylcobalamin is required to

remove cyanide from the circulation through conversion to cyanocobalamin. However, in CKD patients, the reduced cyanide clearance prevents conversion of cyanocobalamin to the active form and therefore supplementation is less effective.⁶

Patients with chronic inflammation, such as the haemodialysis population, display decreased production of transcobalamin due to impaired uptake of circulating Vit-B12 by peripheral tissues. This can determine increased synthesis of transcobalamin's I and III that brings to further accumulation of B12 in blood. Therefore, in the context of inflammatory syndromes, despite high vitamin B12 blood levels, there is a vitamin B12 deficiency in target tissues, potentially leading to hyperhomocysteinemia and increased cardiovascular risk (Figure 2).⁷

Administration of intravenous B-Complex vitamins is proven to be more efficient in reducing homocysteine serum levels and restoring their methylation pathway in CKD patients.^{8,9}

METHODS

The "Study of Vitamin B12 Deficiency in Chronic Kidney Disease" is the observational cross-sectional study done on 80 cases in SMIMER.

The present study was conducted on randomly selected cases of CKD coming to SMIMER Hospital from January 2018 to August 2019. Patients with radiology USG kidney showing changes of CKD, and S. creatinine, S. blood urea, S. Calcium S. Phosp and urine routine showing CKD features with S. Vitamin B12 level were included. Patients history and examination, all the information regarding sociodemographic Data was collected in the predesigned, pretested and Semi structured Questionnaire by interview method by the Investigator. Participants fasting morning plasma samples were taken and Vitamin B12 was measured.

Inclusion criteria

All indoor cases willing to participate in the study, with History of CKD, admitted in Dialysis unit of SMIMER hospital were included in the study.

Exclusion criteria

- Age <18 years
- Strict vegetarian diets
- Vitamine-B12 deficiency anaemia due to any other etiology
 - Conditions affecting small Intestine such as ileal Resection, Crohn's Disease, celiac disease, Bacterial growth or a parasite
 - Drugs like Methotrexate, Sodium Valproate,
 - Pernicious Anaemia, Gastrectomy, Atropic Gastritis

- Autoimmune diseases, including Type 1 Diabetes, Graves' disease

Statistical analysis

Statistical methods were descriptive and inferential statistic an analysis has been carried out in the present study. Results on continuous measurements are presented

On Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%).

Significance is assessed at 5% level of significance. The following assumptions on data are made, Dependent variables should be normally distributed, and samples drawn from the population should be random, Cases of the samples should be independent.

Analysis of Variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients. Student T-test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

Suggestive significance (p value: 0.05<p<0.10),
 *Moderately significant (p value: 0.01<p<0.05),
 **Strongly significant (p value:p<0.01).

Statistical software was the Statistical software namely SPSS15.0, Stata10.1, MedCalc9.0.1were used for the analysis of the data and Microsoft word and Excel have been used to generate tables.

RESULTS

Table 1 shows a total of 80 cases were reported and analysed in this study. Majority of the respondents were above middle aged Between 40- 60 Years, around 61.2 % of the respondents were male and nearly 42.5% are non-working, and dependent. Nearly 77.5% cases are taken from patients residing in Surat city, which came into urban area, and 22.5% cases are from rural areas, which are mostly villages and small towns near Surat city.

Table 2 shows majority of cases had symptoms of chronic kidney disease which includes, swelling of Legs upto feet and ankles 63.7%,second most common complaint was fatigue and not feeling hungry (Severe Anorexia) ,which was reported in upto 46.2% of cases, besides other symptoms Like itching, breathlessness ,too much urine initially followed by very less urine at later stage of disease. In reference to Vitamin B12 Deficiency symptoms in CKD subjects 45% had common symptoms

of tingling and numbness, burning feet, particularly at night time.

Table 1: Socio Demographic profile of subjects.

Gender	Frequency	%
Male	49	61.2 %
Female	31	38.8 %
Age(years)	Frequency	%
<40	7	8.8 %
40-60	48	60.0%
>60	25	31.2%
Residence	Frequency	%
Rural	18	22.5
Urban	62	77.5
Occupation	Frequency	%
Labourer	12	15
Housework	26	32.5
Non-Working	34	42.5
Others	8	10

Table 2: Distribution of cases according to symptoms.

Symptoms	Frequency	Percent
Swelling of legs (Pedal edema)	51	63.7
Tingling, numbness, burning feet	36	45.0
Fatigue and anorexia	37	46.2

Table 3: Distribution of cases according to past history of diabetes mellitus, hypertension family h/o CKD/renal stone.

Past history DM	Cases	%
Present	31	38.8
Absent	49	61.2
Past History Hypertension	Cases	%
Present	63	78.75
Absent	17	21.25
Family History CKD	Cases	%
Present	4	5
Absent	76	95
Total	80	100
Renal stone	Cases	%
Present	12	15
Absent	68	85

Around 78% subjects had Hypertension, out of which 62% patients previously had hypertension and 16% patient was developed hypertension after they diagnosed as CKD. Out of 80 cases in our study 38.8% of cases had Diabetes (28 cases Type 2 DM+ 3 cases Type 1 DM Nephropathy), with duration more than >6 Years, rest 5% cases had family history of kidney disease, (3 had Polycystic kidney disease 1 was undiagnosed family history) (Table 3).

Peripheral Blood smear examination of 58.8% patient had increased Mean corpuscular volume (MCV >100 fl) and Macrocyte (Larger than normal RBC),.....% cases had blood picture showing low platelets count, Neutrophil granulocytes with hyper segmented nuclei, Anisocytosis (increased variation in RBC size), Poikilocytosis (abnormally shaped RBC), Howell-Jolly bodies Present (Table 4).

Table 4: Distribution of cases according MCV and vitamin B12 deficiency Level/ Peripheral Blood Smear picture (Figure 1).

MCV (>100 fL) Macrocytis	Frequency	Percent
Raised	47	58.8
Normal	33	41.2
Platelet count reduced		
Present	55	68.75
Absent	25	31.25
Vitamin B12 deficiency		
Present	47	58.8
Absent	33	41.2
Hyper segmented, Neutrophil Anisocytosis, Poikilocytosis		
Present	27	33.75
Absent	53	66.25

It was observed that among the vitamin B12 deficient group, all cases had reduced Kidney size, shrunken kidney, while among the Vitamin B12 normal group only 25 cases had reduced Kidney size and rest 8 cases had normal Kidney size. Data reflects incidence of Vitamin B12 Increases as the size of kidney reduces (Table 5).

Table 5: Comparison of vitamin B12 deficiency with kidney size.

Kidney size	Deficient vit B12		Normal vit B12		Total	
	No.	%	No.	%	No.	%
Reduce	47	100.0	25	75.8	72	90.0
Normal	0	0	8	24.2	8	10.0
Total	47	100.0	33	100.0	80	100.0

Table 6 shows, out of 80 cases authors studied, authors observed that incidence of vitamin B12 deficiency increases with the increase duration of CKD, cut off was kept 6 years for duration of CKD.

Table 6: Comparison of Vitamin B12 deficiency with duration of CKD.

Duration of CKD	Deficient vit B12		Normal vit B12		Total	
	No.	%	No.	%	No.	%
<6 years	20	42.6	21	63.6	41	51.3
>6 years	27	57.4	12	36.4	39	48.8

DISCUSSION

In the present study it was observed that out of 80 cases, 47 cases had vitamin B12 deficiency while 33 cases did not have vitamin B12 deficiency. The incidence of CKD was more among males than in females, may be due to more incidence of Hypertension, Diabetes (Risk factor for CKD) 10 in males than females, The average Age of presentation of CKD is 40-60, as CKD is chronic disease takes time to develop full blown features of CKD, In the study 62 cases were from Urban areas than 18 cases in rural areas, it could be attributed probably due to poor living or working conditions pollution, etc.

Or incidence of Hypertension, Type 2 DM more in urban population compare to rural areas. Regarding occupation 34 cases were Non-Working, and dependent, due to frequent follow up for hemodialysis (Thrice weekly schedule) reflecting high morbidity in CKD.¹¹

In reference to vitamin B12 deficiency symptoms in CKD subjects 45% had common symptoms of tingling and numbness, burning feet, particularly at night time, there Peripheral Blood smear examination of shows decreased RBC count and haemoglobin level, 58.8% patient had increased Mean corpuscular volume (MCV >100 fl) and Macrocyte (Larger than normal RBC),.....% cases had blood picture showing low platelets count, Neutrophil granulocytes with Hyper segmented nuclei, Anisocytosis (increased variation in RBC size), Poikilocytosis (abnormally shaped RBC), Howell-Jolly bodies.

In the present study, the mean haemoglobin of the participants in vitamin B12 deficient group was 8.62±2.125 and vitamin B12 normal group was 9.02±1.631. The association between mean haemoglobin of participants among both group was statistically insignificant.

Anemia is a common manifestation of CKD and the prevalence of anemia increases as the eGFR declines. Anaemia’s associated with a poorer quality of life and the rapid decline of renal function, as well as cardiovascular mortality.¹²

Anemia is mainly caused by insufficient kidney EPO production and a deficiency of the available iron to support on-going erythropoiesis in CKD patients.^{13,14}

However, several different factors including inflammation, malnutrition, and metabolic disease, have been considered to contribute to the anemia of CKD. The mean duration of CKD of the participants in vitamin B12 deficient group was 6.59±2.894 and Vitamin B12 normal group was 5.181±2.324. The association between mean duration of CKD of participants among both groups was statistically significant (p-value 0.02). It was observed that incidence of Vitamin B12 deficiency increases with the increase duration of CKD. It was also observed that

among the Vitamin B12 deficient group, all cases had reduced kidney size, shrunken kidney, while among the vitamin B12 normal group only 25 cases had reduced kidney size and rest 8 cases had normal kidney size. relatively increase incidence of vitamin B12 deficiency as the size of kidney reduces.

CONCLUSION

From the study, it is concluded that, there is high prevalence of vitamin B12 deficiency in CKD patients besides other causes of anemia. Hence, serum vitamin B12 level testing should be recommended routinely in patients with chronic kidney disease and all the treating nephrologists/physicians should anticipate the deficiency of vitamin B12 in CKD patients and take appropriate measures to prevent associated morbidity and mortality of CKD.¹⁵

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