IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 9 Ver. III (September. 2016), PP 22-25
www.iosrjournals.org

Vitamin B_{12} Deficiency In Chronic Kidney Disease

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Abstract
Introduction: *Anaemia has long been recognised as a feature of CKD. Severe Chronic Kidney Disease has an adverse effect on haematopoiesis. There is imbalance between haematopoiesis and increased destruction. Many Patients with CKD show smear and megaloblastosis on examination of the bone marrow. This suggests that Vitamin B_{12}& folic acid deficiency might be additional factors contributing to inadequate haematopoiesis in uraemia. The most common causes of megaloblastosis are cobalamin (vitamin B_{12}) and folate deficiencies. Various studies carried out on Asian Indians with normal renal function show that they have low levels of Vitamin B_{12} and high levels of homocysteine and methylmalonic acid.*
Objectives:*1) To Define prevalence of Vitamin B_{12} deficiency in Chronic Kidney Disease (CKD) patients; 2) To study the contributory role of dietary factors to Vitamin B_{12}deficiency.*
Materials&Methods: *A hospital based cross sectional study was conducted including 50 patients suffering from Chronic Kidney Disease. After taking informed consent, patients underwent history recording, clinical examination along with relevant anthropometrical measurements.Laboratory investigations included complete blood count, urine examination, blood sugar profile, lipid profile and renal function test. Serum vitaminB_{12}& homocysteine levels were done by Kit based Chemiluminescent Micro-particle Immunoassay (CMIA).*
Results: *Out of total 50 subjects, 31 were males and 19 were females with a mean age of 45.26 +/- 9.63 years. Vitamin B_{12} deficiency was observed in 56% of CKD patients. Significant association was observed between presence of neurological symptoms and presence of vitamin B_{12} deficiency. Similarly mean duration of CKD was also significantly associated with presence of Vitamin B_{12}deficiency.*
Conclusion: *Present study showed high prevalence of Vitamin B_{12} deficiency in CKD patients. Most of the patients had associated neurological, hematological and gastro-intestinal symptoms. Hence all the treating nephrologists should anticipate the deficiency of Vitamin B_{12}in CKD patients and take appropriate measures for its control.*
Keywords: *Chronic Kidney Disease, homocysteinemia, Megaloblastic Anemia, Vitamin B_{12} Levels*

I. Introduction

Chronic Kidney Disease (CKD) is a growing health burden in the world, with estimates of nearly 20 million affected [1]. CKD is defined as either sustained reduction in kidney function with a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 or evidence of kidney damage [2]. Although kidney damage may be defined by radiologic or pathologic findings, it is diagnosed most frequently by the presence of microalbuminuria. Levels of urinary albumin excretion above 30 mg/day (or urinary albumin to creatinine ratios of 17 mg/g or higher for men or 25 mg/g or higher for women) on at least 2 measurements are consistent with CKD, regardless of the level of GFR [3].

Anaemia has long been recognised as a feature of CKD. The anaemia of CKD is multifactorial. Anaemia is considered to be one of the most important factors 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 [4].

Severe Chronic Kidney Disease has an adverse effect on haematopoiesis. There is imbalance between haematopoiesis and increased destruction. The major defect appears to be one of like relative bone marrow failure. It may be circulating toxins like PTH (parathyroid hormone) that play major part and depress the marrow directly. Lack of erythropoietin, iron deficiency anaemia and shortened red cell lifespan are the major factors contributing to anaemia in CRF [5,6]. Another possibility is nutritional deficiency or deranged metabolism of vitamins in uremic patients. Many Patients with CKD show smear and megaloblastosis on examination of the bone marrow [7]. This suggests that Vitamin B_{12}& folic acid deficiency might be additional factors contributing to inadequate haematopoiesis in uraemia [8].

The most common causes of megaloblastosis are cobalamin (vitamin B_{12}) and folate deficiencies. This deficiency is caused by: Inadequate nutrition and loss through the haemodialysis procedure. Most of the Indian population is vegetarian for cultural or religious reasons and even in the non-vegetarian population the amount of non-veg consumed contains less animal proteins than in typical western diet. The frequency of consumption of non-vegetarian food items is very low [9]. Various studies carried out on Asian Indians with normal renal

function show that they have low levels of Vitamin B_{12} and high levels of homocysteine and methylmalonic acid [9,10] Hence this study was undertaken to determine the contribution of Vitamin B_{12} deficiency to the overall picture of anaemia in Indian patients of CKD. We also attempted to study the contributory role of dietary factors to Vitamin B12 deficiency.

II. Material & Methods

It was a hospital based cross sectional study conducted at Department Of Medicine of a tertiary care hospital. Study included 50 patients suffering from Chronic Kidney Diseasethat were either admitted in medicine wards or enrolled from Nephrology Unit. Ethical clearance was obtained from the ethics review committee of the institute. After taking informed consent, patients underwent history recording, clinical examination along with relevant anthropometrical measurements.Criteria used for Diagnosis of Chronic Kidney Disease (CKD):

- Glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m2
- Evidence of kidney damage(radiologic or pathologic findings)

Levels of urinary albumin excretion above 30 mg/day (or urinary albumin to creatinine ratios of 17 mg/g or higher for men or 25 mg/g or higher for women) on at least 2 measurements, regardless of the level of GFR.Laboratory investigations included complete blood count, urine examination, blood sugar profile, lipid profileand renal function test. Serum vitaminB_{12}&homocysteine levelswere done by Kit based Chemiluminescent Micro-particle Immunoassay (CMIA).

The individual venous blood samples (3ml) in plain bulb was taken and assayed within the laboratory for Vitamin B_{12}levels by CMIA method in 'Architect 2000' machine. Vitamin B_{12} levels <200 pg/mL was considered deficient whereas B_{12} levels >350 pg/mL was considered normal. Blood levels of B_{12} between 100 and 350 pg/mL was considered indeterminate and the corresponding blood specimens were sent for homocysteine levels (reference range, 5.08 –15.39 Micromol/L) by CMIA method in 'Architect 2000' machine. Specimens with homocysteine levels above the upper limit of the laboratory reference range were considered elevated and indicative of B12 deficiency.Data was analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) using appropriate statistical tests.

III. Results

Out of total 50 subjects, 31 were males and 19 were females with a mean age of 45.26 +/- 9.63 years. Most common associated co-morbidity was hypertension (86%) followed by diabetes (52%). Pallor and pedal edema was seen in 52% cases each while cyanosis and clubbing was seen in 12% and 10% subjects respectively. Vitamin B_{12} deficiency was observed in 56% of CKD patients (Table 1). Significant association was observed between presence of neurological symptoms (like tingling, numbness, loss of balance, weakness) and presence of vitamin B_{12} deficiency (Table 2). Similarly mean duration of CKD was also significantly associated with presence of Vitamin B_{12}deficiency (Table 3).

IV. Discussion

Vitamin B_{12} (B_{12}) is a water-soluble vitamin that plays a key role in the normal function of the nervous system and blood formation along with serving as a cofactor for the formation of methionine from homocysteine [11]. Normally, B_{12} is released from dietary protein in the stomach and binds to intrinsic factor (IF). The B_{12}-IF complex is absorbed in the ileum via the cubilin receptor [11]. Defects in cubilin, a proximal tubular membrane protein, have been associated with both megaloblastic anemia and tubular proteinuria [11-14]. Cubilin also acts to reabsorb the majority of filtered albumin from the urine and recently, genome-wide association studies have identified SNPs in CUBN in association with albuminuria [15] and B_{12}levels [16, 17].

Vitamin B_{12} deficiency was observed in 56% of CKD patients in present study. Similar results were observed by Kartik et al., who observed macrocytosis in 54% of patients of CKD [18]. Other authors also reported similar findings [19-21]. The potential mechanism for the same can be explained as: Vitamin B_{12} in the blood is primarily protein-bound. Approximately 20% of circulating B_{12} is bound to holotranscobalamin (TC2) with the remainder to haptocorrin. TC2-bound B_{12} is the biologically active form as B_{12} bound to haptocorrin cannot be taken up into cells. A congenital form of megaloblastic anemia has been described in infants lacking TC2 despite normal total B_{12} levels. The kidney plays an important role in TC2 metabolism. TC2 is filtered at the glomerulus and is reabsorbed in the proximal tubule by megalin. B_{12} is then returned to the blood bound to newly synthesized TC2. Thus, defects in protein reabsorption in the proximal tubule could lead to a loss of biologically active TC2 in the urine [22].

B_{12} deficiency is associated with anemia and neurological disorders. In present study a significant association was observed between presence of neurological symptoms (like tingling, numbness, loss of balance, weakness) and presence of vitamin B_{12} deficiency in CKD Patients. Similar results were observed by various other authors [22-26].

In present study we also observed that mean duration of CKD was significantly associated with presence of Vitamin B_{12} deficiency in patients. The landmark study by Obrador et al. [27] showed that among predialysis patients, 68% of those with advanced chronic kidney disease who required renal replacement therapy had a hematocrit less than 30 mg/dL; of these, 51% of patients had a hematocrit less than 28 mg/dL. Furthermore, although anemia is not as common in earlier stages of chronic kidney disease, patients with stage III disease have a prevalence of concurrent anemia of 5.2%, whereas those with stage IV disease have a prevalence of concurrent anemia of 44.1% [28]. There is also a greater prevalence of anemia of chronic kidney disease in those older than 60 years, as compared to those aged between 46 and 60 years. This is probably secondary to the greater rate of chronic kidney disease in older individuals, as well as the lower estimated glomerular filtration rates (GFRs) that are associated with aging.

V. Conclusion

Present study showed high prevalence of Vitamin B_{12} deficiency in CKD patients. Most of the patients had associated neurological, hematological and gastro-intestinal symptoms. Hence all the treating nephrologists should anticipate the deficiency of Vitamin B_{12}in CKD patients and take appropriate measures for its control.

VI. Recommendations

Vitamin B_{12} supplementation should be considered in CKD patients as a part of treatment protocol to prevent the complications associated with its deficiency. We also recommend further large scale prospective studies to validate our findings.

Acknowledgement

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/ editors/ publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

Conflict Of Interest

None declared

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Tables

Table 1: Distribution of subjects based on Vitamin B_{12} levels

Vitamin B 12 levels	**N**	**%**
Normal	22	44.0%
Deficient	28	56.0%
Total	50	100.0%

Table 2: Association of Vitamin B_{12} deficiency with Clinical Symptoms, Gender & Diet History

Variables	**Vitamin B12 levels**		**Total**	**p- value**
	Normal (n-22)	**Deficient (n-28)**		
Neurological Symptoms	3	12	15	**0.03**
	13.6%	42.9%	100.0%	
GIT Symptoms	2	4	6	**0.68**
	33.3%	66.7%	100.0%	
Haematological Symptoms	12	14	26	**0.78**
	46.2%	53.8%	100.0%	
Male Gender	13	18	31	**0.77**
	41.9%	58.1%	100.0%	
Vegetarian Diet	9	15	24	**0.41**
	37.5%	62.5%	100.0%	

Table 3: Association of Vitamin B_{12} levels with CKD duration and GFR

Variables	**Vitamin B12 levels**	**Mean**	**SD**	**p- value**
CKD Duration (yrs)	**Normal**	5.32	3.73	**< 0.01**
	Deficient	8.42	3.51	
GFR	**Yes**	13.1	9.1	**0.613**
	No	14.5	10.5	