Original Article

Evaluation of Folic Acid Deficiency Anaemia in Predialysis Chronic Kidney Disease Patients: A Hospital-based Study

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Abstract

Background: *Chronic kidney disease (CKD) is defined as decreasing kidney function for more than 3 months. Anemia is a common complication of CKD due to a decrease in the hormone erythropoietin related to hemoglobin levels. Folic acid helps with the process of nucleoprotein synthesis and erythropoiesis maintenance.* ***Objectives:*** *The aim of the study was to determine the folic acid level in predialytic anaemic chronic kidney disease patients.* ***Materials and Methods:*** *It was a cross-sectional study conducted in the department of Nephrology of Eastern Medical College & Hospital from September 2020 to August 2021 on predialysis CKD anaemic patient of stage-3 to stage-5. A total of 100 subjects were selected by purposive sampling. The age group was 18 to 70 years.* ***Results:*** *Among the 100 subjects mild, Moderate and Severe aneamia were found in 27%, 44% and 29% respectively. Maximum cases showed normocytic normochromic anaeamia (54%) and 7% cases showed macrocytic aneamia. Serum folic acid levels were found to have decreased in 1 (16.7%), 2 (8.33%) and 7 (10.0%) cases and increased in 2 (33.3%), 5 (20.83%) and 21 (30.0%) cases in stage-3, stage-4 and stage-5 respectively.* ***Conclusion:*** *Anemia is a frequent complication of chronic kidney disease. Inadequate production of erythropoietin by the failing kidneys leads to decreased stimulation of the bone marrow to produce red blood cells. Folic acid deficiency may represent an influential factor in renal anemia.*

Key words: Chronic Kidney Disease, Predialysis, Anaeamia, Folic acid deficiency.
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Introduction

Chronic kidney disease causes irreversible deterioration of renal function that usually develops over a period of year. It manifests only as a biochemical abnormality but eventually loss of the excretory metabolic and endocrine function. Aneamia is common in patients with CKD. Anaemia contributes to many nonspecific symptoms including fatigue and shortness of breath. Aneamia occurs mostly due to erythropoietic deficiency but also due to folic acid deficiency[1].

Chronic Kidney Disease (CKD) is defined as a decreasing kidney function based on a glomerular filtration rate (GFR) less than 60 ml/minute/1.73 m^2. Based on the glomerular filtration rate, the CKD classification is divided into five stages, and a GFR value less than 15 ml/minute will lead to end-stage renal disease (ESRD)[2]. According to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), using data on the percentage of CKD stages 1-4 in a population aged 18 years or older in the United States in 2013-2016, approximately 15% suffered from this disease. Based on gender, the prevalence in women was higher (15%) than men (12%)[3].

According to the results of Indonesian Basic Health Research (2018), the prevalence of CKD in the population aged over 15 years has increased by 0.38% compared to that in 2013. According to age characteristics, the highest prevalence is in the age groups of 65-74 (0.82%) and older than 75 years (0.75%). The prevalence of CKD was higher in men (0.42%) than women (0.35). The most important diseases underlying the occurrence of CKD were diabetes mellitus and hypertension[4]. Atherosclerosis and arteriosclerosis in hypertensive patients damage the renal arteries, causing an increase in intraglomerular pressure and hyperfiltration and resulting in glomerulosclerosis[5]. In addition, increased activity of the Renin Angiotensin Aldosterone System (RAAS) can increase the angiotensin-II level, which has a vasoconstrictive

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effect and can decrease peritubular capillary blood flow in the glomerulus and cause sclerosis, leading to kidney damage[6].

Meanwhile, in diabetes mellitus, hyperglycemia can damage the blood vessels of the kidneys so that protein (albumin) can penetrate the glomerulus. The persistent proteinuria will lead to a progressive decline in kidney function and decrease the value of the glomerular filtration rate. Proteinuria or albuminuria, accompanied by a decreasing GFR value can cause ESRD and increase diabetic patients' mortality[7-9]. Clinical manifestations of CKD are asymptomatic or do not show metabolic disturbances at the early stage (stage 1-2) of CKD. At stages 3-5 anemia, hypertension, electrolyte disturbances, metabolic acidosis and osteodystrophy often appear. Signs and symptoms of CKD will develop with increasing kidney damage[10,11]. Decreased kidney function can cause a decrease in hemoglobin (Hb) level. Anemia is a complication that often occurs in CKD patients. It occurs due to peritubular cell damage that leads to inadequate secretion of erythropoietin (EPO). The hormone EPO, produced in the kidney, plays a significant role in the proliferation and differentiation of erythrocytes[12].

Pharmacological therapy that can be given is iron supplementation, Erythropoietin stimulating agent (ESA) therapy at Hb level below 10.0 g/dl. In addition, anemia due to folate and vitamin B12 deficiency and undergoing hemodialysis can be treated with folic acid and vitamin B12. Another therapy that can be given when the Hb level is below 7.0 g/dl is Packed Red Cells (PRC) transfusion[13,14]. Folic acid is one of the pharmacological therapies that can be given to chronic kidney disease patients. Folic acid has a major role in DNA synthesis and erythropoiesis maintenance. Aneamia being major comorbidity of CKD, it occurs in all stages but becomes more pronounced at the latter stage of kidney failure. A significant increase in the prevalence of anemia develops as the creatinine clearance fall to 70 ml/min or lowering among males and 50 ml/min as lower among female[15].

Hemoglobin can be as low as 5-7 gm/dl in CKD stage-5. Although it is less severe or absent in patients with polycystic kidney disease. Iron deficiency is common among patients with CKD and even more prevalent is there on hemodialysis because of hemodialysis in the dialysis circuit, folic acid deficiency is also another important cause of anaemia in CKD[16]. If folic acid deficiency is not correct by supplementation of Iron, then iron deficiency, folic acid deficiency and other cause of aneamia have been excluded or corrected. Recombinant human erythropoietic is very effective in correcting the aneamia of CKD and improves symptoms. The target hemoglobin is usually between 10.0 and 12.0 gm/dl[17]. Erythropoietin is less effective in the presence of iron, folic acid deficiency, active inflammation, malignancy and in particular myeloma. The average daily diet contains 5-30µg of vitamin B12 mainly in meat, fish, eggs and milk-well more than the lug daily requirement. In the stomach, gastric enzymes release folic acid from food and then in gastric pH it binds to a carrier protein termed R-protein. The gastric parietal cells produce intrinsic factor, a folic acid binding protein that optimally binds folic acid released from the diet switches from the R-protein to intrinsic factor[18]. The folic acid-intrinsic factor complex binds to specific receptors in the terminal ileum and folic acid is actively tranported by the enterocytes to plasma where it binds to transcobalamin-II, a transport protien produced by the liver which carries it to the tissues for utilization. The liver stores enough folic acid for 3 years and this together with the enterohepatic circulation means that folic acid deficiency takes years to become mainfest even if all dietary inatake is stopped or severe folic acid malabsorption supervenes[19].

Blood levels of folic acid provide a reasonable indication of tissue stores are usually diagnostic of deficiency and remain the fast line tests for most laboratories. Additional tests have been evaluated including measurement of methylmalonic acid and plasma homocysteine levels but do not add much in most clinical situations. Levels of cobalamins fall in normal pregnancy. Reference ranges vary between laboratories but levels below 150 mg/L are considered deficient. Low folic acid values occur in women using the oral contraceptive pill and in patient with myeloma in which paraproteins can interfere with folic acid[20].

Materials and Methods

This cross-sectional study was conducted in the Department of Nephrology of Eastern Medical College & Hospital from September 2020 to August 2021 on 100 admitted CKD anaemic patients of stage-3 to stage-5 with ethical approval from IERB. Inclusion criteria were prediagnosed stable predialysis CKD patients who were anaemic and the age group were 18 to 70 years. Exclusion criteria were subject who did not give consent, suffering from active bleeding or having hemolytic disorder, severe cardiac and respiratory failure and aneamia of chronic disease except CKD.

After meeting inclusion and exclusion criteria a purposive sampling technique was applied. CKD patients were identified by review of their past medical records. Patients who had eGFR<60 ml/min/1.73m^2 for more than three months were considered as CKD patients. The eGFR was calculated by MDRD formula. In case of male CKD

patients, who had hemoglobin level <13 gm/dl and in case of female CKD patients' hemoglobin level <12 gm/dl are considered as aneamia. Selected patients were interviewed by a standard case record form.

Results

A total of 100 CKD patients with anaemia were included in this study in which 64 were male and 36 were female patients (Figure-1). On the initial visit, details of history were taken regarding current illness and clinical examinations were done. Relevant investigations were carried out for all patients. Data was expressed as Mean ± SD. Then data were presented in the forms of tables and figures.

Table-I demonstrated that, among the aneamic CKD patient majority were normocytic normochromic aneamia (54%), which were followed by microcytic hypochromic (25%), diamorphic (11%), macrocytic (7%) and microcytic normochromic anaemia (3%). On the other hand, among CKD patients' majority were moderately anaemic (44%) followed by severe anaemia (29%). Only 27% of subjects were mildly anaemic. Table-III stated that 59% of anaemic patients had normal value, 30% had an increase level and 11% had decreased value of serum folic acid level. There was no association of the severity of anaemia with the levels of folic acid (p>0.05).

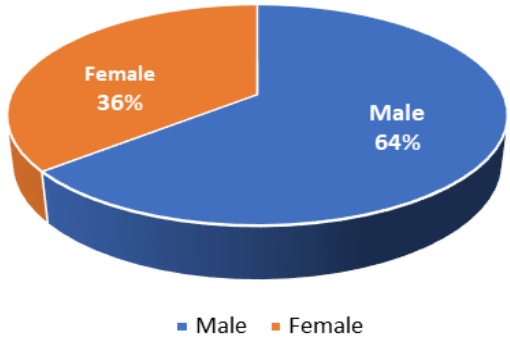

Figure-1: Pie chart showing the gender distribution in study subjects (n=100)

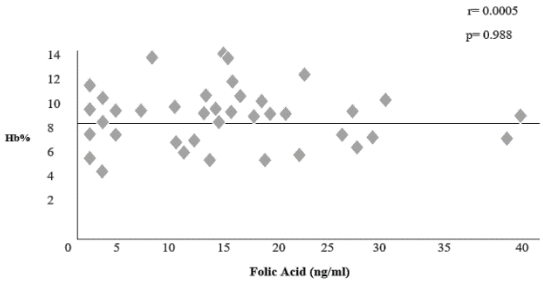

Figure-2: Scatter plot shows the correlation between Hb concentration and serum folic acid level (r=0.0005, p=0.988) among the study population (n=100)

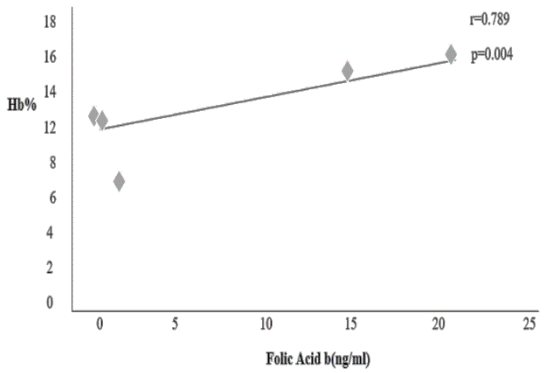

Figure-3: Scatter plot shows the correlation between Hb concentration and folic acid level (r=0.789, p=0.004) among macrocytic anaemic patients (n=7)

Figure-2 showed that there was no correlation between Haemoglobin (Hb) concentration and serum folic acid level (r=0.0005, p=0.988) among the study population.

Figure-3 showed that there was significant correlation between Hb concentration and folic acid level (r=0.789, p=0.004) among the macrocytic anaemic patients.

Table-I: Peripheral blood film (PBF) findings among the study subjects (n=100)

Peripheral blood film (PBF) findings	Frequency	Percentage (%)
Normocytic Normochromic (NN)	54	54.0
Microcytic Hypochromic (MH)	25	25.0
Dimorphic (NN/MH)	11	11.0
Macrocytic	7	7.0
Microcytic Normochromic	3	3.0
Total	100	100.0

Table-II: Severity of anaemia in study population (n=100)

Severity of Anaemia	Frequency	Percentage (%)
Mild	27	27.0
Moderate	44	44.0
Severe	29	29.0
Total	100	100.0

Table-III: Association of the Severity of anaemia with serum folic acid level (n=100)

Serum Folic acid Leveling (ng/ml)	Severity of Anaemia				
	Mild	Moderate	Severe	Total	χ^2 test
	N (%)	N (%)	N (%)	N (%)	
Normal (7.22-15.4)	15 (25.4)	26 (44.07)	18 (30.51)	59 (100)	P=0.24
Increase (>15.4)	10 (33.33)	10 (33.33)	10 (33.33)	30 (100)	
Decrease (<3)	2 (18.09)	8 (72.72)	1 (90)	11 (100)	

Discussion

This hospital-based study recruited 100 CKD patients of stage-3, stage-4 and stage-5 who are admitted at Eastern Medical College Hospital, Cumilla, Bangladesh. Among the 100 CKD patients 64 were male and 36 were female patients. After evaluation of history chronic glomerulonephritis and diabetes mellitus were identified as the main underlying diseases for CKD in this study. The morphology of 100 anaemic CKD patients was normocytic in 54% cases, microcytic hypochromic in 25% cases, dimorphic picture (normocytic normochromic & hypochromic) in 11% cases, macrocytic in 7% cases and 3% cases had macrocytic anaemia. It is well known that anaemia of CKD is normocytic normochromic type[21].

Another study among CKD patients at BIRDEM academy, Shahbag, Dhaka showed normocytic normochromic anaemia presented in 93% cases which was followed by microcytic hypochromic anaemia in 5% cases and anisochromia in 2% cases. There were no macrocytic anaemic patients in their study[22].

Anemia is more prevalent and severe as the estimated glomerular filtration rate (eGFR) decreases often leads to decline in the quality of life and increased risk of cardiovascular diseases, cognitive impairment, hospitalizations and mortality[1]. According to the category of anaemia, most of the CKD patients of this study were moderately anaemic (44%) followed by severely anaemic (29%). Also, 27% of subjects were mildly anaemic.

The main cause of anemia in CKD is the inadequate production of endogenous erythropoietin, a hormone that acts on the differentiation and maturation of the red blood cells precursors. Other contributing factors have been recognized in recent years as an impaired response of the bone marrow to erythropoietin caused by uremic toxins, inflammation, decreased availability of iron for erythropoiesis and increased levels of hepcidin, a shortened of red blood cells (RBC) half-life or vitamin deficiencies (vitamin B_{12} or folic acid), among others[23].

Folic acid, the synthetic form of vitamin B_9, is critical in the conversion of homocysteine to methionine. If there is not enough intake of folic acid, there is not enough conversion and homocysteine levels are raised, which is regarded as an independent predictor of cardiovascular morbidity and mortality in end-stage renal disease[24].

Serum folic acid levels were found to have decreased in 1 (16.7%), 2 (8.33%) and 7 (10.0%) cases and found to have increased in 2 (33.3%), 5 (20.83%) and 21 (30.0%) cases in stage-3, stage-4 and stage-5 respectively in total study population. The rest of the patient's serum folic acid was at normal level. This study showed no correlation between Hb concentration and serum folic acid level among the study population. In patients with CKD, folate deficiency may represent an influential factor in renal anemia and hypo-responsiveness to EPO therapy. As such, the possibility and the requirement of a regular supplementation is still a matter of debate[25].

In this study, macrocytic anaemia was found in 7% cases and there was significant correlation between haemoglobin concentration and serum folic acid level, p=0.004. A study by Mohammed MR, et al[26] found 12.5% cases of macrocytic anaemia.

Macrocytic anemia that developed in these patients which can be explained by the facts that folate and Vitamin B_{12} deficiency could occur in this patient playing additional role for inadequate hematopoiesis in the uremic patients and macrocytic anemia also can occur in the patients undergoes chronic dialysis without folate replacement therapy, also malnutrition specially in the patients who survive for long period, suffering from renal failures and defects in the protein reabsorption in proximal tubules which lead to a loss of biologically active transcobalamin two in the urine[27-29].

Conclusion

Anemia is a frequent complication of chronic kidney disease. Inadequate production of erythropoietin by the failing kidneys leads to decreased stimulation of the bone marrow to produce red blood cells. Folic acid deficiency may represent an influential factor in renal anemia. Treatments for anemia in CKD may ease symptoms and improve the quality of life but also reduce hospitalizations of CKD patients due to cardiovascular events.

Conflict of interest

The authors declared that they have no conflict of interest.

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