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Original Article

Anemia of Inflammation & Health-Related Quality of Life in Chronic Kidney Disease

Liton Chandra Ghosh[1], Mahbuba Akhter[2], Swapon Kumer Saha[3], Nayan Ranjan Sarker[4]

[1]Associate Professor, Department of Nephrology, Dhaka National Medical College[2]Associate Professor, Department of Nephrology, Ashiyan Medical College Hospital[3]Associate Professor, Department of Nephrology, Rajshahi Medical College[4]Assistant Professor, Department of Nephrology, Sir Salimullah Medical College

Abstract

Background:

Anemia is a common comorbidity of chronic kidney disease (CKD). As the diseased kidney loses its ability to produce the erythropoietin essential to the production of hemoglobin, anemia ensues. Anemia is observed in the course of chronic kidney disease (CKD) and it is associated with diminishing the quality of a patient's life. Moreover, it enhances morbidity and mortality and hastens the CKD progression rate.

Objective:

To analyze the health-related quality of life (HRQOL) in anemic CKD patients with the effects of anemia and inflammation

Methods:

This cross-sectional study was conducted in the Department of Nephrology,(Dhaka national medical college and hospital), Dhaka, for 2 years; from January 2018 to December 2019. A total of 50 subjects fulfilling the inclusion criteria were enrolled as study subjects. Data were processed and analyzed using the software SPSS (Statistical Package for Social Sciences) version 11.5.

Result:

Among the study subjects, most patients (30, 60.0%) belonged to the age group of > 55 years, followed by 15 (30.0%) patients were from 50-55 years of age and the rest 5 (10.0%) patients were from 45-50 years of age. About 60% of the patients were male and 40% were female in this study. Concerning the degree of anemia, most of the patients (25, 50.0%) suffered from severe anemia followed by 17 (34.0%) patients had moderate anemia, and the rest 8 (16.0%) patients had mild anemia. According to extent of CKD, most of the patients (25,50.0%) had stage 5 CKD (ESRD), followed by 15 (30.0%) patients had stage 3 CKD, and the rest 10 (20.0%) patients suffered from stage 4 kidney disease. Among the patients who had stage 3 kidney disease, 8 (16.0%) patients had mild anemia, followed by 4 (8.0%) patients had moderate anemia, and the rest 3 (6.0%) patients had severe anemia. Among the patients with stage 4 CKD, 6 (12.0%) patients had moderate anemia and 4 (8.0%) patients had severe anemia. Among the patients who had the end-stage renal disease (ESRD) or stage 5 CKD, 7 (14.0%) patients had moderate anemia and 18 (36.0%) patients had severe anemia**.** Considering inflammatory parameters according to the degree of anemia, the neutrophil count was <6000 U/L, 6000-6500 U/L, and 6500-7500 U/L in mild, moderate, and severe anemia respectively. Lymphocyte count was <5000 U/L, 5000-5400 U/L, and 5000-5500 U/L in mild, moderate, and severe anemia respectively. CRP (mg/dl) level was 0.9- 2 in mild anemia, 5-40 in moderate anemia, and 10-50 in severe anemia.

Conclusion:

This study highlighted the profound impact of CKD on health-related quality of life (HRQOL) and potential areas that can be targeted for therapeutic intervention. Furthermore, this study showed, chronic diseases can lead to an inflammatory process which ultimately results in anemia through various mechanisms. Moreover, early identification and correction of anemia may improve the quality of life.

Keywords: CKD, ESRD, Anemia, Inflammation

Introduction

The annual mortality rate associated with cardiovascular diseases (CVD) in chronic kidney disease (CKD) patients is approximately 9%, which is almost 10–20 times higher than in the general population.[1] International guidelines define this condition as decreased kidney function shown by a glomerular filtration rate (GFR) of less than

60 mL/min per 1·73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause. The best available indicator of overall kidney function is GFR.[2] Most patients with chronic kidney disease eventually become anemic.[3] Many factors contribute to declining hemoglobin as CKD progresses, but impaired production of erythropoietin by failing kidneys is a central cause. Hepcidin-mediated iron restriction also contributes to anemia by downregulating both intestinal iron absorption and the release of stored iron for erythropoiesis. The core components of anemia management remain erythropoiesis-stimulating agents (ESA) and iron supplementation.[4] Hemoglobin levels in individuals with chronic kidney disease fluctuate frequently above or below the recommended target levels within short periods even though the calculated mean hemoglobin remains within the target range of 11 to 12 g/dl.[5] Inflammation causes an increase in the production of hepcidin, which is a potent mediator of anemia of chronic diseases. Anemia in chronic kidney disease is mainly due to erythropoietin deficiency but these patients often have a chronic inflammatory state.[6] Inflammation is an immune response to injury and infection. The inflammatory process causes hypoferremia as an acute-phase response to fight against infection. It involves the secretion of cytokines to regulate iron redistribution, creating hypoferremia that delays pathogen growth, thereby causing the invaders to be engulfed by phagocytes. The manifestation of the pro-inflammatory process in a spectrum results in variation in hepcidin levels and the magnitudes of anemia phenotype. Anemia of chronic disease (ACD), therefore, is caused by a complex interplay of proinflammatory cytokines which induce dysregulation in iron homeostasis, erythroid progenitor cell differentiation, erythropoietin synthesis, and red cell longevity, all culminating in the pathogenesis of anemia.[7]Several studies noticed a progressive decline in HRQOL with worsening renal function. Furthermore, HRQOL was found to decline over time, with the main predictors of this decline being age, co-morbidities, and changes in hemoglobin and albumin levels.[8] This study aimed to analyze the health-related quality of life (HRQOL) in anemic CKD patients with the effects of anemia and inflammation.

Material & Methods

This cross-sectional study was conducted in the Department of Nephrology, Dhaka National Medical College and Hospital(DNMC), Dhaka, for 2 years; from January 2018 to December 2019. A total of 50 subjects fulfilling the inclusion criteria were enrolled as study subjects. Written consent was obtained from each subject.Patients older than 44 years & who had given consent to participate were included in the study. Patients who had other chronic diseases except for CKD. & who did not give consent were excluded from the study. A structured questionnaire (research instrument) was developed containing all the variables of interest. All patients underwent necessary laboratory investigations. Data were processed and analyzed using the software SPSS (Statistical Package for Social Sciences) version 11.5. For all analytical tests, the level of significance was set at 0.05, and $p < 0.05$ was considered significant. Prior permission was taken for this study from the Ethical Committee of Dhaka national medical college and hospital, Dhaka, Bangladesh.

Results

Among the study subjects, most patients (30, 60.0%) belonged to the age group of > 55 years, followed by 15 (30.0%) patients from 50-55 years of age and the rest 5 (10.0%) patients were from 45-50 years of age. **[Table 1]** About 60% of the patients were male and 40% were female in this study. **[Figure 1]** Concerning the degree of anemia, most of the patients (25, 50.0%) suffered from severe anemia followed by 17 (34.0%) patients had moderate anemia, and the rest 8 (16.0%) patients had mild anemia. **[Table 2]** According to extent of CKD, most of the patients (25,50.0%) had stage 5 CKD (ESRD), followed by 15 (30.0%) patients had stage 3 CKD and the rest 10 (20.0%) patients suffered from stage 4 kidney disease. **[Table 3]** Among the patients who had stage 3 kidney disease, 8 (16.0%) patients had mild anemia, followed by 4 (8.0%) patients had moderate anemia and the rest 3 (6.0%) patients had severe anemia. Among the patients with stage 4 CKD, 6 (12.0%) patients had moderate anemia and 4 (8.0%) patients had severe anemia. Among the patients who had the end-stage renal disease (ESRD) or stage 5 CKD, 7 (14.0%) patients had moderate anemia and 18 (36.0%) patients had severe anemia**.**

[Table 4] Considering inflammatory parameters according to the degree of anemia, the neutrophil count was <6000 U/L, 6000-6500 U/L, and 6500-7500 U/L in mild, moderate, and severe anemia respectively. Lymphocyte count was <5000 U/L, 5000-5400 U/L, and 5000-5500 U/L in mild, moderate, and severe anemia respectively. CRP (mg/dl) level was 0.9- 2 in mild anemia, 5-40 in moderate anemia, and 10-50 in severe anemia. **[Table -V]**

Table 1: Distribution of age of the study subjects. (N=50)

Age (years)	Percentage	Percentage %
45-50	05	10.0
50-55	15	30.0
>55	30	60.0

Figure 1: Distribution of subjects according to sex. (N=50)

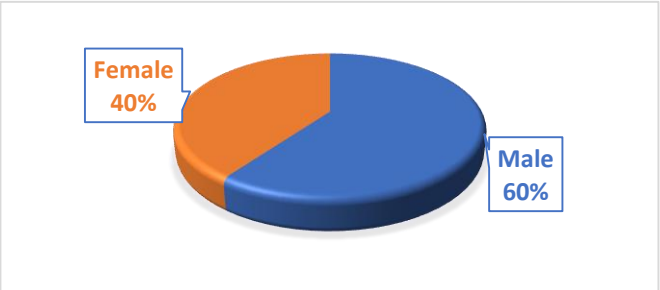

Table 2: Distribution of patients according to the degree of anemia. (N=50)

Degree of anemia	Percentage	Percentage %
Mild	08	16.0
Moderate	17	34.0
Severe	25	50.0

Table 3: Distribution of respondents according to the degree of CKD. (N=50)

Stage of CKD	Percentage	Percentage %
Stage 3	15	30.0
Stage 4	10	20.0
Stage 5 (ESRD)	25	50.0

Table 4: Distribution of patients according to eGFR and degree of anemia. (N=50)

	Degree of anemia		
	Mild (%)	Moderate (%)	Severe (%)
Stage-3 (30-59 ml/min)	8 (16.0)	04 (8.0)	03 (6.0)
Stage-4 (15-29 ml/min)	0 (0.0)	06 (12.0)	04 (8.0)
Stage-5 (<15 ml/min)	0 (0.0)	07 (14.0)	18 (36.0)

Table 5: Distribution of inflammatory parameters according to the degree of anemia. (N=50)

Inflammatory parameters	Mild anemia	Moderate anemia	Severe anemia
Neutrophil count (U/L)	<6000	6000-6500	6500-7500
Lymphocyte count (U/L)	<5000	5000-5400	5000-5500
Total WBC count (U/L)	<11000	11500-1200	12000-15500
CRP (mg/dl)	0.9-2	5-40	10-50

Discussion

Among the study subjects, most patients (30, 60.0%) belonged to the age group of > 55 years, followed by 15 (30.0%) patients from 50-55 years of age and the rest 5 (10.0%) patients were from 45-50 years of age. About 60% of the patients were male and 40% were female in this study which was found similar to other studies.[9,10] Concerning the degree of anemia, most of the patients (25, 50.0%) suffered from severe anemia followed by 17 (34.0%) patients had moderate anemia, and the rest 8 (16.0%) patients had mild anemia in this study. Another study showed various extents of anemia in patients with chronic disease.[11]According to extent of CKD, most of the patients (25,50.0%) had stage 5 CKD (ESRD), followed by 15 (30.0%) patients had stage 3 CKD, and the rest 10 (20.0%) patients suffered from stage 4 kidney disease. Among the patients who had stage 3 kidney disease, 8 (16.0%) patients had mild anemia, followed by 4 (8.0%) patients had moderate anemia, and the rest 3 (6.0%) patients had severe anemia. Among the patients with stage 4 CKD, 6 (12.0%) patients had moderate anemia and 4 (8.0%) patients had severe anemia. Among the patients who had the end-stage renal disease (ESRD) or stage 5 CKD, 7 (14.0%) patients had moderate anemia and 18 (36.0%) patients had severe anemia in the present study. According to another study, Anemia was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5. A total of 22.8% of CKD patients presented with anemia.[12] Considering inflammatory parameters according to the degree of anemia, the neutrophil count was <6000 U/L, 6000-6500 U/L, and 6500-7500 U/L in mild, moderate, and severe anemia respectively. Lymphocyte count was <5000 U/L, 5000-5400 U/L, and 5000-5500 U/L in mild, moderate, and severe anemia respectively. CRP (mg/dl) level was 0.9- 2 in mild anemia, 5-40 in moderate anemia, and 10-50 in severe anemia, which was quite similar to a study conducted by another author.[13]Another author stated,

inflammation has been found in ~35 to 65% of hemodialysis patients with CKD.[14] Another study stated that ESRD patients with NLR ≥ 3.5 had significantly higher TNF-α levels when compared with patients with NLR < 3.5.[15] According to a study, up to 40% of all anemias worldwide can be considered AI (Anemia of Inflammation) or combined anemias with important AI contributions, which, in total, account for >1 billion affected individuals.[16] An association between raised NLR and increased concentrations of pro-inflammatory cytokines was reported in a study. The association between the leukocyte ratios and outcomes in various critically ill patients has also been reported in that study. It was suggested that the ratios may be predictive of patients' response to inflammatory insult, with neutrophils increasing due to stress and lymphocytes decreasing in the population due to apoptosis.[17] Regarding the quality of life in CKD patients with anemia, a study stated that, maximal improvement in HRQOL occurred in the range of 10.0–12.0 g/dL, with blunting of the beneficial effects at higher levels. Although the favorable effect of anemia correction on HRQOL is well recognized, the endeavor to identify optimal hemoglobin targets that limit the adverse outcomes in patients persists.[8]

Conclusion

Anemia of chronic disease (as in CKD) is caused by a complex interplay of proinflammatory cytokines which induce dysregulation in iron homeostasis, erythroid progenitor cell differentiation, erythropoietin synthesis, and red cell longevity, all culminating in the pathogenesis of anemia. This study highlighted the profound impact of CKD on HRQOL and potential areas that can be targeted for therapeutic intervention. Furthermore, this study showed, chronic diseases can lead to an inflammatory process which ultimately results in anemia through various mechanisms. Moreover, early identification and correction of anemia may improve the quality of life.

Recommendation

More studies in multiple centers with a large sample size will be needed to get robust data for all components of HRQOL in CKD and to demonstrate the components which are responsible for anemia of inflammation in chronic kidney disease. Early identification and correction may improve the overall well-being of patients. Clinical trials are required to demonstrate whether treatment interventions benefit HRQOL in this high-risk population.

Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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