Inflammatory status as a contributor for anemia in patients with chronic kidney disease in Karbala, Iraq

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Objective In chronic kidney disease (CKD), there is primary deficiency of erythropoietin, thereby leading to anemia. In addition, chronic immune activation and the inflammatory process could be involved in the pathophysiology of anemia in patients with (CKD). However, anemia and inflammation are present in earlier stages of renal impairment. The objective of this study was to evaluate the possible association of some of the markers of inflammation with anemia in patients with CKD with and without dialysis treatment.
Methods The markers of inflammation such as white blood cell (WBC) count, granulocytes % and C-reactive protein (CRP) were determined. Similarly, serum albumin, platelets count and hemoglobin level were measured in blood samples from 61 patients with CKD attending Nephrology Unit at Al-Hussein Medical City and 20 healthy controls. The selected patients were stratified into two subgroups; 31 patients without hemodialysis (HD) and other 30 patients on HD.
Results A significantly lower hemoglobin level, serum albumin and platelets count were observed in patients with CKD on hemodialysis therapy compared to controls, (P value = 0.0001). There was a significant correlation between WBC count and granulocytes % with regard to the low hemoglobin level in patients with CKD especially those on hemodialysis HD, (P value < 0.05).
Conclusion Renal failure anemia was found to be strongly associated with high WBC count and gronulocytes percentage which are known markers of inflammatory status.
Key words inflammatory markers, anemia, chronic kidney disease

Introduction

Anemia is a well-known complication in patients with chronic kidney disease (CKD). In those patients, there is primary deficiency of erythropoietin production, thereby leading to anemia.[1] However, it was stated that erythropoetin deficiency isn't the only cause of renal anemia and that inflammatory process is one of the causes involved in the pathophysiology of this type of anemia especially in patients with end-stage renal failure and dialysis. However, a controversy was developed in this regards, because anemia and inflammation are present in patients with previous stages of renal failure.[2] The objective of this study was to evaluate the possible association of inflammatory status with anemia in patients with CKD with and without hemodialysis (HD) treatment.

Subjects and methods

Seventy patients (34 women; and 36 men); age range 21–70 years who attended Nephrology Unit at Al-Hussein Medical City. The selected patients were doctor-diagnosed with CKD for varying time of disease onset. The patients were recruited to participate in this study during the period from October, 2015 through February, 2016. Meanwhile, other 20 healthy persons were chosen as control group. The selected patients were stratified into two subgroups; (31 patients) with CKD without HD (mean S. creatinine 2.87 ± 0.71) and other (30 patients) on regular HD therapy (mean S. creatinine 5.65 ± 1.79). Blood specimens were collected from 61 patients and 20 healthy unrelated controls after taking informed consent from each participant. Nine patients were excluded because they were found to be CRP positive. Markers of inflammatory status such as white blood cell (WBC) count, granulocytes % and C-reactive protein (CRP) were determined. In addition, serum albumin, platelets count and hemoglobin level were measured in patients' and controls' blood.

Statistical analysis

The data were analyzed using the statistic software "Graph pad, Prism". Results are expressed as mean ± SD. Differences of the studied markers among the groups were compared using one-way ANOVA test. To predict the association of different inflammatory markers with anemia in patients with CKD, Pearson's correlation coefficient in normally distributed variables was used. The results with P value < 0.05 were regarded statistically significant.

Results

Data of the current study revealed a significantly lower blood hemoglobin level, serum albumin and platelets count in patients with CKD on HD therapy compared to those without HD and the healthy controls, P value = 0.0001 tested by one-way ANOVA, (see Fig. 1). About 58% of CKD group and 87% of HD group were found to be anemic. Furthermore, there is a significant association of WBC count and granulocytes % with hemoglobin level in patients on HD, P value = 0.0213 and 0.0081, respectively. However, no significant association was observed among all the tested markers with hemoglobin level in the other two groups (CKD without HD and healthy control groups), except an association between serum albumin and hemoglobin level in the control group, see (Table 1).

Discussion

Anemia is a common complication in the case of kidney function impairment, as it was found in the current study. Herein, about 61.7% of the CKD group and 87.8% of the HD group were found to have abnormally low level of blood hemoglobin. Likewise, Obrador et al. stated that among predialysis patients, 68% of

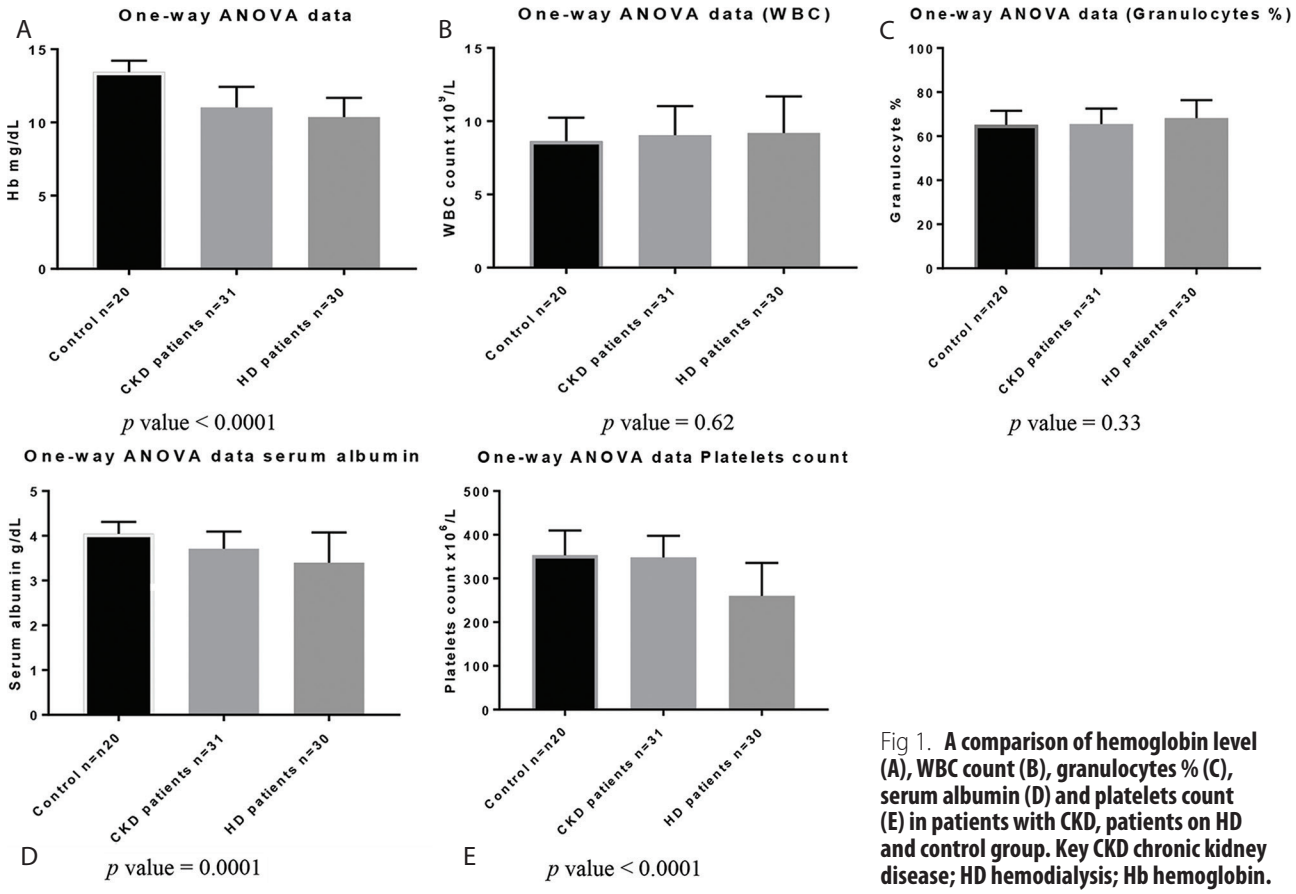

Fig 1. **A comparison of hemoglobin level (A), WBC count (B), granulocytes % (C), serum albumin (D) and platelets count (E) in patients with CKD, patients on HD and control group. Key CKD chronic kidney disease; HD hemodialysis; Hb hemoglobin.**

Table 1. **Correlation of hemoglobin level with WBC count, platelets count, granulocyte % and serum albumin in patients with CKD (± HD) and control group**

1. Patients with CKD	Hb vs. granulocyte %	Hb vs. WBC count	Hb vs. Platelets	Hb vs. Serum albumin
Pearson *r*	0.3501	0.1197	0.05983	–0.3161
95% confidence interval	–0.004 to 0.62	–0.245 to 0.454	–0.3009 to 0.405	–0.6 to 0.04
R squared	0.1226	0.0143	0.0035	0.0999
P value(two-tailed)	0.0535	0.5212	0.7492	0.0888
2. Patients with HD				
Pearson *r*	–0.6185	–0.4186	0.1432	0.1256
95% confidence interval	–0.847 to –0.196	–0.676 to –0.068	–0.228 to 0.478	–0.26 to 0.48
R squared	0.3826	0.1753	0.02052	0.01577
P value (two-tailed)	0.0081*	0.0213*	0.4501	0.5326
3. Control Group				
Pearson *r*	0.4387	0.3276	0.1444	0.5603
95% confidence interval	–0.004 to 0.737	–0.134 to 0.672	–0.318 to 0.551	0.15 to 0.8
R squared	0.1924	0.1073	0.02087	0.3139
P value (two-tailed)	0.0530	0.1586	0.5435	0.0102*

those with advanced CKD 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.[3] Furthermore, although anemia is not as common in the earlier stages of CKD, 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%.[4]

Data of the current study revealed a significant association between renal failure anemia and some markers of inflammation, namely WBC count granulocytes percentage especially in patients on regular HD therapy.

Previous studies have widely investigated the role of cellular and molecular markers of inflammation in this type of anemia. It was stated that inflammatory condition is not only a cause of anemia, but that it is the most prevalent cause of temporary resistance to erythropoietin therapy in renal anemia.[2,5]

The data of the current study revealed abnormally increased number of WBCs (especially granulocytosis) in patients with

CKD, and it is significantly associated with anemia in these patients. Several molecular factors contribute to polymorphonuclear (PMN) leukocytosis by inhibiting apoptosis potential of these inflammatory cells. Some of these molecules are free immunoglobulin light chains (IgLCs) as PMNL apoptosis inhibiting proteins,[6] phenylacetic acid[7] and *p*-hydroxy-hippuric acid,[8] an erythrocyte plasma membrane Ca2+-ATPase inhibitor accumulating in uremic sera,[9] attenuate PMNL apoptosis. The complement factor C5a also delays apoptosis of human PMNLs.[10,11] The role of leukocytosis in renal anemia could be summarized by the increased expression of pro-inflammatory cytokines which interfere with erythropoietin action in varying mechanisms including competitive inhibition due to receptor domain similarity. An increased level of the proinflammatory cytokine, interferon gamma, was detected in renal failure and some sort of competition for common receptors between Erythropoietin and interferon gamma was suggested.[2,12] Similarly, it was found that inflammatory factors contribute to anemia in renal patients in all the stages of renal failure and cytokines like interleukin 1 and 6 were associated with anemia in those patients.[13]

Another proposed role of the inflammatory cytokines, such as interleukins (IL-1 and IL-6), and tumor necrosis factor (TNF-alpha), is that they are believed to cause the destruction of RBC precursors and decrease the number of erythropoietin receptors on progenitor cells.[14]

Data analysis of this study also express significantly reduced level of serum albumin especially in HD group. This finding is consistent with many previous studies which investigated this state of dialysis-associated hypoalbuminemia. Different physiologic mechanisms and suggestions to alleviate this condition were suggested by such studies.[15–25]

In addition, an association of serum albumin level with hemoglobin level in healthy control group. This finding could be due to confounding results related to inadequately small sample size of the study group. However, a previous finding in patients with CKD was detected, in which the author found an association between serum albumin and responsiveness to erythropoietin in renal failure anemia and the author recommended further investigation regarding this association.[2]

Conclusion

Owing to the above data, renal failure anemia was found to be strongly associated with high WBC count and gronulocytes percentage which are known markers of inflammatory status.

Recommendation

Future studies with larger sample size are recommended to investigate other cellular and molecular markers of inflammatory status namely T-h1 derived cytokines and their role in "renal" anemia.

Conflict of Interest

None.

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