

Iron Deficiency among Anemic Pre-Dialysis Chronic Kidney Disease Patients

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Abstract: Introduction: Anemia of chronic kidney disease (CKD) is associated with poor outcome, including higher death risk in both maintenance dialysis patients and individuals who have CKD stages 3 to 5 and are not yet on dialysis. The cause of anemia in CKD is multi-factorial and includes erythropoietin deficiency, decreased responsiveness to erythropoietin, shortened red blood cell survival, iron deficiency, and chronic inflammation. The identification, evaluation and optimal treatment of anemia of CKD have been detailed in some guidelines and other studies. Essentially these involve determining complete blood count, absolute reticulocyte count, determining serum ferritin to assess iron store and serum transferrin saturation (TSAT) to assess adequacy of iron for erythropoiesis.

Aim of Study: Studying the prevalence and predisposing factors of iron deficiency anemia among anemic pre-dialysis CKD patients. **Patients and Methods:** The study was conducted on 100 anemic pre-dialysis CKD patients (stages IV & V) attended at outpatient clinics of Ain Shams University Hospital. Every patient was subjected to full history taking, full clinical examination, laboratory investigations; kidney function tests (KFT), complete blood count (CBC), and Iron profile. Statistical analysis of data was performed using the SPSS software version 15.0.

Results: The study included 38 females and 62 males, their mean age was 50.42 ± 11.5 . The most common causes of renal failure were hypertensive kidney disease (HKD) (34%) and diabetic nephropathy (DN) (22%). According to the mean corpuscular volume (MCV); patients were divided into those having normocytic and microcytic anemia (58% and 42% respectively). The prevalence of iron deficiency anemia among the studied patients was 54%. Iron deficiency anemic patients included 20 females and 34 males, their mean age was 49.92 ± 11.13 . By Comparison between iron deficiency patients and non iron deficiency patients there were significant differences as regards their serum Iron, Transferrin Saturation (TSAT), serum ferritin and MCV ($p \leq 0.05$); being lower among Iron deficiency patients. Among Iron deficiency patients, there were positive correlations between MCV and each of TSAT and serum ferritin ($r=0.88$, $p=0.00$ and $r=0.62$, $p=0.001$). Also a positive correlation between hemoglobin (Hb) and serum ferritin was found ($r=0.65$, $p=0.00$). Positive correlations were found between TSAT and each of serum iron and Total Iron Binding Capacity (TIBC) ($r=0.84$, $p=0.00$ and $r=0.52$, $p=0.005$ respectively). Also positive correlations were found between serum ferritin and each of serum iron and TIBC ($r=0.59$, $p=0.001$ and $r=0.39$, $p=0.04$). **Conclusion:** Age, sex, duration of CKD & KFT were insignificant factors affecting the prevalence of Iron deficiency in pre-dialysis patients. MCV was a strong indicator of Iron deficiency anemia when iron study is unavailable or impose economic burden in our developing country.

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1. Introduction

Anemia is a common complication of chronic kidney disease (CKD) and was found to be present in 47.7-68% of pre-dialysis patients in some studies^{1,2}. The anemia of CKD is a complex disorder determined by a variety of factors. Although, the primary defect is decreased erythropoietin (EPO) production from the kidneys, a number of other factors may play contributory roles, for example: iron, B12 and folate deficiency due to nutritional insufficiency or increased blood loss³, shortened blood cells survival, hyper-parathyroidism, mild chronic inflammation and aluminium toxicity⁴.

Anemia appears to have pronounced effects on patient well-being and may ultimately determine overall prognosis both before and after initiation of

renal replacement therapy⁵. A particularly important effect of anemia is its potential role in cardiovascular disease in CKD. The relationship between anemia and cardiovascular morbidity and mortality in dialysis patients is well established⁶.

An important factor in many anemic patients with CKD is iron deficiency. Iron deficiency can be categorized as absolute or functional. Absolute iron deficiency is defined by a reduction in bone marrow reticulo-endothelial iron, absolute iron deficiency is suggested by a ferritin level of <100 ng/mL (<200 ng/mL for hemodialysis patients) or TSAT $<20\%$ ⁷. Absolute iron deficiency results from a combination of iron utilization in response to erythropoiesis-stimulating agent (ESA) therapy, impaired gastrointestinal iron absorption, and blood loss

(thereby iron loss) via the dialytic circuit, access surgery/intervention, and frequent phlebotomy⁸.

Functional iron deficiency is defined as the presence of adequate bone marrow iron stores, but an impaired ability to mobilize these stores for erythropoiesis in the presence of the stimulating effect of an ESA; it is typically diagnosed when TSAT is < 20% but serum ferritin levels are normal or elevated. Functional iron deficiency often occurs in patients with underlying malnutrition and systemic inflammation⁹.

According to the National Kidney Foundation Disease Outcomes Quality Initiative NKF-K/DOQI guidelines, when stage 3 CKD is identified by the clinician's calculation or the laboratory's report of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², the next step is to assess the hemoglobin level¹⁰. If the hemoglobin level is <12 g/dL in a man or postmenopausal woman or <11 g/dL in a premenopausal woman, the NKF-K/DOQI recommends an anemia workup, including RBC indices, reticulocyte count, and iron parameters¹¹. The anemia of CKD is typically normocytic and normochromic, while iron deficiency anemia is usually microcytic and hypochromic, and vitamin B12 and folate deficiency anemia are most often macrocytic¹⁰.

Early treatment of anemia in CKD may postpone the onset of end-stage renal disease and improve survival. The identification, evaluation and optimal treatment of anemia of CKD have been detailed in some guidelines and other studies^{12,13}. Treatment of anemia in CKD when indicated may involve iron therapy, and use of erythropoiesis stimulating agents, and correction of anemia to a target hemoglobin concentration of 11-12 g/dL¹⁴.

Aim of Study:

Studying the prevalence and predisposing factors of iron deficiency anemia among anemic pre-dialysis CKD patients.

2. Patients and Methods

The present study was conducted on 100 anemic pre-dialysis CKD stages IV, V patients attending the outpatient clinics of Ain Shams University Hospital. Exclusion criteria;

1. Patients with known cause of iron deficiency not related to CKD.
2. Patients with history of recent blood transfusion within the last 3 months.
3. Patients already receiving hematinics or ESA.

Every patient was subjected to:

1. Full history including demographic data, assumed cause of CKD, dietary history, history of chronic blood loss, blood transfusion, drug history especially

hematinics & Erythropoiesis-stimulating agents ESAs.

Clinical examination.

Laboratory investigations:

- a. Kidney function tests; Serum creatinine & Blood urea nitrogen (BUN) & estimated GFR with cockcroft Gault formula.
- b. CBC including Hb level, MCV & hematocrit (Hct) value.
- c. Iron profile (Serum Iron, TIBC, TSAT & Serum Ferritin).

Statistical analysis

Data were collected and tabled. Tables and figures were done using Microsoft Office Excel 2007. Statistical analysis was done using SPSS v. 15.0 (SPSS Inc., Chicago, IL). Data are expressed as means ± Standard Deviation (SD) unless otherwise specified. Data were compared by Student's t-test, chi-square test or Pearson's correlation coefficient as appropriate.

3. Results

The study included 100 predialysis CKD patients with the following etiologies; 34 (34%) patients with HKD, 22 (22%) with DN, 10 (10%) polycystic kidney (PCK), 10 (10%) glomerulonephritis (GN) and 10 patients (10%) with CKD of unknown etiology (UE), 8 patients with chronic pyelonephritis (CPN), 4 with obstructive uropathy & 2 patients with lupus nephritis (LN) (Figure 1).

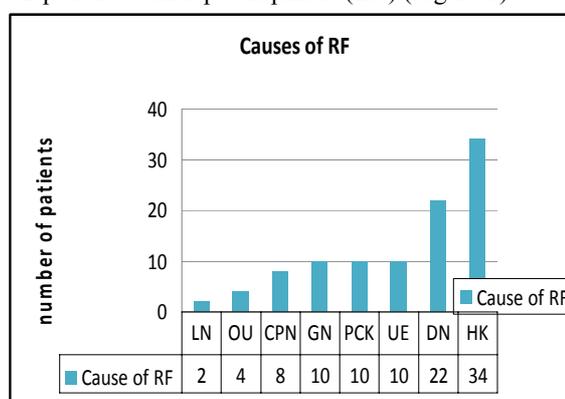


Figure (1): Causes of renal failure among the studied cases

Among the studied group, 38 (38%) were females and 62 (62%) males; their mean age was 50.42 years old ±11.5. The mean serum creatinine and estimated glomerular filtration rate GFR were 3.23 mg/dl ±0.62 and 25.47 ml/min ±3.44, respectively. Their mean Hb level was 8.96 (gm/dl) ±1.23, with a mean Hct of 28.98 % ±3.98 and mean MCV of 78.37 fl ±11.84. The iron profile of all the studied patients showed that the mean serum iron was

78.49 ($\mu\text{g}/\text{dl}$) \pm 29.19, mean TIBC was 344.16 ($\mu\text{g}/\text{dl}$) \pm 65.8, mean TSAT was 22.96 % \pm 8.8 and mean serum Ferritin was 91.92(ng/dl) \pm 59.22. According to the red cell MCV, the studied anemic patients were divided into 58 (58%) with microcytic anemia and 42 (42%) with normocytic anemia. Out of the 58 microcytic anemic patients, 54 (93%) patients had Iron deficiency. (Table 1).

Table (1): Demographic & laboratory data of the studied 100 anemic predialysis CKD patients:

	Range	Mean \pm SD
Age	18-70	50.42 \pm 11.5
Weight (Kg)	40-109	70.14 \pm 13.42
Sex		
Female	19	38%
Male	31	62%
S. Creatinine (mg/dl)	2-4.8	3.23 \pm 0.62
eGFR (ml/min)	12.8-29.9	25.47 \pm 3.44
HB (gm/dl)	6.4-11.7	8.96 \pm 1.23
Hct (%)	21.3-40.5	28.98 \pm 3.98
MCV (fl)	58-100	78.37 \pm 11.84
S. Ferritin (ng/dl)	12-214	92.1 \pm 59.23
S. Iron ($\mu\text{g}/\text{dl}$)	12.5-157	78.49 \pm 29.19
TIBC ($\mu\text{g}/\text{dl}$)	168-496	344.16 \pm 65.8
TSAT %	7.4-48.4	22.96 \pm 8.8

Iron deficiency anemic patients were 54 patients; 20 (37%) females and 34 (63%) males, their mean age was 49.92 years old \pm 11.13. The mean

serum creatinine level was 3.24 mg/dl \pm 0.65 with a mean eGFR of 26 \pm 3.17. The most common four causes of renal failure among this group of patients were; 20 (37%) HKD, 10 (18.5%) GN, 8 (15%) DN and 6 (11.1%) PCK (Figure 2).

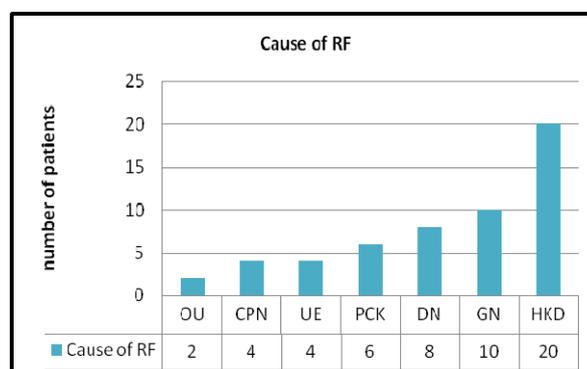


Figure (2): Cause of renal failure among the Iron deficiency anemic patients

Among the 54 iron deficient anemic patients, the mean Hb was 8.81 mg/dl \pm 1.18 with a mean Hct % of 28.63 % \pm 4.55 and a mean MCV of 68.83 fl \pm 4.69. Their mean serum iron was 58.78 ($\mu\text{g}/\text{dl}$) \pm 19.6, mean TIBC was 356.63 ($\mu\text{g}/\text{dl}$) \pm 81.97, mean TSAT was 16% \pm 3.31 and mean serum Ferritin was of 46.19 (ng/dl) \pm 23.19 (Table 2).

Table 2: comparison between Iron deficient and non iron deficient anemic patients

	Iron deficiency (n=54)	non Iron deficiency (n=46)	t	p
Age	49.92 \pm 11.13	51 \pm 12.15	0.46	0.64
S. Creatinine (mg/dl)	3.24 \pm 0.65	3.21 \pm 0.59	0.24	0.81
eGFR (ml/min)	26 \pm 3.17	24.84 \pm 3.71	1.68	0.09
HB (gm/dl)	8.81 \pm 1.18	9.12 \pm 1.3	1.24	0.21
TIBC ($\mu\text{g}/\text{dl}$)	356.63 \pm 81.97	329.54 \pm 35.88	2.07	0.04*
TSAT %	16 \pm 3.31	31.12 \pm 5.53	16.86	0.0001**
Serum Ferritin (ng/dl)	46.19 \pm 23.19	146 \pm 39.42	15.69	0.0001**
Serum Iron ($\mu\text{g}/\text{dl}$)	58.78 \pm 19.6	101.63 \pm 20.17	10.75	0.0001**
Hct (%)	28.63 \pm 4.55	29.4 \pm 3.24	0.95	0.34
MCV (fl)	68.83 \pm 4.69	89.58 \pm 6.54	18.59	0.0001**

Comparing between the iron deficient (n=54) & non iron deficient (n= 46) patients, there were insignificant differences between both groups regarding the age, sex (figure 3), Hb and Hct ($p>0.05$). While highly significant differences were found regarding serum Iron, TSAT, serum Ferritin and MCV being lower among Iron deficiency group

of patients ($p\leq 0.001$) while TIBC was significantly higher in Iron deficiency anemic patients ($p\leq 0.05$) (table 2).

There was insignificant correlations between age, serum creatinine, eGFR and duration of CKD with either TSAT & serum ferritin. On the other hand, there was a significant positive correlation between

MCV and each of TSAT and serum Ferritin among Iron deficiency patients ($r=0.68$, $p=0.00$ and $r=0.62$, $p=0.001$, respectively). (table 3).

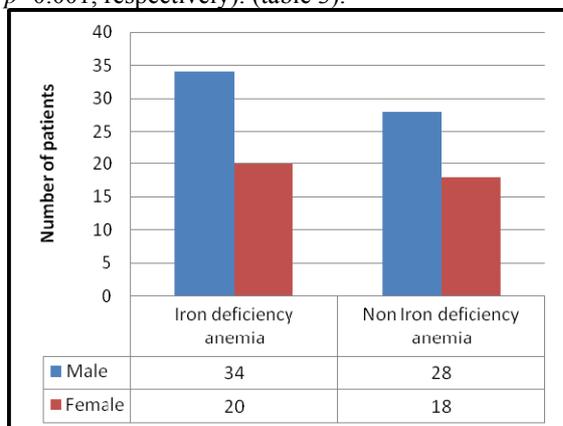


Figure 3: Sex difference between Iron deficiency and non Iron deficiency anemic patients

Table (3): Correlation between the Age, duration of CKD, serum creatinine, eGFR and MCV with each of TSAT & serum ferritin among the 54 iron deficient anemic CKD patients

	r	P value
Age-T sat.	0.018	0.93
Age-serum Ferritin	-0.35	0.86
Duration of CKD-T sat.	-0.02	0.9
Duration of CKD - serum Ferritin	0.09	0.65
S.Cr-T sat.	-0.27	0.16
S.Cr-serum Ferritin	-0.05	0.7
eGFR-T sat.	-0.3	0.11
eGFR-serum Ferritin	-0.29	0.14
MCV-T sat.	0.68	0.00**
MCV-serum Ferritin	0.62	0.001**

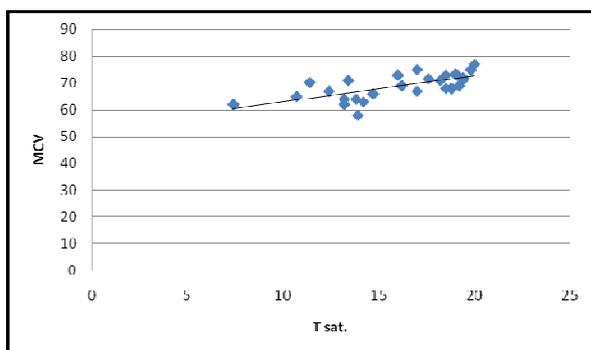


Figure (4): High significant positive correlation between MCV and TSAT.

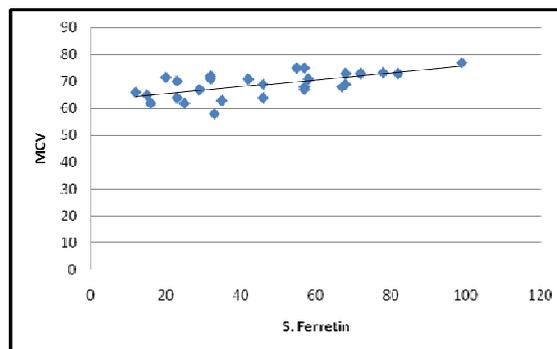


Figure (5): High significant positive correlation between MCV and serum Ferritin

4. Discussion

This study included 100 anemic pre-dialysis chronic kidney disease patients. It was found that 58 (58%) patients had microcytic anemia and 42% normocytic anemia. Iron study showed that Iron deficiency was found in 54 (54%) of the studied patients. This agrees with *Galloway and Smellie*¹⁵, who concluded from their study that microcytic anemia is often assumed to indicate iron deficiency, but up to 20-30% of patients will have another diagnosis, particularly anemia of chronic inflammation or myelo-dysplasia.

But our findings disagrees with *Afshar et al.*,¹⁶ who found that the most common morphologic feature of anemia among pre-dialysis CKD patients in Iran was normocytosis in (80%), microcytosis in (15%) and macrocytosis in (5 %). It is possible that the higher degree of microcytic anemia in our study might be explained in part by other causes peculiar to the environment, including helminthes and other infestations and malnutrition.

The causes of renal failure in our study were variable; (34%) were due to HKD, (22%) DN, (10%) GN, (10%) UE, (10%) PCK, (8%) CPN, (4%) OU, and (2%) LN. *Szeto et al.*,¹⁷ found that causes of renal failure in their study were 94 (28.3%) GN, DN 55 (16.6%), hypertensive nephrosclerosis 36 (10.8%), PCK 20 (6%), OU 17 (5.1%) and others/unknown 110 (33.1%). *Afshar et al.*,¹⁶ found in their study that the most frequent causes of CKD were diabetes mellitus (49.1%), hypertension (28.3%), glomerular disease (17.1%) and polycystic kidney disease (5.6%).

Out of the studied patients, iron deficiency anemic patients, there were 37% females and 63% males; their mean age was 49.92 ± 11.13 . The mean serum Creatinine level of these patients was 3.24 ± 0.65 , the mean HB was 8.81 ± 1.18 , the mean TSAT was 16 ± 3.31 and the mean serum Ferritin was $46.19\% \pm 23.19$. *Ferrari et al.*,¹⁸ studied the relationship between parenteral Fe therapy,

conventional serum Fe markers, and liver iron concentration (LIC) measured using magnetic resonance R2 relaxometry (FerriScan) in 25 Fe-deficient pre-dialysis chronic kidney disease patients. The patients' mean age was 65±15 and the male/female ratio was 17/8. The mean serum Creatinine was 2.96±1.30, the mean HB 10.7±8 the mean TSAT was 15±6 and the mean serum Ferritin 67±56.

TSAT and serum Ferritin have remained the favored markers for assessment of iron status. TSAT of 20% seems to be relatively good in terms of sensitivity, meaning that few patients are truly iron deficient with a TSAT much higher than 20%, but a ferritin cutoff of 100 or even 200 ng/ml tends to miss close to a majority of patients who ultimately may respond to intravenous iron¹⁹.

In our study, the mean serum Ferritin level and mean TSAT were highly significantly lower in Iron deficiency patients than in non Iron deficiency patients ($p \leq 0.001$).

Among the studied iron-deficiency patients, there was insignificant correlation between each of serum Creatinine and age, and serum Ferritin ($p > 0.05$). And this partially agrees with *Branten et al.*,²⁰ who studied serum Ferritin levels in 142 male patients with glomerular diseases and proteinuria. They found that serum ferritin was not significantly correlated with serum Creatinine ($r = 0.16$, $p = 0.054$) but significantly positively correlated with the age ($r = 0.23$, $p = 0.007$).

Comparing the Hb between Iron deficiency anemic patients (Ferritin ≤ 100 ng/dl, TSAT ≤ 20) and non Iron deficiency anemic patients (Ferritin > 100 ng/dl, TSAT ≥ 20), it was found that the mean Hb levels were 8.81±1.18 and 9.12±1.3 respectively, but this difference was statistically insignificant ($p > 0.05$). *Hsu et al.*,²¹ whose study included 378 female and 191 male, found that among subjects with eGFR ≤ 70 ml/min, meeting the NKF K/DOQI targets was associated with higher hemoglobin, independent of renal function and demographic features. They compared men & women with TSAT $> 20\%$ with those with with TSAT $\leq 20\%$ & found that the later group had a mean hemoglobin lower by 0.4 and 0.3 g/dl, respectively ($P = 0.004$ and 0.001 , respectively).

Conclusion

The prevalence of Iron deficiency anemia among the studied anemic pre-dialysis patients was 54%. The most common cause of renal failure was HKD. MCV was a strong indicator of Iron deficiency anemia when iron study is unavailable or impose economic burden in our developing country.

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