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General Medicine

STUDY OF ANAEMIA & IRON PROFILE IN CHRONIC KIDNEY DISEASE (CKD) PATIENTS ON MAINTENANCE DIALYSIS AND ITS CORRELATION WITH DIABETES MELLITUS

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ABSTRACT Most patients with chronic kidney disease (CKD) have anaemia, the cause of which is erythropoietin and iron deficiency. Anaemia in patients on haemodialysis is associated with poor patient outcomes. Diabetes remains one of the predominant aetiologies of CKD all over the world. The study was undertaken to study the iron profile in haemodialyzed patients and its corelation with diabetes mellitus. Sixty-six patients were enrolled in the study with the aim to study the prevalence of anaemia and diabetes in haemodialyzed patients as well as the iron profile in these patients. Patients were studied as a single group as well as divided into two groups, a non-diabetic group comprising of 36 patients and a diabetic group comprising of 30 patients. Anaemia was found to be prevalent in 56(84.84%) patients out of which 28(50%) were diabetics. Also, diabetics comprised of 45.45% of the study group. Various parameters like haemoglobin with blood indices and iron profile was studied and compared in both groups. There was no significant difference in the various parameters in both groups except a significantly low MCH and MCHC and significantly high ferritin levels in the diabetic group. We concluded that the low MCH and MCHC might be suggestive of an increased cardiovascular risk in diabetic patients while higher levels of serum ferritin may suggest sub-clinical inflammation rather than iron overload. In conclusion diabetes remains to be the single most important aetiology for the causation of end stage renal disease and appropriate management of anaemia in terms of EPO and iron therapy remains the mainstay of therapy in haemodialyzed patients.

KEYWORDS : Anaemia, Diabetes, Ferritin, Haemodialysis

INTRODUCTION:

Majority of patients with chronic kidney disease (CKD) on haemodialysis have anaemia. The cause of anaemia in these patients is a lack of endogenous production of erythropoietin (EPO) and hence exogenous erythropoietin remains the mainstay of therapy in these patients (1). Many of these patients however, are in a negative iron balance mainly because of increased losses during dialysis, impaired absorption of iron from gastrointestinal tract and reduced dietary intake (2). Anaemia in CKD especially in patients on haemodialysis has been associated with poor outcomes in terms of mortality translating in higher death rates. Since these patients are both deficient in erythropoietin and iron, supplementation of both EPO as well as iron are essential to manage the anaemia of CKD effectively (3). The deficiency of iron in these patients is one of the reasons for anaemia to remain refractory despite adequate EPO therapy (1).

Diabetic kidney disease is a major cause of CKD and anaemia is common in diabetics having nephropathy (4). The management of renal disease in diabetes has always remained focused on strict glycaemic control, blood pressure lowering and lipid lowering so as to minimise the occurrence of vascular disease while the aspect of anaemia management in diabetic kidney disease has been neglected at large (5). It is believed that anaemia associated with diabetic kidney disease happens to be more severe (6) and lower haemoglobin is related to a more rapid decline in the glomerular filtration rate (7). The main cause of anaemia in diabetes mellitus is thought to be the lack of EPO. This has been attributed to various factors like reduced number of EPO synthesizing cells due to interstitial fibrosis or vascular lesions, urinary loss of EPO in proteinuric patients, EPO receptor glycation due to hyperglycaemia and cytokine induced inhibition of EPO synthesis (8). Apart from this, there is increased iron excretion in early DKD which gets exacerbated with development of nephrotic range proteinuria. Increased urinary loss and increased catabolism of transferrin both can contribute to development of iron deficiency in patients with nephrotic range proteinuria in diabetes (9). Iron deficiency whether absolute or functional remains an important factor of non-responsiveness or hypo-responsiveness to EPO and hence should be corrected appropriately in all patients of CKD. EPO use can also lead to increased demand of iron in CKD patients especially those on haemodialysis who also face the added problem of blood loss leading to iron loss (10). There is a lack of literature regarding the status of iron profile in haemodialysis dependent CKD especially in relation to diabetes mellitus. Considering that iron deficiency plays an important role along with EPO in causation of anaemia in CKD patients and also to study the effect of diabetes mellitus on the same this study was undertaken.

MATERIAL AND METHODS:

The study was carried out as a prospective observational study at a tertiary care centre in Ahmedabad between November 2019 to January 2020. Sixty-six patients who were on maintenance haemodialysis for chronic kidney disease were enrolled as per pre-defined inclusion and exclusion criteria. The aims and objectives of the study were:

Primary objective:

- Study of Anaemia and Iron Profile in dialysed (chronic kidney disease) patients and its correlation with presence of diabetes mellitus.

Secondary objectives:

- Prevalence of diabetes in dialysed (chronic kidney disease) patients.
- Prevalence of Anaemia in dialysed (chronic kidney disease) patients.

INCLUSION CRITERIA:

- Chronic kidney disease patient on maintenance dialysis
- Age > 18 yrs.

EXCLUSION CRITERIA

- Patients of Acute kidney injury
- Pregnant patients
- Terminally ill patients

Consent was sought from all study participants before enrolment. Anaemia and its severity were defined as per WHO criteria, haemoglobin (Hb) of less than 13g/dl in males and 12g/dl in females was considered as anaemia. Hb level of less than 8g/dl was considered to be severe anaemia, between 8-10.9g/dl as moderate anaemia and from 11g/dl to gender defined limits as mild anaemia (11). Absolute iron deficiency in presence of CKD was defined as Transferrin saturation (TSAT) ≤ 20% and serum ferritin ≤ 200 ng/ml. Functional iron deficiency was defined as TSAT ≤ 20% and high ferritin levels. Patients without functional iron deficiency with S. ferritin levels of ≥500ng/ml were classified as those having iron overload (12). The presence or absence of diabetes was determined as per history and previous case records of the patient as the determination of blood sugars and HbA1c may not confer to standard definitions of diabetes in case of chronic kidney disease especially in stage 5 CKD patients (13). Patients were studied as a single group as well as divided into two groups, diabetic as well as non-diabetic group. Various haematological parameters like haemoglobin and blood indices in form of mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH)

and mean corpuscular haemoglobin concentration (MCHC) were studied. Iron profile was done in all patients. Serum iron, serum ferritin and transferrin saturation (TSAT) were studied and statistical inferences were drawn. Statistical analysis was performed in terms of ratios, percentages, means, standard deviations, Chi square test, unpaired student's t-test and Pearson's correlation coefficient. Confidence interval was set at 95% and significance at p-value of less than 0.05.

RESULTS:

A total of 66 patients were enrolled in the study. Out of 66 patients, 30(45.4%) patients had diabetes. Fifty-six (84.8%) patients had anaemia and 28(50%) of the anaemic patients had diabetes mellitus. The study had 40 male participants and 26 female participants in a M:F ratio of 1.5:1. The ratio was 1:1 in non-diabetic patients while it was 2.75:1 in diabetic patients. Mean age of the patients was 59.5±7.6 years. Fifty (75.7%) patients were between the age group of 45-64 years, the remaining were more than 64 years old (Figure 1).

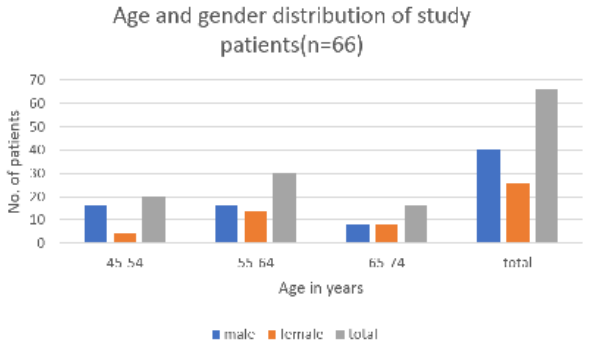

Figure 1. Age and distribution of study patients across various age groups.

In the anaemic group there were 32 males and 24 females. Gender had no significant effect on the presence of anaemia in these patients (Table-1).

	Male	Female	Total
Anaemia present	32 (33.94) [0.11]	24 (22.06) [0.17]	56
Anaemia absent	08 (6.06) [0.62]	02 (3.94) [0.95]	10
Total	40	26	66

The chi-square statistic is 1.8567. The p-value is .173006. Not significant at p < .05.

Table-1. Effect of gender on the presence or absence of anaemia.

The mean Hb of the study group was 10.09±2.23 g/dl. Mean corpuscular volume (MCV) was 88.93±8.19 fl, MCH was 28.19±3.34 pg and MCHC was 31.86±1.78 g/dl. Mean serum iron was 95.89±120.96 mcg/dl, mean serum ferritin was 634.58±364.59 ng/ml and mean transferrin saturation (TSAT) was 39.24±48.10 %. Eighteen of sixty-six (27.27%) patients had a TSAT of < 20%. Twelve patients (66.66%) were non-diabetics and six patients (33.34%) were diabetics. This difference was however, not found to be statistically significant [$\chi 2$ (1, N=66) =1.466, p=0.22]. Out of these eighteen, 4(22.22%) patients had absolute iron deficiency and 14(77.77%) patients had functional iron deficiency. Haemoglobin, MCV, MCH and MCHC as well as iron profile values were also calculated individually between patients with diabetes and non-diabetes in terms of means and standard deviation (Table-2).

Variable	Non-diabetic (n=36)	Diabetic (n=30)	p-value
Age(years)	59.8±8.01	59.1±7.48	0.78
M:F ratio	1:1	2.75:1	-
Haemoglobin(g/dl)	10.45±2.61	9.65±1.66	0.31
MCV (fl)	91.4±7.08	85.9±8.67	0.05
MCH (pg)	29.3±2.98	26.7±3.29	0.02
MCHC (g/dl)	32.4±1.8	31.12±1.39	0.02
S. Iron (mcg/dl)	80.7±49.9	114.09±172.54	0.43
S. Ferritin (ng/ml)	563.8±381.0	728.89±333.62	0.22
TSAT (%)	30.12±20.01	50.18±67.58	0.23

p-value calculated using unpaired Student's t-test.

Table-2. Comparison of various parameters between diabetic and non-diabetic patients.

Haemoglobin, MCV, MCH and MCHC were all found to be lower in diabetics as compared to non-diabetics. However, there was no significant statistical difference between Hb and MCV values, whereas MCH and MCHC was found to be significantly lower in diabetic patients (using unpaired t-test). There was no statistically significant difference (using unpaired t-test) between serum iron, serum ferritin and TSAT values between the two groups. We also found that presence of diabetes had no difference of statistical significance on the severity of anaemia in our patients (Table-3).

	Non-diabetic (n=36)	Diabetic (n=30)	Total (%)
Severe anaemia	4 (4.36) [0.03]	4 (3.64) [0.04]	8(12.12)
Moderate anaemia	20 (22.91) [0.37]	22 (19.09) [0.44]	42(63.63)
Mild anaemia	4 (3.27) [0.16]	2 (2.73) [0.19]	6(9.09)
No anaemia	8 (5.45) [1.19]	2 (4.55) [1.43]	10(15.15)
Total	36	30	66(100)

The chi-square statistic is 3.8483. The p-value is .278323. The result is not significant at p < .05. Moderate anaemia most prevalent in both groups of patients.

Table-3. Distribution and comparison of severity of anaemia between non-diabetics and diabetics.

We also tried to find the correlation of various parameters with haemoglobin using Pearson's correlation coefficient. A mildly negative correlation was found between Hb and RBS at presentation (r=-0.1001, p=0.57), Hb and TSAT values (r=-0.05, p=0.78) and Hb and age (r=-0.13, p=0.47). However, as evident none of the values reached statistical significance.

The presence of iron overload was also evaluated in both the groups. Out of the 66 patients, 32 (48.48%) patients had ferritin levels of ≥500 ng/dl in the absence of functional iron deficiency, 12(37.5%) patients were non-diabetics and 20(62.5%) were diabetics in this category. A Chi-square test of independence showed that the relationship between the presence of diabetes mellitus and iron overload was highly significant [$\chi 2$(1, N=66) =7.2794, p=0.006].

DISCUSSION:

Anaemia was present in 56(84.8%) of our patients. This is consistent with study of Loutradis et al, who found that the prevalence of anaemia was almost 90% in CKD stage 5 patients (14).

The prevalence of diabetes in our study population was 45.4%. This is consistent with national as well as international data. A report from US in the year 2014 showed that out of 1,20,000 patients who started treatment for ESRD, 44% were believed to have diabetes mellitus as the cause of ESRD (15). Another study from India also showed diabetic nephropathy to be a cause of ESRD in 44% patients (16).

In our study, the M:F ratio was 1:1 for non-diabetic patients and 2.75:1 for diabetic patients. The overall M:F ratio was 1.5:1. As is evident from Figure-1, the age group of 45-54 years has more skewed sex ratio. Beyond the age of 54 years, the ratio came closer. There may be several reasons for these findings. In the Chronic Renal Insufficiency Cohort (CRIC) study, it was found that male gender was associated with a higher risk of renal disease progression as well as worse outcomes in non-diabetic kidney disease. It is believed that pre-menopausal status confers protection against developing advanced renal disease in women (17). A study done in Finland showed that the cumulative risk of developing ESRD was 93% higher in diabetic men as compared to women (18). Several factors have been attributed to this fact one of them being the role of sex hormones in pre-menopausal women. Also, women are less prone to develop type 2 diabetes mellitus as compared to men. However, it has been found that more women are at risk of developing ESRD once they develop diabetes the overall risk of renal disease progression is slower in women. Women having diabetes seem to develop renal disease progression almost 10 years later than men. However, as age progresses, diabetic women are at a higher risk of developing ESRD as compared to men (19).

In our study, we did not find a significant difference between the different haematological parameters or iron profile as seen in Table-2 except MCH and MCHC. The study done by Loutradis et al also had similar findings. In this study, the haematological parameters were significantly different between diabetics and non- diabetics until stage 3a CKD beyond which there was no significant difference between the haematological parameters of both groups except for ferritin which

was significantly higher in diabetics across all CKD stages (14). Our study however, did show significantly lower MCH and MCHC values in our patients. In a study conducted by Yamaguchi et al, it was concluded that a low MCHC in dialysed patients was independently associated with non-atherosclerotic cardiovascular disease. These patients were found to have increased left ventricular thickness and left atrial diameter. Considering that diabetics are more prone to atherosclerotic cardiovascular disease it may be extrapolated that low MCHC and MCH in our diabetic patients may be indicative of them being at a higher risk of development of cardiovascular disease (20). Although the history of pre-existing cardiovascular disease was not sought in our patients but even though the association cannot be neglected.

We also evaluated our patients for iron overload. We found high ferritin levels in 62.5% diabetic patients as compared to 37.5% non-diabetic patients. The difference was found to be statistically significant. Ferritin is an acute phase reactant and a marker of inflammatory process apart from being a significator of iron overload. Diabetes also predisposes to infections and inflammatory processes. In patients with CKD, it is believed that ferritin levels below 2000ng/ml may not be associated with high body levels of iron stores. Also, chronic inflammation is common in CKD, again a cause of hyperferritinaemia. Increased serum ferritin levels have also been found to be a cause of hypo responsiveness to EPO (21). The study by Loutradis et al. confirms our findings of high ferritin levels in diabetic vs non- diabetic CKD patients. In the said study, sub-clinical inflammation was considered to be a factor for high ferritin levels in diabetics across all stages of CKD (14).

CONCLUSION:

The important conclusions that can be drawn from our study are that diabetes remains an important cause of ESRD across the world and probably affects male gender more. Almost 80-90% of patients who are on maintenance dialysis are anaemic and the management of anaemia remains paramount in the management of these patients. Iron deficiency along with EPO should be the mainstay of managing anaemia in these patients. The haematological parameters do not exhibit significant difference between diabetics vs non- diabetics. Serum ferritin is an indicator of inflammation and not necessarily iron overload in these patients; however, this possibility remains significantly higher in diabetics as compared to non-diabetics.

REFERENCES:

1. Nissenson, A. R., & Strobos, J. (1999). Iron deficiency in patients with renal failure. *Kidney international. Supplement*, *69*, S18–S21. https://doi.org/10.1046/j.1523-1755.1999.055suppl.69018.x
2. Macdougall, I. C., Bircher, A. J., Eckardt, K. U., Obrador, G. T., Pollock, C. A., Stenvinkel, P., Swinkels, D. W., Wanner, C., Weiss, G., Chertow, G. M., & Conference Participants (2016). Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney international*, *89*(1), 28–39. https://doi.org/10.1016/j.kint.2015.10.002
3. Madore, F., Lowrie, E. G., Brugnara, C., Lew, N. L., Lazarus, J. M., Bridges, K., & Owen, W. F. (1997). Anaemia in haemodialysis patients: variables affecting this outcome predictor. *Journal of the American Society of Nephrology : JASN*, *8*(12), 1921–1929. https://doi.org/10.1681/ASN.V8121921
4. Mohanram, A., Zhang, Z., Shahinfar, S., Keane, W. F., Brenner, B. M., & Toto, R. D. (2004). Anaemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. *Kidney international*, *66*(3), 1131–1138. https://doi.org/10.1111/j.1523-1755.2004.00863.x
5. Thomas, S. and Stevens, P.E. (2006), Anaemia in diabetic kidney disease: An area for improvement?. *Pract Diab Int,* 23: 22-26. https://doi.org/10.1002/pdi.885
6. Ravanan, R., Spiro, J. R., Mathieson, P. W., & Smith, R. M. (2007). Impact of diabetes on haemoglobin levels in renal disease. *Diabetologia*, *50*(1), 26–31. https://doi.org/10.1007/s00125-006-0514-y
7. Zainab, A.J., Haider, K.Z. and Mahmoud, H.H. (2018) Serum Erythropoietin Level in Type II Diabetic Nephropathy. *Journal of Clinical and Diagnostic Research*. Jun, Vol-12(6): BC05-BC08. DOI: 10.7860/JCDR/2018/32813.11631
8. Deray, G., Heurtier, A., Grimaldi, A., Launay Vacher, V., & Isnard Bagnis, C. (2004). Anaemia and diabetes. *American journal of nephrology*, *24*(5), 522–526. https://doi.org/10.1159/000081058
9. Mehdi, U., & Toto, R. D. (2009). Anaemia, diabetes, and chronic kidney disease. *Diabetes care*, *32*(7), 1320–1326. https://doi.org/10.2337/dc08-0779
10. Bajaj, S., Makkar, B. M., Abichandani, V. K., Talwalkar, P. G., Saboo, B., Srikanta, S. S., Das, A., Chandrasekaran, S., Krishnan, P. V., Shah, A., Abraham, G., Tikku, P., & Kumar, S. (2016). Management of anaemia in patients with diabetic kidney disease: A consensus statement. *Indian journal of endocrinology and metabolism*, *20*(2), 268–281. https://doi.org/10.4103/2230-8210.176348
11. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Published 2011. Accessed August 07, 2021. https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_ NMH_NHD_ MNM_11.1_eng.pdf?ua=1
12. Plastina, J., Obara, V. Y., Barbosa, D. S., Morimoto, H. K., Reiche, E., Graciano, A., & Delfino, V. (2019). Functional iron deficiency in patients on haemodialysis: prevalence, nutritional assessment, and biomarkers of oxidative stress and inflammation. *Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia*, *41*(4), 472–480. https://doi.org/10.1590/2175-8239-JBN-2018-0092
13. Kuo, I. C., Lin, H. Y., Niu, S. W., Lee, J. J., Chiu, Y. W., Hung, C. C., Hwang, S. J., & Chen, H. C. (2018). Anaemia modifies the prognostic value of glycated haemoglobin in patients with diabetic chronic kidney disease. *PloS one*, *13*(6), e0199378. https://doi.org/10.1371/journal.pone.0199378
14. Loutradis, C., Skodra, A., Georgianos, P., Tolika, P., Alexandrou, D., Avdelidou, A., & Sarafidis, P. A. (2016). Diabetes mellitus increases the prevalence of anemia in patients with chronic kidney disease: A nested case-control study. *World journal of nephrology*, *5*(4), 358–366. https://doi.org/10.5527/wjn.v5.i4.358
15. Burrows, N. R., Hora, I., Geiss, L. S., Gregg, E. W., & Albright, A. (2017). Incidence of End-Stage Renal Disease Attributed to Diabetes Among Persons with Diagnosed Diabetes - United States and Puerto Rico, 2000-2014. *MMWR. Morbidity and mortality weekly report*, *66*(43), 1165–1170. https://doi.org/10.15585/mmwr.mm6643a2
16. Modi, G. K., & Jha, V. (2006). The incidence of end-stage renal disease in India: a population-based study. *Kidney international*, *70*(12), 2131–2133. https://doi.org/10.1038/sj.ki.5001958
17. Maric-Bilkan C. (2020). Sex Differences in Diabetic Kidney Disease. *Mayo Clinic proceedings*, *95*(3), 587–599. https://doi.org/10.1016/j.mayocp.2019.08.026
18. Finne, P., Groop, P. H., Arffman, M., Kervinen, M., Helve, J., Grönhagen-Riska, C., & Sund, R. (2019). Cumulative Risk of End-Stage Renal Disease Among Patients With Type 2 Diabetes: A Nationwide Inception Cohort Study. *Diabetes care*, *42*(4), 539–544. https://doi.org/10.2337/dc18-1485
19. Shepard B. D. (2019). Sex differences in diabetes and kidney disease: mechanisms and consequences. *American journal of physiology. Renal physiology*, *317*(2), F456–F462. https://doi.org/10.1152/ajprenal.00249.2019
20. Yamaguchi, S., Hamano, T., Oka, T. *et al.* (2021) Mean corpuscular hemoglobin concentration: an anemia parameter predicting cardiovascular disease in incident dialysis patients. *J Nephrol*. https://doi.org/10.1007/s40620-021-01107-w
21. Kalantar-Zadeh, K., Kalantar-Zadeh, K., & Lee, G. H. (2006). The fascinating but deceptive ferritin: to measure it or not to measure it in chronic kidney disease?. *Clinical journal of the American Society of Nephrology : CJASN*, *1 Suppl 1*, S9–S18. https://doi.org/10.2215/CJN.01390406