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Original Article

Biochemistry Section

Iron Profile in Multiple Myeloma and Chronic Kidney Disease

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ABSTRACT

Introduction: In normal individuals serum ferritin levels would indicate the body iron stores. Ferritin levels are known to be increased despite the low body iron stores in conditions like chronic inflammation and malignancies. However, the increased levels of ferritin and its correlation with the other iron profile parameters need to be validated in Chronic Kidney Disease (CKD) and Multiple Myeloma (MM).

Aim: To compare the abnormalities of iron profile markers in CKD and MM with age and sex matched controls and to find out whether Serum Ferritin (SF) levels correlate with body iron stores in these clinical states.

Materials and Methods: This was a hospital-based retrospective study done in tertiary care Nephrourology Centre, Bangalore, Karnataka, India from April 2017 to April 2018. Patients attending routine nephrology OPD were included in the study. There were three study groups, group I (n=50) included non-dialysed CKD patients, group II (n=50) included newly diagnosed cases of MM using International Myeloma Working Group (IMWG) criteria and group III (n=50) consisted of controls included age and sex matched normal subjects who had been referred to the laboratory centre for routine check-up. Iron profile which includes Serum Iron (SI), Total Iron Binding Capacity (TIBC), Transferrin Saturation (TS), and SF, was done in all the subjects enrolled in the study. Data analysis was done by Statistical Package for Social Science (SPSS) version 17. The significance level, or p-value, was calculated using the unpaired t-test.

Results: In the CKD group (n=50), only seven patients had normal iron profile. Forty-three patients had deranged iron profile. Among these 43 cases, the mean SI was 34±10 ug/dL, mean TIBC was 206±39 ug/dL, mean TS was 17±9 ug/dL. SF levels were >100 ng/dL in 20 CKD patients and <100 ng/dL in 30 CKD patients. In MM patients (n=50), five had normal iron profile. Forty five patients had abnormal iron profile with mean SI levels 29±9 ug/dL, low TIBC 163±10 ug/dL, low TS 13±4 ug/dL, and SF was 793±20 ng/dL. On comparison of CKD and MM patients with controls; the mean values of SI, TIBC and TS were significantly lower than controls ($p<0.05$). Also, the mean SF values of CKD and MM group patients were significantly higher than the controls ($p<0.05$). Also, the values of all these parameters (SI, TIBC, TS, SF) were much more deranged in MM group compared with the CKD group and this was statistically significant (p-value <0.05).

Conclusion: High ferritin values in these patient groups should not be mistaken for iron overload; rather a prompt correction of iron deficiency must be sought based on total iron profile assessment.

Keywords: Ferritin, Serum iron, Total iron binding capacity

INTRODUCTION

Iron is an essential element for life, a component of haemoglobin, myoglobin, and diverse enzymes involved in critical body functions-thus required for many cellular processes including DNA synthesis, oxygen transport and cell growth [1,2]. Iron is toxic when in excess, and thus there are many mechanisms in the human body to keep both cellular and body iron concentrations within the required range [3]. This normal iron metabolism may be disrupted in many physiologic and pathological conditions, such as hypoxia [4], endocrine [5], metabolic [6] and inflammatory [7,8] states leading to decreased availability of iron in the circulation. In the present study, the disruption of iron metabolism is studied in two inflammatory states namely CKD and MM.

MM is a malignant disease affecting mainly elderly population characterised by the proliferation of neoplastic clone of plasma cells in the bone marrow [9]. It is a common haematologic malignancy accounting for 10% of all haematologic malignancies and 1% of all other malignancies, with the clinical manifestations ranging from skeletal disease (70%), anaemia (40%), impaired humoral immunity (80%) to renal impairment (20-40%) [10-12]. Myeloma associated anaemia has been described as anaemia of chronic inflammation wherein, up regulation of hepcidin- a hepatic hormone, in response to inflammatory stimuli has also been suggested as a mechanism of anaemia. Hepcidin causes trapping of iron in the reticulo-endothelial system resulting in decreased availability of iron leading to anaemia [13,14]. Iron is an important cofactor for the enzyme ribonucleotide reductase inside the cell, which is essential for DNA synthesis, and is often overexpressed in cancer cells. Due to the high rate of proliferation of cancer cells, there is an increased need for iron, making them more susceptible to the disruption of iron metabolism leading to reduced availability of plasma iron in MM [15]. Although iron deficiency state is more common in MM, a few studies have also demonstrated a pattern of iron overload in MM [16,17]. Hence, further studies are required to assess iron status in MM.

Apart from anaemia, one more frequent complication of MM is renal dysfunction, prevalent in about 20% of newly diagnosed MM patients and in over 50% of known MM patients during the course of their disease [18]. Prevalence of CKD in MM poses a higher tumour burden and worsen the prognosis [19-21]. Anaemia is a cardinal feature of CKD. Type of anaemia in CKD is either iron deficiency anaemia as described by few studies where iron deficiency is due to reduced dietary intake, low intestinal absorption, and gastrointestinal bleeding [22,23]; or anaemia of chronic disease as described by few other studies where hepcidin mechanism is the causative factor, resulting in reduced availability of iron [13,14]. Also, there is sparse literature on non-dialysed CKD patients with respect to iron status, which makes the present study unique.

Measurement of iron deficiency in these clinical states is very important as chronic iron deficiency is known to affect functioning of various body systems, including cardiovascular system leading to left ventricular dysfunction and eventually leads to cardiomyopathy [24,25]. In normal individuals, measurement of SF levels would indicate the plasma iron availability [26]. However, in case of chronic inflammations and cancers, the SF levels are known to be elevated inspite of low iron stores due to upregulation hepcidin mechanism [27-29]. Thus, most often iron deficiency remains undiagnosed and untreated in inflammatory conditions [30]. Thus, increased levels of ferritin and its correlation with body iron stores need to be validated in CKD and MM. In view of these differed opinions, the present study was conducted with an aim to find out whether serum ferritin levels correlate with body iron stores in these clinical states.

MATERIALS AND METHODS

This was a retrospective study which was conducted in the Institute of Nephrourology, Bangalore, Karnataka, India; which is a tertiary care Centre and the duration of the study was from April 2017 to April 2018. All the data were collected from hospital records for the selection of the cases and control. The procedures followed were in accordance with the Helsinki Declaration of 1975 that was revised in 2000. Fifty diagnosed cases for each CKD and MM group attending routine nephrology OPD for follow-up were included in the study. There were three study groups, group I (n=50) included non-dialysed CKD patients, group II (n=50) included newly diagnosed cases of MM using IMWG criteria [31] and group III (n=50) consisted of controls which included age and sex matched normal subjects who had been referred to the laboratory centre for routine check-up. Iron profile includes SI, TIBC, TS, and SF, was done in all the subjects enrolled in the study after taking the informed consent from each one of them.

Inclusion and Exclusion Criteria for Non-Dialysed CKD (group I)

Fifty consecutive adults above 20 years of age of either sex, diagnosed with CKD (pre-dialysis) attending Nephrourology OPD for follow-up, were randomly selected. Patients on dialysis, haematinics, recombinant human erythropoietin and blood transfusion in the last three months were excluded from the study. Patients with malignancy or known haematological disorder or with recent severe haemorrhagic episode were excluded.

Inclusion and Exclusion Criteria for Multiple Myeloma (group II)

Fifty random cases of MM attending the nephrourology OPD for follow-up, were identified and enrolled in this study. Patients with other malignancies, known liver disease, history of blood transfusion and haematological disorders, were excluded from the study.

Sample Collection and Analysis

Blood sample was collected randomly by standard venipuncture technique into plain plastic tubes using aseptic precautions. Complete clot formation was ensured prior to centrifugation. Serum was separated after centrifuging for 15 minutes, and was analysed for all the parameters on the same day. Analysis of serum was done by Abbott ci4100 chemistry and immunoassay autoanalyser in biochemistry laboratory. Ready to use kits from abbott architect c and i systems were used for the analyses. Spectrophotometric method was used in the measurement of SI using Ferene method, Unsaturated Iron Binding Capacity (UIBC) using Alumina adsorption method. TIBC was calculated using the formula TIBC=UIBC+iron. Transferrin by Immunoturbidimetric method, and Ferritin by Microparticle Enzyme Immunoassay (MEIA) method. Urea by colorimetric method using urease method and creatinine using alkaline picrate method.

STATISTICAL ANALYSIS

Data were analysed by Statistical Package for Social Science (SPSS) version 17. Results were presented as mean±Standard Deviation (SD) for quantitative variables. The significance level, or p-value, was calculated using the unpaired t-test. A p-value <0.05 were considered as statistically significant.

RESULTS

Cases were divided into two groups, group I with CKD, (n=50), and group II with MM (n=50). Controls were in group III (n=50). Male Female ratio (M/F) in all the three groups was 39/11 in CKD, 33/17 in MM and 30/20 in controls.

In the CKD group (n=50), only seven patients had normal iron profile. Forty-three patients had deranged iron profile. Among these 43 cases, the mean SI was 34±10 ug/dL, mean TIBC was 206±39 ug/dL, mean TS was 17±9 ug/dL. In MM patients (n=50), five had normal iron profile. Forty five patients had abnormal iron profile with mean SI levels 29±9 ug/dL, low TIBC 163±10 ug/dL, low TS 13±4 ug/dL, and ferritin 793±20 ng/dL [Table/Fig-1]. On comparison of CKD and MM patients with controls; the mean values of SI, TIBC and TS were significantly lower than controls (p<0.05). Also, the mean SF values of CKD and MM group patients were significantly higher than the controls (p<0.05).

The values of all these parameters (SI, TIBC, TS, FS) were much more deranged in MM group compared with the CKD group and this was statistically significant (p-value <0.05) [Table/Fig-2]. Ferritin levels in CKD and multiple myeloma patients were further categorised into 3 groups, (<100, >100 and >1000 ng/dL) which is illustrated in [Table/Fig-3]. It was also found that 18 among 50 multiple myeloma cases had biochemical markers (high urea and creatinine) of renal dysfunction. These 18 patients who had associated renal dysfunction had very high ferritin levels with an average of 1145±120 ng/dL.

Parameters	Reference range	CKD (n=50) M/F:39/11 mean±sd	MM (n=50) M/F:33/17 mean±sd	Controls (n=50) M/F:30/20	*p1	*p2
Age		53±14	55±11	52±6	0.1	0.1
Urea (mg/dL)	10-44	132±39	100±40	26±10	<0.0001	<0.0001
Creatinine (mg/dL)	0.72-1.42	7±3	6±2	0.7±0.4	0.0001	≤0.0001
Iron (ug/dL)	37-145	34±10	29±9	110±30	<0.0001	<0.0001
TIBC (ug/dL)	228-428	206±39	163±10,	326±42	<0.001	<0.001
Transferrin saturation (ug/dL)	20-55	17±9	13±4,	33±9	<0.0001	<0.0001
Ferritin (ng/mL)	13-150	212±12	793±20	80±16	<0.005	<0.0001

[Table/Fig-1]: Comparison of iron profile between cases and controls.
*p1: p-value for CKD and controls
*p2: p-value for multiple myeloma and controls.
CKD: Chronic kidney disease; MM: Multiple myeloma; TIBC: Total iron binding capacity. Unpaited t-test was used

Parameters	Reference range	CKD (n=50) mean±sd	MM (n=50) mean±sd	p-value	Statistical significance
Age (years)		53±14	55±11	0.115	Not significant
Urea (mg/dL)	10-44	132±39	100±40	0.001	Very significant
Creatinine (mg/dL)	0.72-1.42	7±3	6±2	0.117	Not significant
Iron (ug/dL)	37-145	34±10	29±9	0.01	Significant
TIBC (ug/dL)	228-428	206±39	163±10,	0.0001	Extremely significant
Transferrin saturation (ug/dL)	20-55	17±9	13±4,	0.005	Very significant
Ferritin (ng/mL)	13-150	212±129	793±20	0.0001	Extremely significant

[Table/Fig-2]: Comparision of iron profile between CKD and multiple myeloma.
Unpaired t-test was used

Ferritin	CKD (n=50)	MM (n=50)
<100 (ng/dL)	30	5
100-1000 (ng/dL)	20	27
>1000 (ng/dL)	0	18

[Table/Fig-3]: Distribution of serum ferritin levels in CKD and MM.

DISCUSSION

Ferritin is the major storage form of iron in the body. It accounts for 15-30% of the total body iron [32]. Clinical significance of serum ferritin values is that it indicates the body iron stores in healthy adults in whom SF concentrations are directly related to storage iron [33]. But there are a few conditions where ferritin concentrations are increased inspite of decreased body iron stores. A study by Gabay C and Kushner I, concluded that an elevated ferritin may reflect iron overload; however, ferritin is an acute phase protein, and hence it may also be increased in liver disease, malignancy, infection and inflammation [34]. The anaemia of chronic diseases was described by Arosio P et al., as normochromic or hypochromic anaemia with a low SI and a low transferrin level and an increased reticulo-endothelial iron which occurs in many infectious, inflammatory and malignant disorders [35].

A study by Peng YY and Uprichard J, have summarised in their review that dysregulation of iron homeostasis forms the basis of the two most common causes of anaemia viz., iron deficiency anaemia and anaemia of chronic disease [36]. Iron studies can be useful in differentiating between the two disease processes and can be used in prompt diagnosis and treatment. Many studies have explained the association between the iron indices and anaemia of chronic disease [36-38]. Ali MA et al., in their prospective study have proved that; SF levels are often elevated irrespective of body iron stores in chronic inflammatory diseases [39]. Another study by Lipshitz DA et al., concluded that patients with chronic inflammation have elevated SF concentration, disproportionate to that of iron stores [40]. Anaemia of chronic disease is known to occur in many clinical conditions such as chronic infections, inflammatory disorders and malignancies. These three causes account for 75% of cases [41].

In the present study, two groups of patients: CKD and MM were considered; out of which CKD is a chronic infection and MM is a malignant condition. In the present study, SF levels were increased in both these clinical states inspite of low body iron stores. Iron deficiency state in CKD cases-as seen in present study, was in concordance with the study by National Health and Nutrition Examination Survey 1988-2004, which suggested that low iron tests were found in non-dialysed CKD patients with reduced creatinine clearance [42]. But, in contrast to the findings of present study, the same study also reported that SF levels were low in these patients with reduced creatinine clearance. The same study also found that, with declining levels of creatinine clearance in women, Serum TS levels decreased, whereas SF levels tended to progressively increase which was similar to the results of present study.

Iron deficiency state in CKD patients on haemodialysis is known to occur because of the causes like excessive blood loss due to dialysis filter, from blood left in the dialyser circuit, frequent blood sampling and, access bleeding, and surgical blood loss [43]. Most of these factors are not present in non-dialysed CKD. Therefore, it is unclear whether iron deficiency is as frequent as in dialysis of CKD patients as compared to non-dialysed CKD patients. However, according to Coresh J et al., iron deficiency anaemia is more common in non-dialysed cases of CKD than dialysed cases of CKD [44]. In contrast, another study by Wish JB, revealed that an absolute iron deficiency, most often will occur in patients who are on haemodialysis [45]. In the present study, absolute iron deficiency was revealed in 50% and functional iron deficiency was revealed in 30% of CKD patients. Absolute iron deficiency is defined as a depletion of tissue stores evidenced by a SF level <100 ng/mL or a TS of <20%. Functional iron deficiency is adequate tissue iron defined as a SF ≥100 ng/mL and a reduction in TS [46].

The probable mechanism for decreased iron levels in CKD is as follows. Chronic inflammation in CKD increases both hepcidin and ferritin levels. Hepcidin is a central regulator of systematic iron homeostasis. Hepcidin inhibits the release of iron into the plasma by down regulating the expression of ferroportin on macrophages, hepatocytes, and enterocytes. The major route of hepcidin clearance in our body is through the kidneys where in hepcidin is filtered and degraded [47]. Thus in CKD patients, hepcidin levels remain elevated leading to deranged iron metabolism. Many studies have demonstrated higher serum hepcidin concentrations in CKD patients than in healthy controls [38,48].

CKD is a serious complication which occurs in about 20-25% of MM patients [18] and in 50%, during the course of their disease. In the present study, even though we enrolled only newly diagnosed cases of MM, we found that at least 36% of them were already complicated with renal insufficiency, evidenced by high blood urea and creatinine in them. Very high ferritin levels in these patients in the present study, supports various studies which have proved that SF levels are rather increased in the later stages of haematologic malignancies, thus ferritin levels have the prognostic significance in haematologic malignancies [49,50]. A study by Song MK et al., showed the importance of SF on 89 patients of newly diagnosed MM, and they observed that the overall survival in the increased SF group was shorter than that in the normal SF group after a median follow-up of 25 months [51]. Another study by Strasser-Weippl K and Ludwig H, has concluded that the SF can be a prognostic parameter of survival as well as disease activity in patients with MM [52].

In normal individuals, SF levels are in close correlation with body iron stores. However, SF levels are affected due to the presence of inflammation, since SF is an acute-phase protein [25]. Also, hepcidin levels which are increased in chronic inflammation [53], are proved to be increased in multiple myeloma [54]. High hepcidin levels in MM also explains the low iron status, viz., low serum iron, low TIBC, and low TS in MM because of the fact that up regulation of hepcidin causes trapping of iron in the reticuloendothelial system resulting in decreased availability of iron leading to low iron status [55]. One more explained mechanism for low iron status in MM is transferrin receptor mechanism; transferrin receptor 1 is over-

expressed on cells with a high rate of proliferation including many types of cancer cells, malignant haematopoietic cells. Due to the high rate of proliferation and increased metabolism, cancer cells have an increased need for iron making them more susceptible to the disruption of iron metabolism [15].

Limitation(s)

Follow-up of the MM patients was not done. Hence, the progonostic importance of ferritin could not be determined in these clinical subgroups. Study was done in a small population, with small sample size. Hence, could not validate these results in a better way.

CONCLUSION(S)

There is markedly deranged iron metabolism in MM compared to CKD. There exists anaemia of chronic disease characterised by low SI, low TIBC and low TS in CKD and MM cases. Ferritin levels are markedly increased in both the conditions inspite of low iron stores. Complete iron profile assessment must be an essential part of the laboratory work-up in these groups.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 10, 2019
- Manual Googling: Dec 04, 2019
- iThenticate Software: Dec 24, 2019 (15%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: No
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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