ORIGINAL ARTICLE

Stages of chronic kidney disease and soluble Transferrin Receptor (sTfR), Ferritin, ratio

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Abstract

Objective: To assess the ratio of soluble transferrin receptor to ferritin in different stages of chronic kidney disease.

Methods: This case-control study was conducted at the Aga Khan University Hospital and the Jinnah Postgraduate Medical Centre, Karachi, from January to September 2014, and comprised chronic kidney disease patients and healthy controls. Group 1 comprised controls, whereas groups 2, 3 and 4 had patients based on their mean glomerular filtration rate. SPSS 19 was used for data analysis.

Results: Of the 170 participants, 126(74.1%) were cases and 44(25.9%) were controls. The overall mean age was 55.87±3.48 years and the mean body mass index was 24.25±2.9 kg/m2. Decreased levels of iron and haemoglobin were observed in cases compared to controls ($p<0.001$), while high serum ferritin was seen in cases compared to the controls ($p<0.001$). Correspondingly, the soluble transferrin receptor-to-ferritin ratio was significantly decreased in groups 2, 3 and 4 ($p<0.001$).

Conclusion: The ratio of soluble transferrin receptor to ferritin was lower in higher stages of chronic kidney disease.

Keywords: Ferritin, sTfR, sTfR/F ratio, Chronic kidney disease. (JPMA 67: 848; 2017)

Introduction

The impairment of renal functions can manifest as chronic kidney disease (CKD) which may end up in end-stage renal disease (ESRD) with increased morbidity as well as mortality.[1] The National Kidney Foundation classifies CKD into five stages according to the level of glomerular filtration rate (GFR).[2] The complications associated with various stages of CKD may be attributed to inflammatory and oxidative stress observed during the progression of disease and can be measured by a number of parameters.[3] One of the recently identified markers is serum ferritin. It is an acute-phase reactant and its level increases in liver damage and inflammatory states while its level decreases in iron deficiency anaemia (IDA) and anaemia of chronic disease (ACD).[4]

Serum transferrin receptor (sTfR) is another marker which is a truncated form of the transferrin receptor present on erythroblasts in bone marrow and many other cells in the body. Measurement of sTfR is considered better for reflecting iron metabolism as its levels focus on both body iron stores and total erythropoiesis.[5] The protein sTfR has been introduced as a promising new diagnostic tool for differentiating between IDA and ACD as its levels are proportional to cellular expression of the membrane-associated transferrin receptor and influenced by increased cellular iron needs and cellular proliferation.[6]

As serum ferritin reflects the stored pool of iron and sTfR reflects the functional iron compartment, the sTfR/ferritin index (sTfR-F index), has been suggested as a good estimate of body iron.[7] The diagnostic performance of sTfR, ferritin and sTfR-F index for detecting iron depletion in several groups of patients (IDA, chronic inflammation or infection, and non-haematologic malignancy) has been used.[8]

The association between inflammation and iron status has been discovered in early stages of CKD.[9] The current study was planned to explore the relationship of sTfR:ferritin ratio as an index of iron status and inflammation in different stages of CKD.

Subjects and Methods

This case-control study was conducted at the Department of Biological and Biomedical Sciences at the Aga Khan University Hospital, and Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Centre (JPMC), Karachi, from January to September 2014, and comprised CKD patients and healthy controls. Patients with liver disease, cardiovascular disease, acute or chronic inflammatory disease and those who were on steroid therapy were excluded. Group 1 comprised controls, whereas groups 2, 3 and 4 had CKD patients based on their mean GFR values.

After, the study was approved by the BSMI review board, and informed consent was obtained from all the participants, baseline demographic and clinical data was obtained from medical records and interviews with

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patients at enrolment. All the participants were requested to come with 10-12 hours of fasting for sample collection. The analysis of biochemical parameter, including urea and creatinine, was done by commercially available kits (Cat # 5.17610.0001; Merck France). GFR was estimated in line with literature.[9] Serum Iron was analysed by enzymatic colorimetric method (Cat # 61075 BioMerieux, France) (reference range: male: 0.65-1.70 mg/dl; female: 0.5-1.70 mg/dl). Serum ferritin (Cat # BC- 1025; BioCheck, United States) (reference range: male: 28-365 ng/dl; female: 5-148 ng/dl) and soluble transferrin receptor (Cat # YHB2785Hu, YH Bioresearch China) (reference range: male: 2.2-5.0 mg/L; female: 1.9-4.4 mg/L) were measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits method.

SPSS 19 was used for data analysis. Data on continuous variables, i.e. biophysical (age, height, weight, body mass index [BMI], blood pressure, etc.) and biochemical (serum cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C[, urea, creatinine, etc.) parameters, was calculated as mean ± standard deviation (SD). Statistical comparisons were computed using Mann-Whitney U test for continuous/quantitative variables. Pearson's correlation (r) was used to determine the correlation between GFR levels and lipid profile. P<0.05 was considered significant.

Results

Of the 170 participants, 126(74.1%) were patients and 44(25.9%) were controls. Group 1 comprising controls had mean GFR of 116±8.3. Groups 2, 3 and 4 had 42(33%) patients each, with mean GFR values of 79± 5.2, 45±2.5 and 20.22±8.5 respectively. The overall mean age and the mean BMI was 55.87±3.48 years and 24.25±2.9kg/m^2, respectively. The mean iron level was 2.50±1.16 mg/dl in group 1, 1.80±0.24 in group 2, 1.04±0.24 in group 3 and 0.22±0.15 in group 4 (p<0.001), whereas haemoglobin level was 13.33±1.78 gm /dl, 11.87±2.41, 10.06±2.41 and 7.89±2.16, respectively (p<0.001). Serum ferritin level was 4.72±1.71 in controls compared to 32.17±9.19, 57.90±12.84 and 89±8.77 in groups 2, 3 and 4, respectively (p<0.001). The sTfR/F ratio was 1.68±0.61 in group 1, 0.34±0.18 in group 2, 0.24±0.13 in group 3 and 0.18±0.05 in group 4 (p<0.001) (Table).

Discussion

Serum ferritin levels in our study increased with reduction in GFR; this finding was comparable to other researchers.[10] The increase can be attributed to non-specific protein synthesis for compensation of protein loss in advanced CKD. The results can be compared with Gupta et al., who observed high serum ferritin levels in CKD patients as compared to controls.[6,11] This can be explained on the basis of increased ferritin expression with progression of inflammation in CKD patients.

Serum transferrin receptor levels have been used as a better indicator of iron deficiency, as it helps in diagnosing coexistent iron deficiency in anaemia of chronic disorders as is uninfluenced by the degree of inflammation.[4] Thus, sTfR is expected to be a better clinical measure of iron status in inflammatory conditions as it is neither effected by erythropoiesis nor inflammation.[12] It also helps in monitoring extent of erythropoiesis.[6] The increased sTfR in our study explains decreased intracellular iron which tends to increase iron absorption.[13] The decreased iron levels with increased

Table: Biophysical & Biochemical Parameters of the study subjects.

Variable	Group I (Control) (n= 44) Mean ± SD	Group II (CKD) (n = 42) Mean ± SD	Group III (CKD) (n = 42) Mean ± SD	Group IV (CKD) (n = 42) Mean ± SD	p value
Age (years)	55.73 ± 2.47	54.78±2.54	55.42±3.42	57.56 ±5.49	>0.5
Weight (kg)	58.7 ± 2.47	62.9±9.7	68.311±9.54	64.9 ± 9.7	<0.5
BMI(kg/m^2)	23.6 ±2.03	22.9±2.56	24.51±3.56	26 ±3.42	>0.5
GFR	116 ± 8.3	79± 5.2	45± 2.5	20.22 ± 8.5	<0.001
Haemoglobin (gm/dl)	13.33±1.78	11.87±2.41	10.06±2.41	7.89±2.16	<0.001
Iron (mg/dl)	2.50±1.16	1.80±0.24	1.04±0.24	0.22±0.15	<0.001
Ferritin (ng/dl)	4.72±1.71	32.17±9.19	57.90±12.84	89±8.77	<0.001
Transferrin receptor (mg/dl)	7.31±1.81	10.13±2.58	13±4.12	15.93±3.58	<0.001
sTfR/Ferritin ratio	1.68±0.61	0.34±0.18	0.24±0.13	0.18±0.05	<0.001

Data is presented as Mean ± S.D. Man-Whitney U test was applied to compare groups. P value of <0.05 was considered significant.
CKD: Chronic kidney disease
BMI: Body mass index
GFR: Glomerular filtration rate
sTfR: Serum transferrin receptor
SD: Standard deviation.

ferritin are also reported in our previous study.[14] and another study by our group suggests sTfR to be a better marker for iron demand in the body.

All the researchers have agreed that ferritin is sensitive to excessive body iron stores and inflammation. On the contrary, sTfR reflects the degree of the tissue iron supply and is not influenced by acute or chronic inflammation. Because of this complementary relationship between these 2 indices with respect to measurements of body iron stores, the sTfR-ferritin ratio was suggested to be a better marker than ferritin to measure a wide range of iron status.[15,16]

Therefore, evaluation of iron status in patients with chronic disease requires different serum ferritin cut-offs according to diagnostic classification, and the sTfR-F index adds information on patients with chronic inflammation or infection. Several researchers have employed sTfR/ log ferritin ratio, sTfR-F index as the tool for the diagnosis of iron deficiency anaemia and a cut-off value of >1.85 has been determined.[17] In another study, the mean index was >1.4, indicating iron deficiency anaemia co-existing with anaemia of chronic disease; however, index up to 1.3 shows merely an anaemia of chronic disease.[6] There are a few prospective studies which have investigated the associations of the sTfR-ferritin ratio with coronary heart disease (CHD). In a small case-control study conducted in Finland, a lower sTfR-ferritin ratio was associated with an elevated risk of CHD;[15] but this association was not present in another retrospective case-control study.[18] We observed that sTfR-ferritin ratio had a positive correlation with GFR.

It is important to assess iron stores to assess the status and risk of premature acute myocardial infarction. In the progression of CKD, cardiovascular events are the major cause of death.[19] Functional iron deficiency at the same time develops during treatment with recombinant human erythropoietin and in the infectious state and during the inflammatory process.[19] The measurement of iron stores at this moment can give an insight to the status of kidney functions in CKD patients. Our study involved different stages of CKD patients, and thus the mean age of the four groups was not comparable. The BMI of the four groups was significantly different, but a recent study shows that change in BMI does not reflect the progress of CKD as it is a vague parameter to judge the nutritional status as well as the body composition in such a disease. The increased BMI in our study groups could be due to water retention as these patients were not yet receiving dialysis treatment.[20]

Our study, however, reveals a decline in haemoglobin as well as iron levels across the four groups. Stancu et al. showed a similar decrease in haemoglobin levels in CKD patients.[21] This could be due to the decreased intestinal iron absorption which is subsequent to increased ferritin concentration in the diseased patients. This is consistent with the reports of the previous study.[22] The association of ratio of sTfR-ferritin with the risk of acute myocardial infarction and anaemia due to chronic inflammation in inflammatory bowel disease has been documented by researchers.[23,24] We have emphasised broader scope of the sTfR-ferritin ratio with renal functions of CKD, nonetheless all integral components involved in progression of CKD need to be further expanded and validated with the recruitment of more patients from other nephrology units in subsequent studies.

Conclusion

The sTfR-ferritin ratio was lower in higher stages of CKD. Therefore, the ratio may be used as an index of measurement of renal function in CKD.

Disclaimer: None.

Conflict of Interest: None.

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