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Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a Bio-marker of Iron Deficiency among Egyptian Haemodialysis Patients

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Abstract

Objectives: Evaluation of NGAL in a small cohort of patients in order to assess any relationships it may have with the iron balance, and its efficacy as a biomarker of iron deficiency.

Methods: The study is a cross sectional study and sample size is 80 CKD patients stage 5 on chronic dialysis therapy with a dialytic rhythm of four-h sittings three times every seven days. The study was done on 80 regular haemodialysis (HD) patients (51 males and 29 females) chosen from dialysis units of Eldakahlia hospitals. The research was performed over a duration of one year.

All cases were on constant dose of rHuEPO for at least one and half month and not injected by IV iron supplementation or packed RBCs in 60 days prior to the beginning of the research.

Patients were subdivided into 2 categories: -

Category (1): - Cases with TSAT<30%, (their number is 50).

Category (2): - Cases with TSAT>30%, (their number is 30).

NGAL is measured in the serum by utilizing the ELISA commercially accessible kit (NOVA) bioneovan company, China according to the manufacture`s instruments and its level is expressed as ng/ml.

Results: There was a high significant difference between two groups regarding serum NGAL level. NGAL levels were significantly increased inHD patients in comparison with non HD group. HD patients withTSAT<30% had less level of NGAL values than HD patients with TSAT>30%. In ROC analysis, The best NGAL cut-off value capable to recognize iron deficiency was ≤ 51.893 ng/mL and it was superior to the 'recommended' cut-off value of ≤ 500ng/mL by KDIGO guideline in both sensitivity and specificity.

Conclusion: In conclusion, our study demonstrates that plasma NGAL level is independently accompanying with iron condition and may induce better than serum ferritin in identifying iron deficiency in HD cases. The possible usage of NGAL calculation in the evaluation of iron condition between cases undergo dialysis might be of high potential; however the outcomes of the current research are preliminary. Similarly, more assessments are needed to establish whether NGAL calculation might be helpful in the control of iron medication, as before recorded for different managements.

Keywords: Haemodialysis; Anemia; Iron deficiency; Iron status; Neutrophil gelatinase associated lipocalin

Introduction

Chronic Kidney Disease (CKD) has become a severe public health problem. The 2007 Annual Data Report of the Unites States Renal Data System (USRDS) estimated a dramatically increasing overall prevalence of CKD [1]. Anemia secondary to CKD is frequently observed among chronic hemodialysis (HD) patients and constitutes an important cause of morbidity and mortality [2]. Anemia is one of the most common co morbidities among CKD patients. Pre dialysis patients, 68% of them having advanced CKD that nesessitated kidney management had a haematocrit<30 mg/dl; of those, 51% had a haematocrit<28 mg/dl [3].

HD patients usually have deficiency of iron due to recurrent blood sampling, gastrointestinal bleeding, dietary restrictions and/or impaired enteric absorption[4]. Kidney Disease Outcomes Quality Initiative (K/DOQI) anemia workgroups suggested that serum ferritin and transferrin saturation (TSAT) should be used as primary tools for evaluating iron status in nephropathic subjects: in particular, serum ferritin level of<500ng/ml and TSAT values of<30% in adult CKD patients would point to an existing low iron deposits, consequently being

utilized as cut-off values for planning the opportune treatment [5].

However, recent evidence has led to re-assessing serum ferritin level as a con-sistent index of iron storage in hemodialysis cases. It is an acute-phase reactant that is significantly affected *via* malnutrition and has significant gender differences, therefore making it a less than ideal index for recognizing deficiency of iron. To clarify more, inflammation could result in apparently paradoxical coexistence of high ferritin (above 500ng/ml) and low TSAT (<30%) concentrations commonly detected in hemodialysis cases. Such situation raises two important clinical dilemmas: whether the patient truly has iron deficiency and whether more iron to be supplemented or not [6]. Also, although TSAT might be affected by concomitant situations, like decreased production of transferrin (because of chronic disease or malnutrition), inflammations or daily fluctuations, it seems to reflect iron stores in hemodialysis patients more consistently compared to serum ferritin [7].

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25 kDa stress protein essentially known for its capability of binding siderophores, small hydrophobic molecules containing iron, transporting them into the cells to initiate cytoplasmic iron-dependent pathways therefore achieving protection against oxidative stress [8]. Nephrologists are now well aware about the value of NGAL as a biomarker of acute kidney injury (AKI), chronic renal suffering and progression of CKD [9,10].

However, to the best of our knowledge, no study yet has evaluated NGAL concentrations in individuals with end-stage kidney disease on chronic HD and correlates its level as a marker of iron status.

Patients and Methods

Study population

Observational The study is a cross sectional study and sample size is 80 CKD patients stage 5 on chronic dialysis therapy with a dialytic rhythm of four-h sittings three times every seven days. The study was done on patients chosen from HD units of Mansoura hospitals. The research was performed over a duration of one year. Patients were subdivided into 2 categories: -

Category (1): - Cases with TSAT<30%, (their number is 50).

Category (2): - Cases with TSAT>30%, (their number is 30).

The causes of ESRD calling for dialysis were primary : hypertension (n=25), diabetic nephropathy (n=21), glomerulonephritis (n=11), PKD (n=4), interstial nephritis (n=7), NSAIDS (n=6) , SLE (1) , unknown (n=5). All cases were dry-weight steady for at least 60 days prior to the beginning of the research. All cases were on constant dose of rHuEPO for at least one and half month and not injected by IV iron supplementation or packed RBCs in 60 days prior to the beginning of the re-search. Exclusion criteria were a recent history of bleeding, malignancy, liver diseases, thyroid diseases, infectious diseases, and treatment with steroids or immunosuppressors.

Laboratory measurements

For Peripheral venous samples were taken under fasting conditions and were ob-tained from all patients in pre dialysis session. The mid-week session was selected for sampling and samples were analyzed regarding to usual approaches utilized in the routine lab tests as follows:

A) Iron status is evaluated by measuring:

1) Total serum iron using OLYMPUS analyzer.

2) Serum ferritin is determined quantitatively by a MicroplateImmunoenzymometric Assay.

3) Total Iron Binding Capacity (TIBC) is assayed with the same method used for iron determination.

4) Serum transferrin is assayed with the same method used for iron determination.

5) TSAT is calculated by using the following formula:

TSAT (%)=(Serum iron×100)/(TIBC).

B) NGAL is measured in the serum by utilizing the ELISA commercially accessible kit (NOVA) bioneovan company, China according to the manufacture`s instruments and its level is expressed as ng/ml.

C) Routine clinical laboratory parameters will be collected from patients sheets such as:

- Serum urea.
- Serum calcium.
- Serum phosphorus.
- CBC.

D) SpKT/V are calculated from the following formula to assess the efficacy of dialy-sis session.

Daugirdas formula

Kt/V=(-1)*log (Ratio-(0.03))+((4-(3.5*Ratio))*(Ultrafiltrate Volume/Weight))

Where, Ratio=Post BUN/Pre BUN.

×

Statistical analysis

The collected data were collected, tabulated and statistically analyzed using statistical package for social science (SPSS), version 22 (SPSS Inc, USA), running on IBM compatible computer, using Microsoft windows 8.1. Categorical variables were represented as relative frequency and percent distribution and for comparison between two groups; we used unpaired T-test for normally distributed values and Mann-Whitney U test (Z) for nonparametric values. Prior to assessing the associations, the whole abnormal dispersed values were log altered to well estimated normal distributions. The Pearson correlation coefficient was established to assess the correlation among NGAL and the different variables measured in the research. ROC curve assessment was established to evaluate and compare the

accurateness of the diagnosis of plasma NGAL and ferritin level in discriminating TSAT<30% from TSAT>30% patients. AUC was estimated for plasma NGAL and ferritin level, and pair wise contrast of the AUCs was conducted. Contrast of AUCs was evaluated by Statistical Software version 20. Results were being essential if the P value was less than 0.05 and highly significant if p value<.001.

Results

The present study included 80 CKD patients stage V treated by chronic dialysis therapy with dialysis duration of 4-h sessions three times per week. Cases have been subdivided into 2 groups according to their iron status measured by TSAT which was calculated from the following formula: TSAT(%)=(Serum iron × 100)/(TIBC).

Group (1): Patients with TSAT<30% (50 patient).

Group (2): Patients with TSAT>30% (30 patient).

Epidemiological data

Males Constituted 51 cases (63.75%) of all studied cases, while females were 29 cases (36.25%). (males represented 60% and 70% of conservative and haemodialysis groups respectively. There was no marked change (NS) among the two groups regarding gender distribution according to Mann-Whitney U test (Z=−.895 and P=0.371).

As regard the original renal diseases, it was hypertension(HTN) in 25 cases (31.25%), it was Diabetes mellitus (DM) in 21 cases (26.25%), it was Glomerulonephritis(GN) in 11cases (13.75%),it was Polycystic kidney disease (PKD) in 4 cases (5%), it was Interstitial nephritis (IN)in 7 cases (8.75%), it was non-steroidal anti-inflammatory drugs (NSAIDS) in 6 cases (7.5%), it was systemic lupus erythrematosis (SLE) in 1 case (1.25%),it was Unknown in 5 cases (6.25%). There was no marked changes (NS) among two groups regarding original renal disease according to Mann-Whitney U test (Z=0.5 and P=0.617).

As regard dialysis vintage (months) it ranged from 3 to 405 month, with a mean of 199.55 ± 120.35. There was a high significant difference (HS) between two groups regarding dialysis vintage according to unpaired T-test (T=3.961 and p<0.01). Group (1) patients had lower dialysis vintage than group (2) patients.

Clinical and laboratory data

There was no marked change (NS) among two groups regarding body weight, blood urea (before and after dialysis session), serum calcium, serum phosphorus, Ca X P ratio according to unpaired T-test. There was a high significant difference between two groups regarding spKT/V according to unpaired T-test (T=3.167 and p<0.01). Group (1) patients had lower spKT/V values than group (2) patients.

There was no significant difference (NS) between two groups regarding eryth-ropoietin dosage per week, hemoglobin percentage, haematocrit percentage, RBCs count, WBCs count according to unpaired T-test.

As regard serum NGAL level for it ranged from 11.43 to 267.04 with a mean of 71.64 ± 70.02.There was a high significant difference (HS) between two groups according to unpaired T-test (T=5.878 and p<0.01). Group (1) patients had lower levelsthan group (2) patients (37.36 ± 25.38VS 128.77 ± 82.86).

There was a high significant difference (HS) between two groups regarding se-rum NGAL level, serum ferritin level, serum iron level, serum transferrin level, TSAT percentage and TIBC level according to unpaired T-test.

Correlations of NGAL and other parameters

NGAL was directly correlated with dialysis vintage (R=0.574 and p<0.01), serum ferritin level (R=0.719 and p<0.01), serum iron level (R=0.76 and p<0.01) and TSAT percentage (R=0.729 and p<0.01), whereas NGAL was inversely correlated with serum transferrin level (R=−0.348 and p<0.01) and TIBC level (R=−0.354 and p<0.01) as shown in **Figures 1-6.**

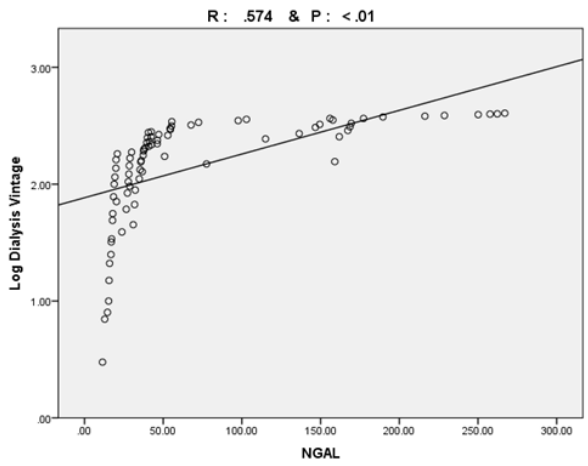

Figure 1: Correlation between NGAL and dialysis vintage.

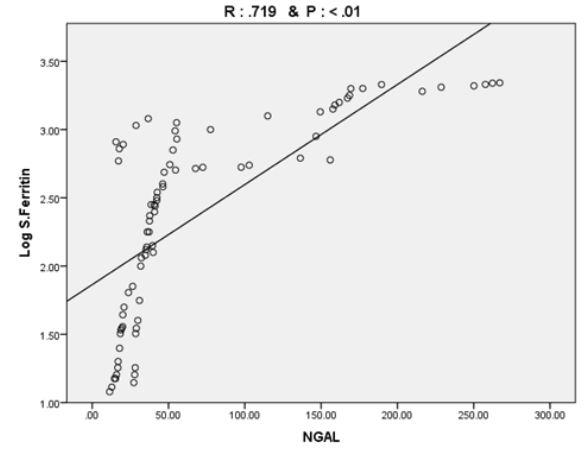

Figure 2: Correlation between NGAL and serum ferritin level.

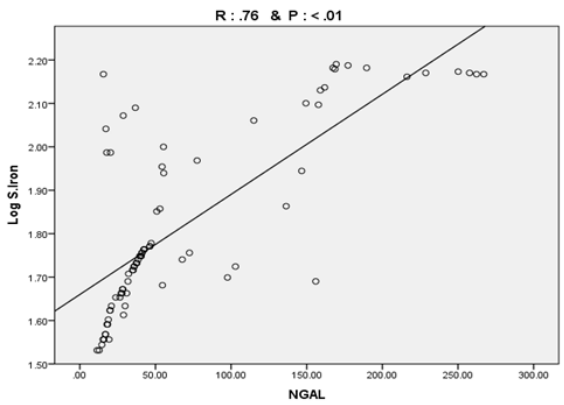

Figure 3: Correlation between NGAL and serum iron level.

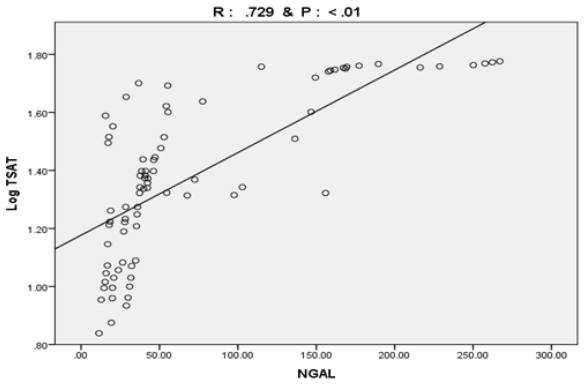

Figure 4: Correlation between NGAL and TSAT percentage.

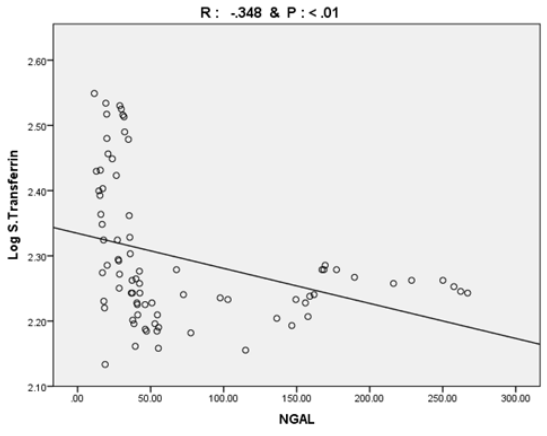

Figure 5: Correlation between NGAL and serum transferrin.

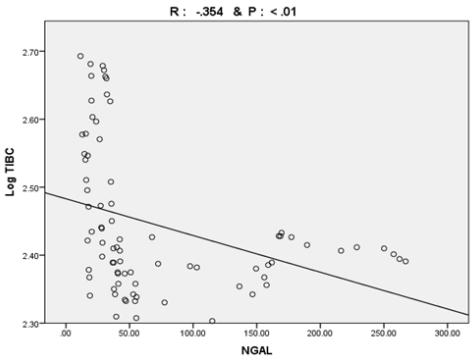

Figure 6: Correlation between NGAL and TIBC level.

Receiver operating characteristic analysis (ROC curve)

Regarding the incidence of iron deficiency (TSAT<30%) as a status variable, ROC assessment was established to evaluate and contrast the diagnostic potentials of NGAL and ferritin level in recognizing iron deficiency between HD patients. The AUC for NGAL and ferritin level were 0.756 (95% confidence interval (CI) (0.701 – 0.808) and 0.652 (95% CI (0.593 – 0.709), correspondingly; however, the change among such areas was marked (P=0.019), recommending that plasma NGAL may conduct markedly better than serum ferritin as shown in **Figure 7.**

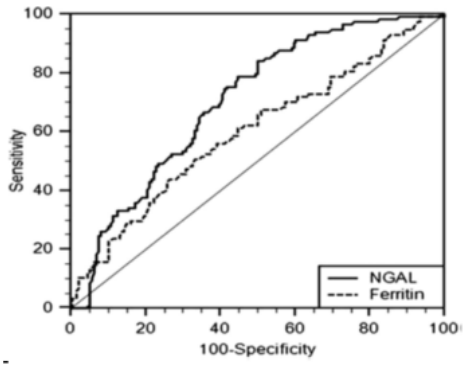

Figure 7: Receiver Operating Characteristics (ROC) Curves of Plasma NGAL and Serum Ferritin Considering Iron Deficiency (TSAT<30%) as a StatusVariable.

The best NGAL cut-off value capable to recognize iron deficiency was ≤ 51.893 ng/mL. For serum ferritin, the best cut-off level was found to be ≤ 267 ng/mL, with specificity of 68.8% (95% CI 61.2–75.7), whereas the 'recommended' cut-off value of ≤ 500 ng/mL by KDIGO guideline had a sensibility of 81.8% (95% CI 73.4–88.6) **(Table 1).**

Table 1: Main clinical and laboratory parameters between two groups.

Parameter	TSAT<30% (n=50)	TSAT>30% (N=30)	T	P
Gender (M/F)	(30 M/20 F)	(21M/9F)	(Z= −0.895)	0.371
Age (Years)	50.34 ± 8.07 (23-66)	54.57 ±9.46 (34-75)	1.119	0.266
Original Renal Disease:				
HTN			-	-
DM	16	9		
GN	14	7		
PKD	7	4		
IN	3	1		
NSAIDS	2	5		
SLE	4	2		
Unknown	1	0		
	3	2		
Dialysis Vintage (Months)	161.64 ± 102.81 (3-365)	262.73 ± 122.44 (15-405)	3.961	<. 01
Weight (Before Dialysis)	73.73 ± 11.83 (45-95)	76.5 ± 13.13 (45-108)	0.973	0.334
Weight (After Dialysis)	71.12 ± 11.63 (42.5-93)	73.85 ± 12.87 (44-104)	0.977	0.332
Urea (Before Dialysis)	112.7 ± 24.58 (80-178)	117.73 ± 20.62 (77-156)	0.94	0.35
Urea (After Dialysis)	40.64 ± 8.82 (26-59)	39.1 ± 8.66 (24-55)	-0.761	0.449
Sp KT/V (Weekly Mean)	1.21 ± .136 (. 91-1.41)	1.31 ± .13 (.99-1.51)	3.167	<. 01
Calcium (Mg/D l)	8.79 ± 1.22 (6-12.6)	8.94 ± 1.06 (6.8-12)	0.53	0.597
Phosphorus (Mg/Dl)	5.46 ± 1.1 (3.5-7.9)	5.62 ± 1.11 (3.5-7.7)	0.656	0.514
Ca×P Product (Mg/D l)	47.79 ± 10.81 (24.5-73.03)	50.06 ± 10.97 (35-73.13)	0.905	0.368
EPO Dosage (IU/ Week)	4640 ± 1481.31 (4000-8000)	4533.33 ± 1382.98 (4000-8000)	-0.32	0.75
Haemoglobin (Mg/D l)	9.5 ± 1.94 (5-15)	9.6 ± 1.77 (6.3-13.5)	0.454	0.651
Haematocrit (%)	28.75 ± 5.84 (16.8-48.7)	29.28 ± 5.25 (20-42.7)	0.402	0.689
Red Blood Cells (N × 10)	3.4 ± .77 (1.85-6.45)	3.54 ± .77 (2.24-5.5)	0.795	0.429
White Blood Cells (N × 10)	5.6 ± 1.92 (2.7-11)	5.57 ± 1.62 (2.9-9.6)	-. 072	0.943
NGAL (Ng/Ml)	37.36 ± 25.38 (11.43-155.94)	128.77 ± 82.86 (15.6-267.04)	5.878	<. 01
Serum Ferritin (Ng/Ml)	178.78 ± 180.64 (12-599)	1373.23 ± 565.38 (554-2200)	11.233	<. 01
Serum Iron (Mcg/Ml)	48.18 ± 7.97 (34-60)	121.73 ± 28.37 (71-155)	13.874	<. 01
Serum Transfer (Mg/Dl)	219.28 ± 64.5 (136-354)	179.4 ± 27.63 (143-270)	-3.826	<. 01
TSAT (%)	17.19 ± 6.18 (6.9-27.9)	48.52 ± 10.34 (30-59.75)	15.063	<. 01
TIBC	308.3 ± 89.71 (204-493)	252.17 ± 38.38 (201-379)	-3.873	<. 01

Discussion

The prevalence of anemia among ESRD patients on regular HD in Egypt is estimated to be 55% [11]. So iron deficiency is one of the major public health problems in HD patients in the developing countries.

K/DOQI anemia workgroups propose that ferritin level and TSAT have to be established as main ways in the evaluation of iron condition in nephrotic cases: in certain, ferritin level of<500ng/ml and TSAT values of<30% in adult CKD cases have to reflect the primary disorder of low iron deposits, therefore being recommended as threshold levels for determining upon appropriate therapeutic methods [5]. However, a great body of newly acquired proof has directed to re- assessment of the function of ferritin level as a consistent marker of iron storing in HD cases. Such protein is significantly affected by malnutrition, and has essential sex variations, therefore making it a minor perfect means for recognizing iron deficiency. Thus making it a less than ideal tool for identifying iron deficiency. For example, the presence of inflammation can explain the apparently paradoxical coexistence of high ferritin (>500ng/ml) and low TSAT (<30%) levels frequently found in HD patients. This condition, moreover, raises two main clinical dilemmas: whether the patient has true and proper iron deficiency and whether additional iron should be administered or not [12].

Nephrology doctors are alert to the importance of NGAL as an indicator of AKI and long-lasting kidney impairment and a predictor of the progression of CKD [9,10]. However, There is a little studies about NGAL level and its relation to iron level and anemia in haemodialysis patients. There is no superiority of serum NGAL over than serum creatinine in predicting CKD in patients admitted in emergency depart [13]. There is early elevation in serum NGAL in chronic kidney injury [14,15]. Serum NGAL was elevated to the highest levels seen in CKD patients in a study of 80 non diabetic CKD patients [16]. Serum and urinary

NGAL levels was elevated in CKD patients with iron deficiency anemia [17]. HD cases have raised circulating NGAL levels in comparison with fit cases, however the principal physiological font of NGAL is signified by neutrophils, it is nowadays broadly agreed that such protein is a factor which can be discharged by nearly all damaged tissue, frequently developing a biomarker of disorder gravity [18].

NGAL is a minor 25 kDa stressful protein primarily recognized for its capacity to attach siderophores, minor particles having iron, transferring them into the cells to stimulate cytoplasmic iron-dependent routes therefore defending the similar cell from reactive oxygen species [8]. However, there are limited researches about NGAL level and its relation to iron level and anemia in HD cases.

In a new model, NGAL tissue concentration were revealed to be greatly raised following various experimental models of induction anemia by phlebotomy, iron deficiency, or phenyl hydrazine intake; such protein might induce a physiological function throughout raised iron usage and transfer from storages. Such remarks provoked us that NGAL may be included in the preservation of the iron equilibrium in cases with dialysis [19].

In our study we analyzed the relationship between NGAL levels and iron status in 80 ESRD patients on regular HD. Cases have been subdivided into 2 groups according to their iron status measured by TSAT because TSAT seems to denote iron supplies in cases undergo dialysis more consistently than ferritin level [7].

Also we analyzed routine investigations done for patients during the period of the study, and we found highly significant difference between the studied groups as regard biochemical and hematological laboratory finding with ($p<0.01$) for each parameter.

There was a high significant difference in serum ferritin level between two groups; there was a marked reduction in ferritin level in group (1) in comparison to group (2). There was a highly significant positive correlation between NGAL and se-rum ferritin. NGAL was associated with ferritin level, this is in agreement [10].Who conducted a study on 56 regular HD patients and found that NGAL concentration were significantly greater in HD cases than in fit ones. HD cases with TSAT<20% have higher NGAL levels than fit ones and lower than HD patients with TSAT>20%, while the improvement of iron lack by a tool of chronic intravenous injection (IV) markedly increase NGAL values. It is established that cases on dialysis have changed NGAL values possibly as such protein is included in the preservation of iron balance [10].

There was a high significant difference in serum iron level between two groups; there was marked reduction in serum iron level in group (1) compared to group (2). There was a highly significant positive correlation between NGAL and serum iron. NGAL was closely associated with serum iron, this is in agreement with [20].Who conducted a study on 419 pre dialysis CKD patients and found that plasma NGAL level is associated with iron status in pre-dialysis CKD patients with anemia.

There was a high significant difference in serum transferrin level between two groups; there was a high significant increase in serum transferrin level in group [1] compared to group [2]. There was a highly significant inverse correlation between NGAL and serum transferrin. NGAL was inversely associated with serum transferrin, this is in agreement with [21]. Who conducted a study on CKD patients with anemia in United States and found that NGAL was inversely correlated with serum transferrin.

There was a highly significant positive correlation between NGAL and TSAT. NGAL was closely associated with TSAT. TSAT is decreased by effect of chronic inflammation of ESRD (functional iron deficiency). Also TAST is affected by diurnal variation, being higher in the morning and lower in the evening; this is in agreement [22].

Serum NGAL levels were directly associated with TSAT and serum ferritin levels, the two chief lab tests used to detect iron deficiency in HD patients in KDIGO guidelines 2012 [5]. also The close participation of NGAL in iron equilibrium is more reinforced by different significant remarks, cases with TSAT levels beneath the optimum 'recommended' level of 30%, therefore with supposed iron lack, exhibited markedly decreased NGAL concentration in comparison with to others.

The NGAL revealed a beneficial diagnosis in recognizing a condition of iron lack between the whole HD cases, as revealed by ROC assessment. The discriminatory capacity of NGAL was excellent to that of ferritin level in terms of both sensibility and specificity; this is in agreement [10].WHO stated that ROC evaluation was established to evaluate and contrast the diagnostic potentials of NGAL and ferritin level in recognizing iron lack between cases on dialysis. The zones below the curve were 0.685 and 0.707, correspondingly; however, the change among such zones was not essential. The best NGAL threshold level capable to recognize iron lack was<473ng/mL. Regarding ferritin level, the greatest threshold level was<254ng/mL, while the 'recommended' threshold level of was 200ng/mL.

There is a high significant increase in serum NGAL level in group (2) compared to group (1).This elevation is significantly higher than normal levels.

There is a high significant difference in dialysis vintage between two groups, there is a significant decrease in dialysis vintage in group (1) compared to group (2).There is a highly significant positive correlation between NGAL and dialysis vintage. NGAL was closely associated with Dialysis Vintage. This positive correlation may be due to the influence of inflammation associated with chronic HD treatment and because NGAL is acute phase reactant [18].

NGAL is well directly correlated with serum ferritin, serum iron, TSAT and dialysis vintage.

In a recent murine model, NGAL tissue levels were shown to be markedly in-creased after different experimental models of induction anemia by phlebotomy, iron deprivation or phenyl hydrazine administration; this protein may therefore play a physiological role during increased iron utilization and mobilization from stores. These observations prompted us that

NGAL might be involved in the maintenance of the iron balance in HD patients [19]. Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25 kDa stress protein mainly known for its capacity to bind siderophores, small hydrophobic molecules containing iron, transporting them inside the cells to activate Cytoplasmic iron-dependent pathways thus protecting the same cell from oxidative stress [23].

Also In our study, there is a high significant difference in dialysis vintage be-tween two groups, there is a significant decrease in dialysis vintage in group(1) compared to group(2).There is a highly significant positive correlation between NGAL and dialysis vintage. NGAL was directly correlated with Dialysis Vintage ($R=0.574$ and $p<0.01$).This positive correlation may be due to the influence of inflammation associated with chronic HD treatment and because NGAL is acute phase reactant as mentioned before [18]. As reported for several other cytokines, extracorporeal treatments can induce the release of NGAL, probably as a stress response [24]. This is in agreement with another study of 96 CKD patient where serums and urinary NGAL at base line were predictors of e GFR decline, also in subjects with CKD, increased serum and urinary NGAL levels correlate with residual renal function [8].

ROC evaluation

Regarding the existence of iron lack as a condition variable, ROC evaluation was established to evaluate and contrast the potential diagnosis of NGAL and ferritin level in recognizing iron lack between HD cases. The AUC for NGAL and ferritin level were 0.756 and 0.652, correspondingly; however, the change among such areas were significant, suggesting that plasma NGAL might perform significantly better than ferritin level.

The greatest NGAL threshold level capable to recognize iron lack was ≤ 51.893ng/mL, with a sensibility of 86.3% and a specification of 52.1%. For serum ferritin, the greatest threshold value was ≤ 267 ng/mL, with a sensibility of 53.1% and a specification of 68.8%, whereas the 'suggested' cut-off value of ≤ 500 ng/mL by KDIGO standard had a sensibility of 81.8% with a specification of 27.6.

Lastly, NGAL may be suggested as a novel mean in evaluation of iron deficiency and regulation of iron treatment for cases on dialysis.

Limitation of the Study

Indeed the current research has some restrictions Firstly; the research cohort was relatively minor: our results have to be validated by researches on greater residents. Secondly, nutrition status must be assessed as malnutrition is called to potentially modify TSAT values, in addition to ferritin levels; the existence of such disorder might have affected the associations among NGAL and iron parameters.

Conclusion

In conclusion, our study demonstrates that plasma NGAL level is independently accompanying with iron condition and may induce better than serum ferritin in identifying iron deficiency in HD cases. The possible usage of NGAL calculation in the evaluation of iron condition between cases undergo dialysis might be of high potential; however the outcomes of the current research are preliminary.

Consequently, no medical use can be considered with no assessing of the actual influence of long-lasting inflammation on circulating NGAL, and creating an efficient economic evaluation as fast NGAL calculation incurs significant cost benefit costs. Similarly, more assessments are needed to establish whether NGAL calculation might be helpful in the control of iron medication, as before recorded for different managements.

Conflict of Interest

The authors have declared that no conflict of interest exists.

Human and Animal Rights (with IRB Approval number) (IRB098654312)

Informed Consent: was obtained from all the patients or first degree relative.

References

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, et al. (2007) Prevalence of chronic kidney disease in the United States. Jama 298:2038-2047.
2. Silverberg DS (2011) The role of erythropoiesis stimulating agents and intravenous (IV) iron in the cardio renal anemia syndrome. Heart Failure Reviews 16: 609-614.
3. Obrador GT, Ruthazer R, Arora P, Kausz AT, Pereira BJ (1999) Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. JASN 10: 1793-1800.
4. National KF (2006) KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis 47: S11-145.
5. McMurray JJV, Parfrey PS, Adamson JW, Aljama P, Berns JS, et al. (2012) Kidney Disease Improving global outcomes (KDIGO) Anemia Work Group: KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl2: 279-335.
6. Rambod M, Kovesdy CP, Kalantar-Zadeh K (2008) Combined high serum ferritin and low iron saturation in hemodialysis patients: the role of inflammation. Clinical Journal of the American Society of Nephrology 3: 1691-1701.
7. Wish JB (2006) Assessing iron status: beyond serum ferritin and transferrin saturation. Clinical Journal of the American Society of Nephrology 1: S4-S8.
8. Yang J, Goetz D, Li JY, Wang W, Mori K, et al. (2002) An iron delivery pathway mediated by a lipocalin. Molecular Cell 10: 1045-1056.
9. Bolignano D, Donato V, Coppolino G, CampoS, Buemi A, et al (2008) Neutrophil gelatinase–associated lipocalin (NGAL) as a marker of kidney damage. Am J Kidney Dis 52: 595-605.
10. Bolignano D, Lacquaniti A, Coppolino G, Donato V, Campo S, et al. (2009) Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clin J Am SocNephrol 4: 337-344.
11. Ali A, Fathy GA, Fathy HA, AbdEl-Ghaffar N (2011)Epidemiology of Iron Deficiency Anaemia: Effect on Physical Growth in Primary

School Children, the Importance of Hookworms. International Journal of Academic Research, 3(1).

12. Rambod M, Kovesdy CP, Kalantar-Zadeh K (2008) Combined high serum ferritin and low iron saturation in hemodialysis patients: the role of inflammation. Clinical Journal of the American Society of Nephrology 3: 1691-1701.

13. Nickolas TL, Barasch J, Devarajan P (2008) Biomarkers in acute and chronic kidney disease. Current Opinion in Nephrology and Hypertension 17: 127-132.

14. Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, et al. (2005)Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. The Journal of Clinical Investigation 115: 610-621.

15. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A (2009) Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. American Journal of Kidney Diseases 54: 1012-1024.

16. Malyszko J, Bachorzewska-Gajewska H, Poniatowski B, Malyszko JS, Dobrzycki S (2009) Urinary and serum biomarkers after cardiac catheterization in diabetic patients with stable angina and without severe chronic kidney disease. Renal failure 31: 910-919.

17. Damman K, Veldhuisen DJ, Navis G, Voors AA, Hillege HL (2008) Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure. European Journal of Heart Failure 10: 997-1000.

18. Xu S, Venge P (2000)Lipocalins as biochemical markers of disease. Biochimica et BiophysicaActa (BBA)-Protein Structure and Molecular Enzymology 1482: 298-307.

19. Jiang W, Constante M, Santos MM (2008) Anemia up regulates lipocalin 2 in the liver and serum. Blood Cells, Molecules, and Diseases 41: 169-174.

20. Kim IY, Kim JH, Lee DW, Lee SB, Rhee H (2018) Plasma neutrophil gelatinase-associated lipocalin is associated with iron status in anemic patients with pre-dialysis chronic kidney disease. Clinical and Experimental Nephrology 22: 28-34.

21. Wish JB (2009) Past, present, and future of chronic kidney disease anemia management in the United States. Advances in Chronic Kidney Disease 16: 101-108.

22. Locatelli F(2004) European Best Practice Guidelines Working Group: Revised European best practice guidelines for the management of anemia in patients with chronic renalfailure. Nephrol Dial Transplant 19: 1-47.

23. Yang J, Goetz D, Li JY, Wang W, Mori K, et al. (2002) An iron delivery pathway mediated by a lipocalin. Molecular Cell 10: 1045-1056.

24. Jönsson P, Ståhl ML, Ohlsson K (1999) Extracorporeal circulation causes release of neutrophil gelatinase-associated lipocalin (NGAL). Mediators of Inflammation 8: 169-171.