Journal of Clinical Pharmacology and Therapeutics

ISSN: 2766-8347

Research Article

Association between Growth Differentiation Factor-15, C-Reactive Protein and Iron Parameters in Children on Regular Hemodialysis

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Abstract

GDF-15 is a stress-induced cytokine of the TGF-β (transforming growth factor-β) super family, which increases during tissue injury and inflammatory states. Little is known about the relationship between Growth Differentiation Factor-15 (GDF-15), and anemia among children on regular hemodialysis.

Aim: The study aimed to evaluate the serum level of growth differentiation and factor-15 (GDF-15) and C-Reactive Protein (CRP) as inflammatory markers and detect of its relation to anemia and iron status in children with chronic kidney diseases on hemodialysis.

Subjects and methods: this case-control study was conducted on forty children on regular hemodialysis (HD) selected from the nephrology hemodialysis unit and outpatient pediatric clinic of Al Zahra hospital, Al Azhar University, also forty children included as controls. Complete blood count, CRP, serum iron, ferritin, total iron binding capacity (TIBC), transferrin saturation% (TSAT%), and GDF-15 levels were measured in both groups.

Results: There was a significant increase in serum GDF-15 levels in cases than controls, the median and (IQR) was 1225 (900 - 1850) ng/l and 300 (290 - 380) ng/l, respectively (P<0.01). Furthermore, there was a significant increase in CRP in patients than controls, the median and (IQR) was 12 (9 - 24) and 3 (2 - 4) ---- respectively with significant negative correlation to hemoglobin (Hb) level (r.-0.324 & p.001). There was a significant positive correlation between GDF-15 with CRP and serum ferritin it was (r, 0.590 p .000 & r, 0.494, p .001) respectively. The frequency of children with functional iron deficiency anemia (FID) was (31.4%) with a significant relation to CRP level.

Conclusion: GDF15 may increase in response to high CRP and serum ferritin levels in HD patients. The numbers of children with functional iron deficiency anemia are not insignificant. The important correlation between both CRP and GDF-15 with serum ferritin detects the high-risk for FID anemia and the utility of preventive strategies that attenuate the inflammatory risk in those patients. GDF-15 emerged as a strong predictor of inflammation in this study.

Keywords: (GDF-15); Anemia; Children; Hemodialysis

Introduction

Evaluation and management of anemia are important to prevent the progress of CKD and for the general well being of the patient. As the renal function worsens, there is a progressive increase in the percentage of CKD patients with anemia [1].

Anemia of chronic kidney disease is thought to be mainly due to inadequate renal production of erythropoietin. However, iron and vitamin deficiencies, blood loss, reduced erythrocyte life span, chronic inflammation, and uremic milieu are also the contributing factors for anemia in CKD patients [2].

Iron deficiency is common in patients on chronic hemodialysis, and most require iron-replacement therapy. In addition to absolute iron deficiency, many patients have functional iron deficiency as shown by a suboptimal response to the use of erythropoietin-stimulating agents(ESAs) [3].

Citation: Mosselhy A, Zein M, Abdelsalam M, Pessar SA. Association between Growth Differentiation Factor-15, CRP and Iron Parameters in Children on Regular Hemodialysis. J Clin Pharmacol Ther. 2020;1(1):1004.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Nov 12th, 2020

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The mechanisms of anaemia in CKD patients include reduced erythropoietin production and reticuloendothelial iron blockade secondary to chronic kidney inflammation [4].

Growth Differentiation Factor-15 (GDF-15) is a divergent member of transforming growth factor-beta super family. Under physiological states, it is weakly expressed in most tissues, but it is elevated in impaired kidney function. High concentrations of GDF-15 have been found in some haemoglobinopathies associated with suppressed concentration of hepcidin and iron overload [5].

Growth Differentiation Factor (GDF) 15 was identified as a hepcidin-suppression factor that is expressed at high levels in patients with ineffective erythropoiesis. Hepcidin is a small defensin-like peptide whose production by hepatocytes is modulated in response to anemia, hypoxia, or inflammation [6].

High levels of GDF-15 suppressed the iron regulatory protein hepcidin and GDF-15 expression increased in iron deficient patients. GDF15 may increase to suppress the high hepcidin level in HD patients who have FID, expression of GDF 15 is upregulated in response to chronic inflammation, present in patients with FID and finally iron depletion, which independently causes GDF15 induction, develops in erythroid precursor cells as a result of iron sequestration in macrophages [7].

Therefore, this study aimed to evaluate serum GDF-15 and CRP levels as surrogates or diagnostic markers of inflammation and detect if their expression is associated with anemia and serum iron parameters in children on regular hemodialysis.

Material and Methods

This case-control study was carried out on 80 children, 42 males and 38 females, aged from 6 to 16 years, selected from those attending the nephrology and hemodialysis pediatric unit of the pediatric nephrology unit and the outpatient clinic of Al-Zahra Hospital, Al-Azhar University, these are the patient's numbers who attended at the pediatric hemodialysis unit during the period of the study, they were on regular hemodialysis more than three months at the time of the study, for 4 hours/setting, 3 times weekly, with low flux polysulphone dialyzer by 4008 Fresenius machine. The most common cause of CKD in patients group was acquired etiology 14 (35.0%), unknown 9 (22.5%) hereditary 9 (22.5%) followed by congenital causes 8 (20%).

Children included in the study were divided into the following two groups: Group I: patients group. 40 children with end-stage renal disease on regular hemodialysis, 21 males and 19 females, aged between 6 and 16 years, formed the patients group. Group II: controls group, 40 apparently healthy children, matched age and sex with patients group. Children with hemoglobinopathies and other chronic disease were excluded from the study. They were subjected to full history taking including etiology, onset of CKD, duration of hemodialysis, and laboratory investigations. Informed consent was obtained from the participating parents in adherence with the guidelines of the ethical committee of Alzhraa hospital, AL-Azhar University, Cairo, Egypt. This study was conducted with the participation of pediatric (nephrology and hemodialysis) unit, Alzhraa hospital, AL-Azhar University, clinical pathology department, hematology unit, Ain Shams University.

Sample collection

7 mL predialysis venous blood samples were withdrawn by venipuncture after an overnight fast of at least 12 h before the start of the mid-week HD session and divided as follows; 2 ml specimens were collected into the K2 EDTA tube for Complete Blood Count (CBC), 5 mL specimens were collected into plain chemistry tube to clot and sera were separated without delay (immediate centrifugation at 3000 RPM; 15 min), then divided into 3 portions; one for CRP, urea and creatinine, one for iron profile (serum iron, total iron binding capacity, serum ferritin) and the last portion aliquoted and stored at -80°C until analysis for the assessment of GDF 15 concentration.

Serum levels of GDF-15 were analyzed by ELISA (Bioassay Technology Laboratory, Yangpu, Shanghai, China); A Solid Phase Sandwich ELISA that has been shown to accurately quantitate GDF-15.

The sensitivity down to 5.57 ng/L with an assay range: 10 - 3000 ng/LGDF-15 levels in healthy individuals and patients varied widely across studies, partly due to the use of different assays, and might therefore not be comparable between studies.

Statistical analysis

Data were collected, revised, coded, and entered the Statistical Package for the Social Science version 20 (IBM Corp., Armonk, NY, USA). Spearman correlation coefficients were used to assess the correlation between two studied parameters in the same group. Receiver Operating Characteristic (ROC) curve was used to assess the best cutoff point with sensitivity and specificity. Interpretation of probability values were as follows: P>0.05 as non-significant, P<0.05 as significant, and P<0.001 as highly significant.

Table 1 shows a comparison between dialysis children and healthy controls regarding demographic data, anthropometric measurements, blood pressure, and laboratory data, it revealed: a significant decrease in weight and height in dialysis children compared to their controls, and also patients group had high blood pressure as expected. There is a significant decrease in WBC, RBCs, Hb and platelets in dialysis meanwhile there is a significant increase in serum urea, creatinine in the dialysis group than their controls.

Table 2 shows a comparison between dialysis children and healthy controls regarding iron parameter, CRP and GDF 15 it revealed significant decrease in the serum iron meanwhile there is a significant increase in the serum ferritin and TIBC meanwhile there is a significant elevated CRP and GDF15 in dialysis group compared to their controls.

Table 1: Comparison between the patients group and the controls regarding age, anthropometric measurements and laboratory data.

Groups/ Variables	Controls group No. = 40 Mean ± SD	Patients group No. = 40 Mean ± SD	t- test	P-value
Age (years)	12.05 ± 3.17	12.05 ± 3.17	0.000*	1.000
WtZ score	-0.04 (-0.33 - 1.54)	-0.64 (-1.04 - 0.16)	-3.741≠	0.000
HtZ score	0.35 (-0.25 - 1.14)	-0.43 (-1.05 - 0.33)	-3.110≠	0.002
BMI Z score	0.67 (-0.19 - 1.13)	-0.60 (-1.12 - 0.02)	-4.776≠	0.000
Systolic BP (mmHg)	110.25 ± 8.32	126.75 ± 26.25	-3.790•	0.000
Diastolic BP (mmHg)	73.25 ± 4.74	83.75 ± 19.70	-3.277•	0.002
WBCs ($\times 10^3$/ mm^3)	7.62 ± 2.00	6.16 ± 1.71	3.490•	0.001
RBCs ($\times 10^6$/ mm^3)	4.60 ± 0.73	3.47 ± 0.67	7.214•	0.000
Hb (g/dl)	13.56 ± 1.07	9.51 ± 1.93	11.606•	0.000
Hct (%)	40.79 ± 3.69	29.16 ± 5.89	10.590•	0.000
MCV (fL)	78.14 ± 3.34	83.71 ± 6.25	-4.972•	0.000
Plt ($\times 10^3$/mm^3)	296.13 ± 69.45	215.48 ± 76.53	4.936•	0.000
Urea (mg/dl)	24.75 ± 7.07	161.15 ± 67.13	-12.781•	0.000
Creat (mg/dl)	0.40 ± 0.14	8.43 ± 2.74	-18.541•	0.000

*: Chi-square test; ≠: Mann-Whitney test; •: Independent t-test

Table 2: Comparison between the patient's group and the controls regarding iron status parameters, serum CRP levels and GDF15.

Groups/ Variables	Controls group No. = 40 Median (IQR)	Patients group No. = 40 Median (IQR)	Independent t-test t- test	P-value
Iron (µg/dl)	111 (98 - 130)	80 (38.5 - 145.5)	-2.206≠	0.027
Ferritin (µg/l)	89.5 (75.5 - 110)	2000 (893.4 - 2000)	-7.578≠	0.000
TIBC (µg/dl)	310 (280 - 327.5)	232 (183 - 286.5)	-4.385≠	0.000
TSAT (%)	37 (31.85 - 40.5)	39.05 (17.3 - 63.6)	-0.443≠	0.658
CRP (mg/l)	3 (2 - 4)	12 (9 - 24)	-7.749≠	0.000
GDF15 (ng/l)	300 (290 - 380)	1225 (900 - 1850)	-7.717≠	0.000

≠: Mann-Whitney test

Figure 1: Demonstrates that children with anemia are 87.5% of the study patients on regular hemodialysis.

Figure 2: Demonstrates that children with functional iron deficiency anemia are 31.4% of the study patients group.

Figures 3 and 4: Demonstrate a significant positive correlation between GDF15 with CRP and serum ferritine respectively.

Figure 5: Demonstrates a positive correlation between serum ferritin level and CRP.

Figures 6 and 7: Demonstrate a negative correlation between CRP with Hb level and TAST% respectively..

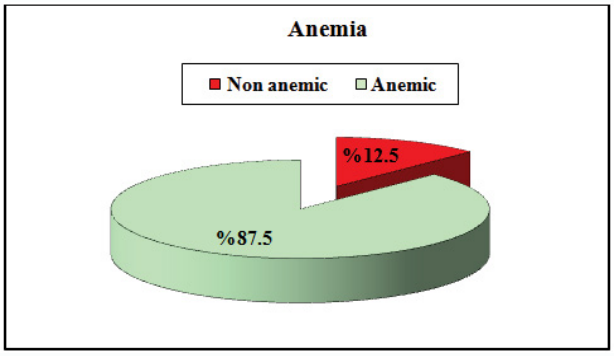

Figure 1: Anemic and non anemic patients in the study group.

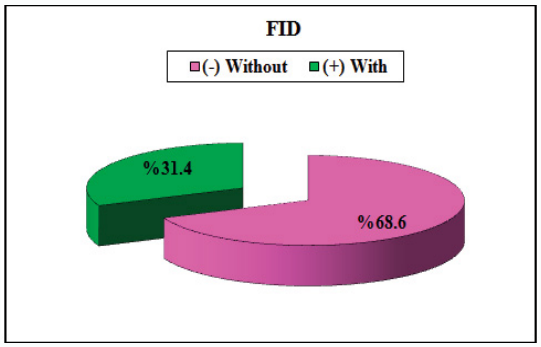

Figure 2: Functional and non -functional anemia frequency&% in the study patients group.
FID: functional iron deficiency

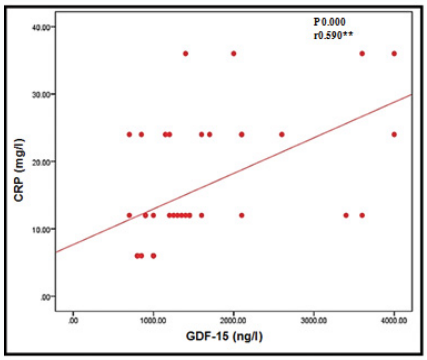

Figure 3: Positive correlation between CRP level and GDF-15 serum level.

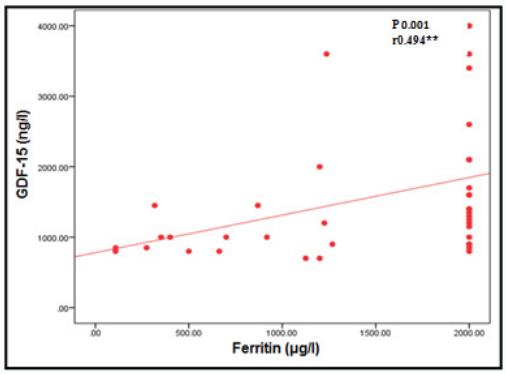

Figure 4: Positive correlation between ferritin level and GDF-15 serum level.

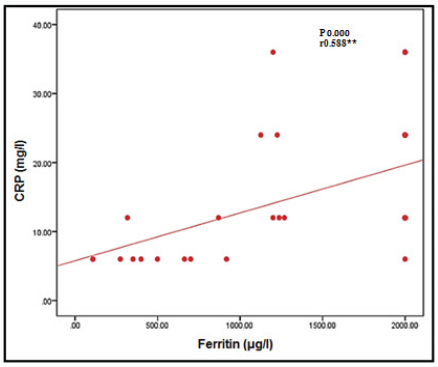

Figure 5: Positive correlation between ferritin level and CRP serum level.

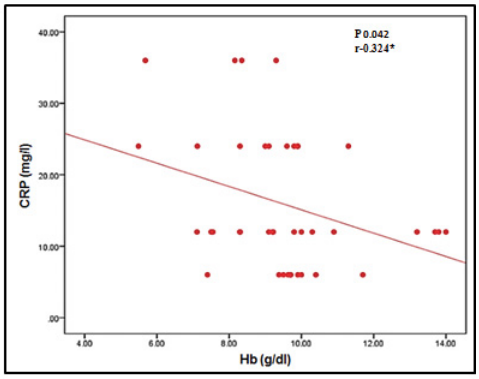

Figure 6: Negative correlation between CRP serum level and hemoglobin.

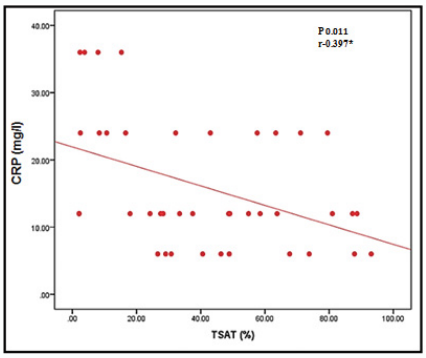

Figure 7: Negative correlation between CRP serum level transferrin saturation.

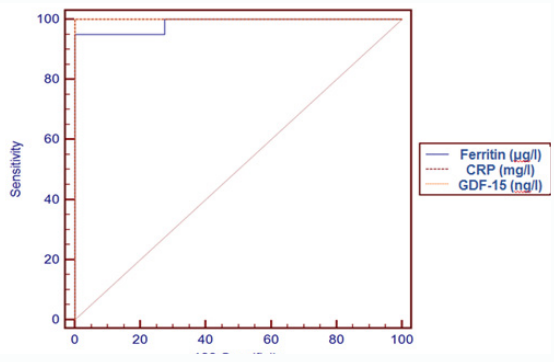

Figure 8: Sensitivity and specificity of serum ferritin, CRP, and GDF15 as a markers of inflammation in children with CKD on hemodialysis.

Table 3 and Figure 8: show the sensitivity and specificity of CRP, GDF 15, and serum ferritin as markers of inflammation in children with CKD on hemodialysis.

Discussion

Previous studies have reported an important link between elevated GDF-15 concentrations and cardiovascular disease but there is no a lot of studies that are concerned to assess its relationship with anemia and iron parameters. In this study, the hypothesis is that there is a relation between anemia and iron profiles with CRP and GDF-15 as a marker of the inflammatory state, we found that serum levels of GDF-15 are significantly elevated in children on regular hemodialysis than their controls and that serum GDF-15 levels are strongly correlated to CRP serum levels. Growth Differentiation Factor-15 (GDF-15) is a member of the TGF-β cytokine super family whose expression is increased in response to tissue ischemia, neuro hormones, and other proinflammatory cytokines [8,9]. Growth Differentiation Factor-15 (GDF-15), an anti-inflammatory cytokine, has been suggested as a significant regulator of hepcidin [10]. Oxidative stress and inflammatory conditions can stimulate secretion of GDF-15 by macrophages [11].

Bargenda et al. [12] reported significantly increased GDF15 in children on hemodialysis than their control group. GDF15 is a product of macrophages activated by proinflammatory cytokines that present in excess in chronic kidney disease and increase after HD sessions, most probably triggered by the direct contact of circulating cells with the dialyzer membrane. Breit et al. [13], Li et al. [5] and Yilmaz et al. [7] reported a similar finding. Interestingly CRP induces GDF15 expression through the regulation of p53 binding sites in the GDF15 promoter and they are also relevant markers of inflammation [14].

In the present study, functional iron deficiency was defined as ferritin above 200 ng/ml with transferrin saturation (TSAT %) below 20% [15,16].

We reported that the anemia in the hemodialysis group was 87.5% and the patients with FID were 31.4%. Renal anemia has been regarded as a special form of 'anemia of chronic disease, iron deficiency stands out among the mechanisms contributing to the impaired erythropoiesis in the setting of reduced kidney function. Iron deficiency plays a significant role in anemia in CKD. This may be due to a true paucity of iron stores (absolute iron deficiency) or a relative (functional) deficiency which prevents the use of available iron stores [17].

Serum GDF-15 was elevated in the FID group but not reached to be of significant difference of nonfunctional iron deficiency meanwhile CRP has significantly increased. Yilmaz et al. [18] documented that the serum level of GDF15 in HD patients who have functional iron deficiency has increased significantly compared to other groups.

Serum GDF-15 levels are elevated in disorders of ineffective erythropoiesis such as thalassemia [19], and GDF-15 is a possible mediator of anemia through hepcidin in adult renal transplant recipients [20].

Table 3: Specificity and sensitivity of ferritin, CRP, and GDF15 as a markers of inflammation in children with CKD on hemodialysis.

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
Ferritin (µg/l)	>130	0.99	95	100	100	95
GDF15 (ng/l)	>650	1	100	100	100	100
CRP (mg/l)	>5.5	1	100	100	100	100

Hepcidin plays an important role in iron metabolism as it negatively regulates plasma iron levels by binding to ferroportin which induces the internalization of iron into the reticuloendothelial system. Hepcidin levels are elevated in kidney failure due to decreased renal clearance and inflammatory up regulation which results in reduced availability of plasma iron and anemia [21].

We found a strong correlation between plasma GDF-15 and serum ferritin that supports the relationship of GDF-15 to the inflammatory status this in addition to the relation to the CRP level, the cytokine blocks hepcidin expression and increases iron absorption, thus leading to iron loading in these anemias [22], but hepcidin levels were not measured in our study patients group. .Besides, in response to anemia, erythroblasts secretes GDF-15, which in turn suppresses hepcidin expression and decrease iron stores [23].

GDF-15 seems to have both protective and adverse effects depending on the state of the cells and the microenvironment [24]. Proinflammatory cytokines such as tumor necrosis factor or Interleukin 6 (IL-6) induce the mRNA expression of GDF15 in activated macrophages, which suggests that GDF15 could function as an autocrine inhibitor during the inflammatory response [11,25]. Subsequently, GDF15 was found to have broad activity, as indicated by the diversity of its nomenclature. Yilmaz et al. [7],Wang et al. [26], reported a significant correlation between GDF15 and serum ferritin but Li et al. [5], reported no significant correlation.

Unsurprisingly to find a strong negative correlation between CRP and Hb, serum CRP and hemoglobin have a linear pattern as the overproduction of CRP inhibit hepatic production of albumin and transferrin which affects iron transport to the hematopoietic sites and leads to lower hemoglobin synthesis as well as hyporesponsiveness to ESA [27].

Also, we found a strong positive correlation between CRP and serum ferritin levels. Ferritin serves as the depot site for iron storage during sequestration responses elicited by inflammatory response inflammatory cytokines regulate ferritin translation through an "acute phase box" in the 5′ region of its transcript [28,29].

Acute-phase proteins including ferritin, C-reactive protein (CRP), rise dramatically as part of the inflammatory response, mediated by increased expression of cytokines such as IL-6 [30]. CKD patients are prone to develop Functional Iron Deficiency (FID) due to the presence of persistent low-grade inflammation which induces Hepcidin and thereby mediates reticuloendothelial cell block.

On the other hand, Deira et al. [31], Beciragic et al. [32], Majoni et al. [33], and Garg et al. [34], were reported that no significant correlation between the serum levels of CRP and ferritin. From our results, the high ferritin levels associated with CRP and GDF-15 may clear the link between iron homeostasis and the inflammatory response through the acquired anemia of inflammation or chronic disease, and more extensive researches is still required to confirm our findings.

In our study, the diagnostic performance of GDF-15 is 100% sensitivity and specificity at a cut off > 650 ng/L as a marker of inflammation in children with CKD on hemodialysis was comparable to CRP and better than ferritin that is mostly elevated by iron overload associating CKD, qualifying GDF-15 as a surrogate marker of inflammatory status in CKD on HD that is directly linked to cardiovascular complications. Similar results were found by Bargenda

et al. [12], Malyszko et al. [20], Lajer et al. [35] and, Thorsteinsdottir et al. [36].

Conclusion

Our data suggest that GDF-15 is involved in orchestrating inflammatory response that may play an important role in anemia of children with end-stage renal disease. The results have demonstrated that persistent inflammation may contribute to the both iron and functional iron deficiency anemia and anti-cytokine treatment strategies in addition to hemodialysis modality is the future directions aiming at the treatment of inflammation-associated anemia and its subsequent complications.

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