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GDF-15 A potential Biomarker of Diabetic Nephropathy in Iraq Patients with Chronic Kidney Disease

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ABSTRACT

Growth differentiation factor-15 (GDF-15) expression increase exposure to tissue injury and has recently emerged as a useful biomarker for multiple diseases. This study is aimed at detecting serum GDF-15 in patients with chronic kidney disease (CKD) and assessing its value in the early diagnosis of diabetic nephropathy (DN). This cross-sectional study, involved a total of 60 patients with CKD aged 15-65 years, selected according to their albumin creatinine ratio (ACR): >30 mg/g (DN 42), and ACR <30 mg/g (without DN 18), patients were compared with 28 healthy participants. Serum GDF-15 level, hematological, and biochemical parameters were measured. In the DN group, levels of GDF-15, C-reactive protein (CRP), urea, and creatinine were significantly higher, while RBCs, Hb, and GFR were significantly lower ($p < 0.05$) in comparison with CKD non-DN group. GDF-15 was significantly negatively correlated with RBCs (R^2=0.548), Hb (R^2=0.559), and GFR (R^2=0.466), while it was positively associated with CRP (R^2=0.532). The receiver operating characteristic (ROC) curve to assess value of GDF-15 indicated AUC 87.7% ± 0.045 (95% CI 0.78–0.99, p<0.0001, 83.2-22.2% sensitivity and specificity). In multivariate analysis, GDF-15 is independently predictive for diagnosing DN (OR=1.01, 95% CI: 1.00-1.03, P=0.009). Furthermore, each of Hb, GFR, and CRP was found a predictor of GDF-15, (β_=-0.42, 2.35, and 0.26). In conclusion, GDF-15 represents a risk biomarker in CKD patients with DN with associated anaemia and inflammation more than in CKD without DN. Additionally, GDF-15 can be a predictive risk stratification factor for achieving the end stage of diabetic kidney disease.

Keywords: Diabetic nephropathy, GDF-15, CKD, Anemia CKD.

Introduction

Diabetic nephropathy (DN) is a frequent and severe microvascular complication of type II diabetes mellitus (T2DM), a 20%-40% end-stage renal disease (ESRD)-associated pathology, also known as diabetic kidney disease.[1,2] Two clinical modalities are primarily used to identify and diagnose DN: assessment of kidney function in terms of calculated glomerular filtration rate (GFR) and evaluation of kidney damage in terms of albuminuria.[3] Furthermore, a reduction in a diabetic patient's renal function is not necessarily followed in the clinic by increased albuminuria.[1] GDF-15 is a member of the TGF-β cytokine superfamily that is widely expressed in cardiomyocytes, adipocytes, macrophages, endothelial cells, and vascular smooth muscle cells and may reflect an early response protein induced after tissue injury.[4] Recent study of Gurley *et al*. found that glomerular injury, tubular damage, inflammatory processes and oxidative stress lead to the progression of DN.[5] However, study of Kim *et al*. documented that high expression of GDF-15 is associated with chronic inflammation, oxidative stress and damage to the tissue. GDF-15 has recently emerged as a biomarker for the prediction and diagnosis of progression in various diseases, such as cardiovascular and chronic inflammatory diseases.[6] The aim of this study, was to investigate GDF-15 in patients with CKD, and assess its association with hematological and biochemical parameters in a potential prediction of early detection of DN**.**

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Materials and Methods

Study population

The current study involved patients attending the kidney disease unit in Al-Sadder education hospitals with an existing diagnosis of CKD (n = 60). The inclusion criteria are; age > 15 years and the average glomerular filtration rate (eGFR) of 60/mL/min/1.75 m^2. Exclusion criteria include: clinically aggressive thrombosis; induced oncology disease, all patients with cardiovascular problems and cardiac failure; transfusions of blood within three months prior to the study and patients on immunosuppressive treatment. The study procedure was accepted by the Ethics Committee of the Kufa University Faculty of Sciences with approval number 4829. All patients were properly briefed and gave their consent for the study. At the time of registration, medical history as well as demographic information were collected.

Blood sample collection and laboratory testing

Blood samples were obtained from all participants in the morning. CKD was diagnosed based on a comprehensive diagnostic approach, including a nephrological and thorough examination of patients, but exclusively on an eGFR vital value of >60 mL/min/1.75 m^2 over more than 3 months. Hematological assays were conducted with EDTA and coagulated blood using fresh venous blood. Serum was centrifuged and kept frozen at -80°C, for further laboratory tests. Patients have been subdivided into two groups: with diabetic nephropathy (CKD-DN) group (n = 42 [70%]) and without diabetic nephropathy (CKD

Non-DN) group (n = 18 [30%]). To achieve standard ranges for the examined parameters, the control group was included in the analysis. The control group used in the study were healthy participants (n = 28) to achieve standard ranges for the analyzed parameters. RBC, hemoglobin, creatinine, urea, glucose and CRP, levels were examined at the hospital central laboratory using normal laboratory methods (automated system). Chronic kidney disease epidemiology (CKDEPI) calculation eGFR was determined using the new KDIGO instruction.[7] The technique of the sandwich enzyme immunoassay was used to measure GDF-15 (ELISA Kit, company Melson medical, China), and CRP (CRP Elisa Kit- company Melson medical, China).

Statistical analysis

Data with normal distribution were defined as mean ± standard deviation (SD) and not normally distributed data as median and interquartile range (IQR). Independent t-test or Mann-Whitney U tests were used to compare continuous variables among DN-CKD and CKD Non-DN groups. Correlation analysis of each parameter was conducted using Pearson or Spearman rank correlation coefficients. A receiver operator characteristic curve (ROC) with an area under the curve (AUC) was then applied to identify the predictive value of GDF-15 for DN among CKD patients. Multiple regression analysis was used to classify independent factors influencing the dependent variables. Factors demonstrating a linear association with GDF-15 ($P < 0.05$) were included in the study. All statistical analyses were performed using SPSS V.24 (Inc., Chicago, IL, USA) computer software.

Results and Discussion

Demographic of the clinical characteristics of CKD patients in comparison with the healthy group

Table 1shows the general characteristics of 60 patients with CKD, and 28 healthy participants as a control group. There was no significant difference ($P > 0.05$) in the mean age of patients with CKD (42.43 ± 14.03 years) when compared with the mean age of healthy groups (40.07 ± 15.13 years). Each category of CKD patients can be identified approximately by hematological and biochemical parameters. The results revealed a significant ($P<0.05$) decrease in the mean levels of RBCs, and HB, which were found to be 3.23 ± 0.58 (10^6/mm^3), and 10.70 ± 1.38 (g/dL) in CKD patients as compared to the healthy groups, 4.60 ± 0.46 (10^6/mm^3), and 12.08 ± 1.30 (g/dL), respectively. The median (IQR) of GFR was statistically significant with an observed decrease from 24.50 (16.00-45.75) in CKD patients as compared to the healthy control group: 99.00 (104-98.00 mL/min/1.73 m^2), while high significant values of Urea (177.92 ± 47.73 vs. 23.89 ± 7.26 mg/mL), and creatinine (7.52 ± 1.83 vs. 0.76 ± 0.10), and blood sugar (152.20±51.22 vs. 99.29±11.95 mg/mL), respectively. These were attributed to the higher significant ($P < 0.05$) increase in GDF15 and CRP levels of patients median IQR: 352.62 (135.44-1027.66), and 6.5 (5.00-8.40) in comparison with that of the healthy group: 70.00 (39.00-126.5), and 1.60 (0.91-1.98) mg/L, respectively.

Comparison of hematological and biochemical parameters between CKD patients with Diabetic Nephropathy (CKD – DN) and CKD Non-DN

The study population was divided into two groups: CKD-DN and CKD Non-DN, the characteristics of the two groups are reported in Table 2. There was a statistically significant decrease in the mean RBCs, Hb, ($p = 0.009$, and $p = 0.008$) in patients with DN-CKD when compared to those without DN-CKD group. In patients with DN-CKD, serum GDF-15 level was significantly higher ($p = 0.0001$) than in CKD Non-DN (Figure 1). Also, mean ± SD of urea and creatinine were significantly ($P<0.05$), increased ($p=0.013$, and $p=0.003$), while GFR was decreased ($p=0.015$) in comparison to the patients without DN-CKD), respectively. Significant increase was observed in the level of CRP in CKD-DN: 4.62 (7.10-8.95) more than in CKD Non-DN group: 4.75 (3.23-6.08) ($p = 0.001$). As shown in Figure 2, ROC curve was used to assess the AUC of GDF-15 levels and to define the optimum cut-off value for the distinction between CKD with or without DN. The GDF-15 AUC was 87.7 ± 0.045% (95% CI 0.788–0.996, $p < 0.0001$). The optimal GDF-15 cut-off value that detected the presence of CKD was 307.4 ng/mL (83.2% sensitivity and 22.2% specificity).

Each category of CKD patients can be identified usually by haematological and biochemical parameters which serve as good indicators in health and disease states. The results revealed a significant decrease in the mean levels of RBC_S and Hb which were found in CKD patients as compared to the healthy group. These were in accordance with a previous study that was done by Mishra *et al.*[8] where they found changes in haematological parameter and a significant decrease in RBCs, Hb, and platelet count in all CKD patients when compared to the control group. Furthermore, they noticed the fall in RBC count in the stage of CKD progression which was significant. The lower RBCs count and Hb in CKD patients may be associated with impaired kidney function or disorder of erythropoietin (EPO) synthesis in bone marrow, thus causing anaemia. EPO is a hormone released from the kidney, it acts on erythroid progenitor cells in the bone marrow regulating iron metabolism and differentiation leading to increased production of RBC.[9,10] Other studies suggest that anaemia is particularly frequent among patients with progressive CKD due to many causes such as reduced erythropoietin production, increased uremic toxins effects of erythropoiesis inhibition, shortened RBC lifespan, disorder in malnutrition, deficiency in iron, vitamin B12, folate metabolism, and blood losses during haemodialysis sessions.[11–13] The study has found a significant difference in many parameters of CKD patients such as GFR (mL/min/1.73 m^2), Urea (mg/mL), Creatinine (mg/mL), as compared with healthy groups. These observations were in agreement with many studies which indicated that GFR and proteinuria-albuminuria are the kidney functional parameters currently used to evaluate CKD severity.[14] There is a significantly high levels of some biochemical parameters like urea, creatinine, in serum of ESRD patients on haemodialysis pre-dialysis. This is due to a decline in the number of nephrons.[15,16] This increase in urea and creatinine level occurs because in CKD patients the kidney loses its ability to eliminate nitrogenous wastes from the blood which results in the accumulation of these substances in the blood. Creatinine is a result of muscle metabolism and its elevated level in blood indicates kidney disease.

Association of GDF-15 with the haematological and biochemical parameters among CKD patients

Table 3 shows serum GDF-15 levels associations with haematological and biochemical parameters, estimated in CKD-DN and CKD Non-DN. The results of the Multiple Linear Regression analysis in DN CKD group show that GDF-15 levels were significantly negatively associated with GFR ($\beta = -2.353$, $R^2 = 0.46$, $p = 0.026$), RBC ($\beta = -0.20$, $R^2=0.548$, $p=0.037$), and Hb ($\beta = -0.42$, $R^2 = 0.559$, $p = 0.003$), (Table 3 and Figure 3A, B and C). Also, GDF-15 tended toward positive significance correlation with CRP ($\beta = 0.26$, $R^2 = 0.532$, $p = 0.032$), (Table 3 and Figure 2D). Urea ($p = 0.415$) and Creatinine ($p = 0.934$) were found not to be correlated with GDF-15. Furthermore, in CKD Non-DN group, GDF-15 was not associated with all these parameters.

GDF-15 is a risk factor in CKD patients with diabetic nephropathy (CKD-DN)

The GDF-15 was a more predictive value for diagnosing DN among CKD patients (OR=1.016, 95% CI: 1.00-1.03, $P = 0.009$) than Urea, Creatinine, GFR, and CRP (Table 4).

In the current study, we explored the association between plasma GDF-15 levels and kidney function in CKD. The principal findings are that after adjusting the other studied parameters, GDF-15 shows an independently predictive factor in CKD and was negatively correlated with GFR. GDF-15 was negatively associated with RBCs and Hb, while positively associated with CRP level; and the rise in GDF-15

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was strongly associated with the existence of diabetic nephropathy in CKD.

Our study showed that CKD patients exhibit high significance ($p<0.05$) increase in serum GDF-15 levels when compared with the healthy individuals (Table 1), This agreed with the study of Kim *et al*.[6] which showed that plasma GDF-15 may be a potential clinical biomarker for kidney dysfunction in old patients. GDF15 or macrophage inhibitory cytokine-1 (MIC-1), a superfamily of transforming growth factor-β (TGF-*β*) is generally expressed in adult tissues in response to tissue ischemia, neurohormones, and other proinflammatory cytokines.[17] It was shown as a useful prognostic and predictive biomarker for cardiovascular and coronary diseases.[18] However, GDF-15 studies are conducted in other diseases such as diabetic complications, inflammatory conditions and tumors.[19,20] Few studies have described the association of GDF-15 levels with progression of kidney dysfunction. A Study of Nair *et al*. [21] found that the intrarenal expression of GDF15 in the tubulointerstitial cavity of CKD patients is reflected in the serum levels of GDF-15, these are significantly correlated with the progression of the disease, as described by a continuous decrease in eGFR or a cumulative endpoint of 30% in eGFR or progression to ESRD, irrespective of many risk factors for kidney disease progression. These results indicate that GDF-15 may well be a risk factor and consequently a biomarker for CKD but also a strong participant in the kidney disease pathway. The results in the current study demonstrated that CKD patients with DN 42 (70%) have higher significant serum GDF15 levels compared to Non-DN patients 18 (30%) (P=0.0001), and correlated independently with DN, positively correlated with CRP, but negatively correlated with GFR (mL/min/1.73 m^2), RBCs and Hb, findings that are compatible with previous research.[22–24] Kempf *et al*.[22] indicated that GDF-15 was related to insulin tolerance and independently correlated with the possible production of disorder in glucose regulation. Many researchers have shown that increased GDF-15 in overweight patients is further increased by diabetic mellitus type II.[25]
More recently, these changes have been reported to reflect both CVD and renal disturbances, inflammation and other pathophysiological processes.[26] A Study of Carlsson *et al*.[19] confirms that serum GDF-15 level is associated with both micro- and macro-vascular disease in patients with DMT2, and discovered new pathways leading to diabetic kidney disease. Recently, Ham *et al*., [27] found that increased GDF-15 was directly associated with a high risk of progression of kidney disease as identified as a 30% decline in eGFR or progressing ESRD, even after Idiopathic Membranous Nephropathy has accounted for potential risk factors. Other previous studies established that high serum GDF-15 was significantly correlated with a faster decrease in kidney function in patients with DMT2, IgA nephropathy, and different stage of CKD.[21,28] In a study with CKD patients, plasma GDF-15 had a significant positive correlation with GDF-15 mRNA expression in the kidneys.[21] These results recommend that kidney injury may raise serum GDF-15, and increased GDF-15 helps to protect against renal injury and imply more chronic kidney injury. Even though GDF-15 protects against renal injury, high GDF-15 is associated with severe renal injury and poor prognosis of renal disease.[29] Diabetic kidney disease leads to as many as half of all ESRD cases worldwide and is one of the most significant risk factors for CVD in diabetic patients. It was based on evaluation of both kidney function and kidney injury and is categorized by approximately GFR of less than 60 mg/mL/1.73 m^2 and/or micro-o r macro-albuminuria in diabetic patients.[30] Anaemia is a common feature of many patients with CKD and is associated with reduced quality of life. Pathogenetic mechanisms of anaemia in CKD include; reduced production of erythropoietin and reticuloendothelial iron invasion caused by chronic renal inflammation.[31] Serum GDF-15 levels are elevated in disorders of ineffective erythropoiesis such as thalassemia and GDF-15 are a possible mediator of anaemia through hepcidin in adult renal transplant recipients.[32] We found strong correlation between serum GDF-15 and hemoglobin which supported the relationship of GDF-15 to erythropoiesis, but hepcidin levels were not measured in our patients. Haemoglobin and GFR are interrelated in CKD and our study revealed haemoglobin and GFR to be equally strong predictors of plasma GDF-15. Meanwhile, many other studies showed a positive correlation between GDF-15 and inflammation markers IL-6 and Highly sensitive C-reactive protein (hsCRP) in ESRD irrespective of age. Interestingly, there is a significant relationship between increase in CKD patients and anaemia.[23,3 3] It may indicate ineffective erythropoiesis and increased erythroid activity.[32] According to this study, patients ≥ 65 years of age and with anaemic status had increased serum concentrations of GDF15, which in themselves were correlated with hemoglobin and glomerular filtration. In addition, hemoglobin was described as a potential predictor of GDF15.[34]

Table 1: Demographic of the clinical characteristics of CKD patients in comparison with the healthy groups

Parameters	**Total CKD Patients N = 60**	**Healthy N = 28**	**p-value**
Age (year) Mean ± SD	42.43 ± 14.03	40.07 ± 15.13	0.476
Duration (month) Median (IQR)	24.00 * (8.00-24.00)	0.00	0.0001
RBCs (10^6/mm^3) Mean ± SD	3.23 ± 0.58 *	4.60 ± 0.46	0.0001
Hb (g/dL) Mean ± SD	10.70 ± 1.38 *	12.08 ± 1.30	0.0001
B. sugar (mg/dL) Mean ± SD	152.20 ± 51.22 *	99.29 ± 11.95	0.0001
GFR (mL/min/1.73m2) Median (IQR)	24.50 * (16.00-45.75)	99.00 (104-98.00)	0.0001
Urea (mg/dL) Mean ± SD	177.92 ± 47.73 *	23.89 ± 7.26	0.0001
Creatinine (mg/dL) Mean ± SD	7.52 ± 1.83 *	0.76 ± 0.10	0.0001
GDF15 (ng/mL) Median (IQR)	352.62 * (135.44-1027.66)	70.00 (126.5-39.00)	0.0001
CRP (mg/L) Median (IQR)	6.50 * (5.00-8.40)	1.60 (0.91-1.98)	0.0001

*Significant differences at p-value <0.05. IQR: inter quarter range, GDF-15: Growth differentiation factor-15, GFR: glomerular filtration rate, CRP: C-reactive protein.

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Table 2: Haematological and biochemical parameters in CKD patients with diabetic nephropathy (CKD-DN) compared with CKD patients without DN (CKD Non-DN)

Parameters	CKD Non- DN N = 18 (30%)	CKD-DN N = 42 (70%)	Z	p- value
Age (year) Mean ± SD	44.00 ± 15.50	41.57 ± 13.19	-0.971	0.332
RBCs (10^6/mm^3) Mean ± SD	3.53 ± 0.64	3.11 ± 0.51 *	-2.617	0.009
Hb (g/dL) Mean ± SD	11.41 ± 1.16	10.40 ± 1.36 *	-2.546	0.008
B. sugar (mg/dL) Median (IQR)	97.50 (69.00-114.50)	166.00 * (152.75-189.50)	-6.099	0.0001
GFR (mL/min/1.73 m2) Median (IQR)	26.50 (22.75-56.25)	19.00 * (13.75-38.50	-2.421	0.015
Urea (mg/dL) Mean ± SD	154.89 ± 39.09	187.81 ± 48.06 *	-2.356	0.013
Creatinine (mg/dL) Mean ± SD	6.47 ± 1.18	7.98 ± 1.89 *	-2.875	0.003
GDF15 (ng/mL) Median (IQR)	143.32 (117.73-267.91)	779.58 * (185.42-1161.77)	-3.565	0.0001
CRP (mg/L) Median (IQR)	4.75 (3.23-6.08)	4.62 * (7.10-8.95)	-3.244	0.001

*significant difference at p-value <0.05. IQR: inter quarter range, Z: standard distribution, B. sugar: blood sugar, Hb: hemoglobin, GFR: glomerular filtration rate, CRP: C-reactive protein.

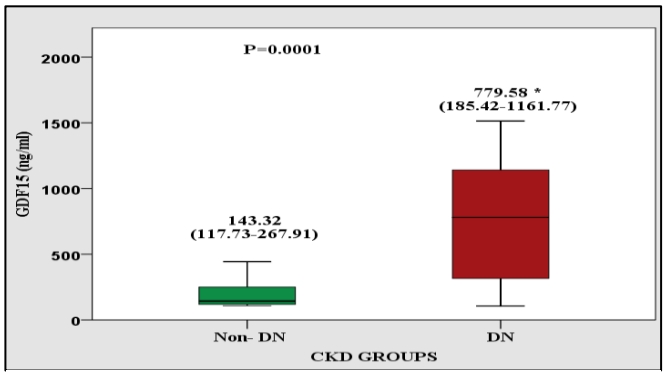

Figure 1: Serum level of GDF-15 in CKD patients with or without Diabetic Nephropathy. *significant differences at p < 0.05, DN: Diabetic Nephropathy

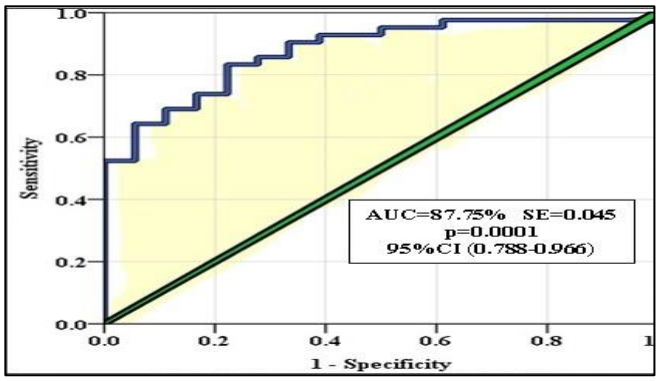

Figure 2: ROC curves of GDF-15 for CKD in Diabetic Nephropathy. ROC: receiver operating characteristic; AUC: area under the curve.

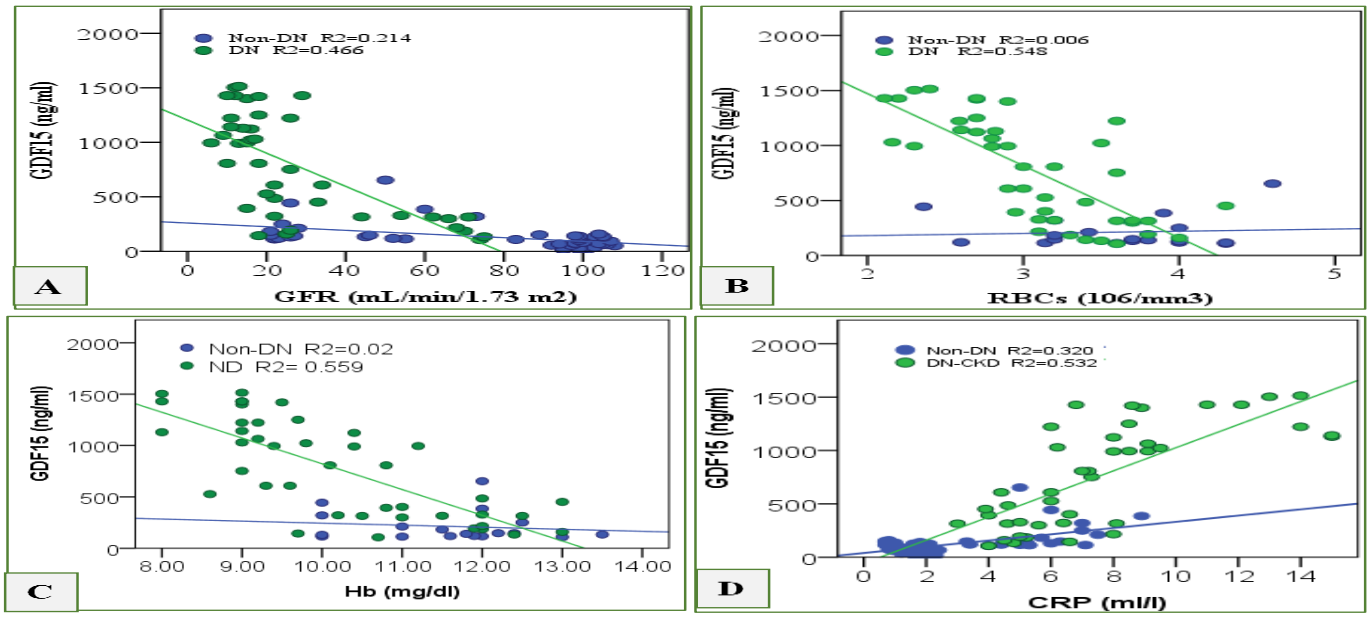

Figure 3: Correlation of GDF-15 with studied parameters among CKD patients. **A:** Positively correlated with CRP (R^2=0.532). **B:** Negatively correlated with GFR (R^2=0.466). **C:** Negative correlated with Hb (R^2=0.559). **D:** Negative correlated with RBCs (R^2=0.548). All these were in the DN group, there were no association in the Non-DN group.

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Table 3: Multiple Linear Regression of log GDF-15 among CKD patients for the prediction of Independent factor in DN-CKD and Non DN-CKD

		Coefficients β	Std. Error	p-value	95.0% CI
CKD Non-DN N = 18 (30%)	(Constant)		497.99	0.045	29.31 to 2221.46
	RBCs (10^6/mm^3)	- 0.39	65.18	0.128	-250.87 to 36.04
	Hb (g/dL)	-0.38	40.02	0.251	-136.55 to 39.62
	GFR (mL/min/1.73 m^2)	0.04	1.36	0.831	-2.70 to 3.29
	Urea (mg/dl)	0.01	0.57	0.943	-1.20 to 1.29
	Creatinine (mg/dL)	-0.11	20.63	0.517	-59.21 to 31.59
	CRP (mg/L)	0.24	21.45	0.289	-23.29 to 71.13
CKD-DN N = 42 (70%)	(Constant)		567.61	0.000	1271.87 to 576.49
	RBCs (10^6/mm^3)	-0.20	95.81	0.037	-375.62 to -13.41
	Hb (g/dL)	-0.42	43.81	0.003	-226.60 to -48.73
	GFR (mL/min/1.73 m^2)	2.353	-0.228	0.026	-9.90 to -0.35
	Urea (mg/dL)	0.06	0.76	0.415	-0.91 to 2.16
	Creatinine (mg/dL)	-0.01	21.10	0.934	-44.61 to 41.07
	CRP (mg/L)	0.26	16.83	0.032	3.33 to 71.65

Data are Represented as β-coefficient, 95% CI: confidence interval and adjusted-R^2. Dependent variable: GDF15 (ng/mL). Model 1 = Enter

Table 4: Predictors of diabetic nephropathy with Independent risk factor biomarker among CKD patients

Model [a] 1	Std. Error	Wald	OR	95% C.I. for OR	p-value
Log GDF15 (ng/mL)	0.006	6.824	1.016	1.00 to 1.03	0.009
RBCs (10^6/mm^3)	1.377	0.089	0.662	0.04 to 9.85	0.765
Hb (g/dL)	0.703	0.525	1.664	0.42 to 6.60	0.469
GFR (mL/min/1.73 m^2)	0.027	1.272	1.031	0.98 to 1.09	0.259
Urea (mg/dL)	0.012	3.075	1.020	1.00 to 1.04	0.080
Creatinine (mg/dL)	0.412	3.679	2.204	0.98 to 4.94	0.055
CRP (mg/L)	0.505	1.891	0.499	0.19 to 1.34	0.169
Constant	9.216	2.759	0.000		0.097

[a] Variable (s) entered on model 1: GDF15 (ng/mL), CRP, RBC2, Hb, GFR, urea, creatinine, OR: Odds Ratio, 95% C.I: confidence interval

Conclusion

Our study indicates that GDF-15 represents a novel risk biomarker in CKD patients with diabetes nephropathy (DN) associated with anaemia and inflammation more than in CKD without DN. Additionally, GDF-15 can be a predictive risk stratification factor for achieving the end stage of diabetic kidney disease. Further understanding of the signaling pathways and the pathophysiological function of GDF-15 may help to discover the interesting role of GDF-15 in CKD.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby assert that the work presented in this Article is original and that they shall be liable for any claims relating to the content of this article.

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