THE CONCENTRATION OF GDF-15 IS RELATED WITH THE INCIDENCE OF HEART FAILURE

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Abstract: Background: Chronic renal failure (CRF) frequently involves anemia, which is linked to a lower standard of living as well as a higher risk to morbidity and mortality. The current study's objectives were to examine early CKD prediction and diagnostic, estimate a few biochemical indicators, and determine the relationship between Haemoglobin concentration, renal function testing, and GDF. Materials and methods: A total of 60 cases, including 20 controls and 40 patients with Chronic renal failure (CRF), have been examined in this study. This age group of the patients was 25 to 65. Age, Body Mass (BMI), Bones Hematological Parameter, and Kidney Function Test (urea and creatinine) are calculated for the study patients. The research also measured total GDF levels inside the CKD patient and control groups. Result: When patients with CKD are compared to controls, the study's findings show a significant decline in hematological characteristics (Hb, RBC, and GFR). In contrast to controls, individuals in CKD had statistically significant increases (p 0.05) in their serum concentrations of urea and creatinine. When compared to the healthy control group, the results revealed a significant rise in GDF in CKD patients. This biomarker also exhibited a positive correlation with BMI and a negative correlation with Hb and GFR in CKD patients. Conclusions: Our investigation came to the conclusion that there was strong evidence linking CKD and anemia. Increased circulating GDF-15 concentrations were associated with higher mortality in adults with CKD. A higher rate of heart failure was likewise associated with elevated GDF-15 levels. The mechanisms linking these circulating biomarkers to cardiovascular disease in CKD patients require further investigation. This GDF is adversely regulated by hemoglobin. Therefore, there is a link among GDF15 concentrations as well as the likelihood of anemia in CKD patients. In CKD patients, there is a favorable connection between GDF and BMI. Therefore, a rise in BMI is a significant risk factor for the development of chronic renal disease. As there is a strong clinical correlation among GDF with renal problems, In CKD patients, GDF and GFR are negatively correlated. Early renal illness causes an increase in GDF, and anemia caused by a drop in Hb causes anemia. The GDF is a good biomarker for predicting kidney disease and anemia at the outset of the disease, as a result of what we have suggested.

Keywords: CKD, Chronic kidney disease, CRF, Chronic renal failure, BMI, Growth differentiation factor 15, GDF

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INTRODUCTION

A existence of the an impairment in kidney structure or function that persists for more than three months is called chronic kidney disease structure or function that lasts longer than three months is referred to as chronic kidney disease [1-2]. One or more of the following are included in this: GFR less than 60 mL/min/1.73 m2, albuminuria (urinary albumin 30 mg/24 hours or urine albumin-to-creatinine ratio [ACR] 30 mg/g), urinary sediment, histological, or imaging abnormalities suggest Kidney damage, renal tubular disease, or a history of kidney transplantation are all signs that one or more of the above conditions apply to you. 5 Repeat evaluations should be done to distinguish chronic kidney disease (CKD) from acute renal injury (change in kidney function occurring within 2–7 days) or acute kidney disease if the length of kidney failure is unclear (kidney damage or decreased kidney function present for 3 months) 25 The clinical history, physical examination, and urine results of the a patient should serve as the basis for determining the cause of CKD [3-4]. Anemia is a frequent side effect of Chronic renal failure (CRF), which is linked to a lower quality of life as well as a higher risk of mortality rates. The processes underlying anemia linked to CKD are numerous and intricate [5] even though erythropoietin is relatively deficient Iron deficiency stands out among the mechanisms causing the defective erythropoiesis in the context of decreased renal function. Production is the primary cause of anemia in CKD. Anemia in CKD is significantly influenced by iron shortage. A actual lack of iron stores (absolute iron insufficiency) or a relative (functional) shortage that hinders the utilisation of the iron stores that are there could be to blame for this. Absolute and functional iron deficiency in CKD is caused by a number of risk factors, including as chronic inflammation, poor iron absorption, and blood losses [6].

MATERIALS AND METHODS

The investigation was carried out at the Al-Kafel Hospital's Artificial Kidney Unit in the Karbala province. We looked at a total of 60 cases, including 20 controls and 40 patients with Chronic renal failure (CRF)

Study Design

All study participants did not smoke and did not have hepatitis when their samples were analyzed; they were all chronic renal failure patients receiving hemodialysis treatment. Ages of the patients range from (25-65 years).

Blood Sample

Five milliliters of blood were taken from a vein using sterile synergies. Sample placed in tube with label. Blood was centrifuged at 6000 rpm for 15 minutes after being left at room temperature for 10 minutes to allow for clotting, after which the serum was extracted and frozen at -80 oC until the laboratory analysis for the study could be completed.

Body Mass Index (BMI)

Weakly dressed patients' weights and lengths were measured. BMI was estimated using a reliable digital weight and length measurement technique by dividing the subject's weight in kilograms by the square of their height in meters, as in the formula: BMI = kilograms / height (meters)2. Sahu et al., (2007).

Assessment of Complete Blood Count (CBC)

In the haematology laboratory, a CBC was performed on anticoagulant blood from Ringelsn County, Turkey.

Biochemical parameters

Blood urea concentration determination

Its serum uric acid concentration was determined using a colorimetric technique. The French company Biolabo SA provided a specialized kit for testing human urea levels in serum.

Determine serum creatinine levels

The serum creatinine concentration was assessed using a colorimetric technique. Creatinine concentration in serum was provided by Biolabo SA, France.

GDF-15 concentration

ELISA, an enzyme-linked immunosorbent assay, was used to measure the serum levels of GDF-15 in accordance with the preparation obtained from Elabscience, China.

Statistical Analysis

Through use of the Spss program, the statistical analysis was carried out with a significant P>0.05 (SPSS version 23). The t-test was used to compare the two groups, and multivariate ANOVA was used to compare the groups that were divided based on the parameters that were measured.

RESULTS

Demographic Characteristics of study subject

A total of 60 cases were examined in this study, including 40 patients with chronic kidney disease (CKD) and 20 controls. As shown in table (1), the age of the patients was between 25 and 65 years old. As illustrated in same table, there is nonsignificantly difference in BMI in patients with CKD (25.35±1.4797) when comparison to control. The result of figure (1), represented the percentage distribution of BMI of the patients with 11% underweight, normal weight 56% of the participants and about 33% suffered from obesity.

Table 1. Comparison of the clinical characteristics between patients with CKD and control groups

Clinical characteristics	Mean ± SE	
	Patient N=40	Control N=20
Age (year)	53.5±3.047	* 21.2 ±.663
BMI (kg/m2)	25.35±1.479751	21.895± 1.8

* P< 0.05 statistically significant with control group

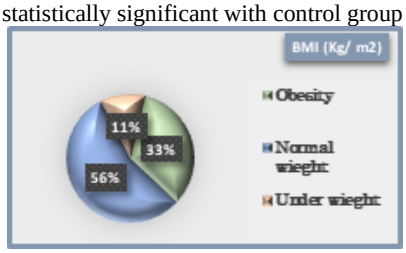

Figure 1. BMI (kg/m2) in patient with CKD

Hematological Characteristics of study subject

As shown in figures (2) and (3) there is significant decrease in (hematological characteristic) Hb, and RBC in patients with CKD in comparison to healthy group.

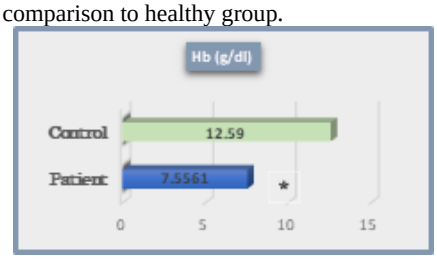

Figure 2. Comparison of the Hemoglobin (g/dl) between Groups of Patients with CKD and healthy group

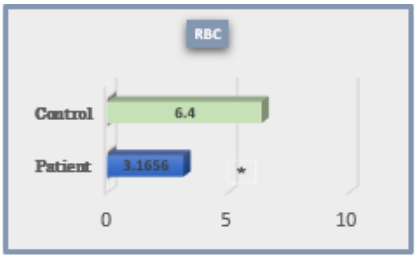

Figure 3. Comparison of the RBC count between Groups of Patients with CKD and healthy group

Kidney function test of study subject

Figures (4) and (5), show the kidney function test levels between the studied groups. As illustrated in these figures, there is significant increases in levels of urea and creatinine in patients connected with CKD in comparison with control.

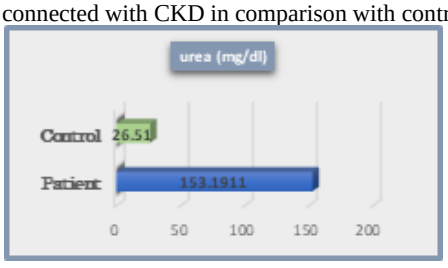

Figure 4. Comparison of the urea (mg/dl) between Groups

of Patients with CKD and healthy group

* P< 0.05 statistically significant with control group

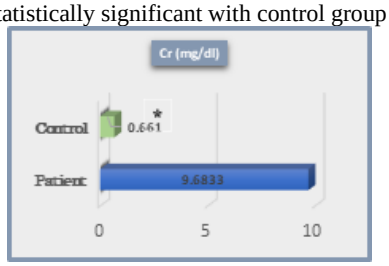

Figure 5. Comparison of the creatinine (mg/dl) between Groups of Patients with CKD and healthy group

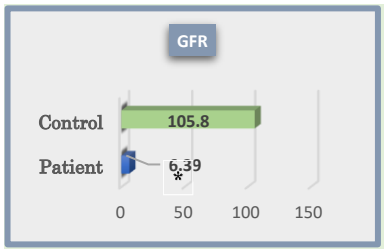

Figure 6. Comparison of the GFR between Groups of Patients with CKD and healthy group

Biomarker test of study subject

The figure (7) shows the specific biomarker test levels between the studied groups According to this figure there was a significant increase ($p<0.05$) of GDF15 level in patients with CKD comparison with healthy group.

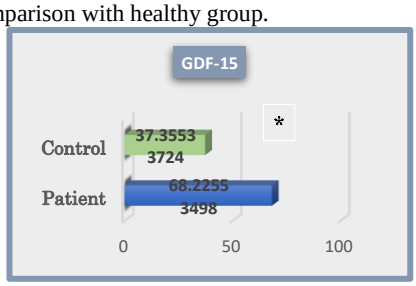

Figure 7. Comparison of the GDF (mg/dl) between Groups of Patients with CKD and healthy group

Correlation

Results of the correlation and linear regression among the Patients with CKD revealed in table (2), there was a significant positive correlation between GDF-15 and BMI of Patients with CKD, While the other result of same table indicated, there was a significant negative correlation between GDF-15 and (Hb concentrations, and GFR) of Patients with CKD.

Table 1. Correlation between the clinical characteristics and patients with CKD

GDF5	Correlations	BMI	AGE	S.CR	UREA	HB	RBC	GFR
	Pearson Correlation	0.447*	-0.199	0.384	0.217	-.549*	-0.039	-0.448*
	Sig. (2-tailed)	0.043	0.43	0.116	0.387	0.018	0.878	0.048

* Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

Figures (2) and (3) show that there is a significant drop in (hematological characteristic) Hb and RBC in CKD patients compared to the healthy group (3). These findings supported the findings of Almahdi and colleagues (2016), who discovered a significant drop in hemoglobin levels in Libyan CKD patients compared to the control group [7]. Our findings were supported by a recent study that discovered severe CKD patients in Nigeria had hemoglobin concentration and RBC counts that were significantly different from the healthy group [8-9]. Also, current study concurred with those of other studies [10]. Iyawe et al. (2018) discused that as renal failure increased, hemoglobin concentration decreased. (8) It has been demonstrated that the stage of CKD is highly correlated with the severity of anemia. This is in keeping with the observation that the Hb concentration decreases in direct proportion to the GFR drop, which is mostly brought on by the decreased erythropoietin synthesis. Iron deficiency may be a secondary cause of anemia in chronic renal disease [11-13]. Anemia is also brought on by a lack of folic acid, vitamin B12, and hyperparathyroidism [14]. The study's findings were consistent with those of the previous study, which indicated that patients' red blood cell counts were much lower than those of the control group [15]. Lack of kidney-produced erythropoietin, which suppresses erythropoiesis, is one of the main causes of a drop in RBC count [16]. Reduced RBC count and reduced RBC life spin were both caused by uremia, which also increased the expression of phosphatidylserine on the outer cell surface of red blood cells, which increased RBC destruction by macrophages and decreased cell survival [17]. According to Pietrement et al. (2013), CKD-related chronic urea elevation raises the rate at which plasma and tissue proteins are carbamylated [20]. This outcome was consistent with the findings of other investigations [18-19]. The gradual accumulation of "uremic toxins," or compounds typically discharged by the kidney, which sometimes have negative effects on several organs, is a hallmark of chronic kidney disease (CKD) [21-22]. Urea, the primary uremic metabolite, is typically thought to have very little toxicity. inclusion of urea traditional dialysis is well tolerated [23], and patient survival is unaffected by an increase in the urea reduction rate from 66% to 75% [24]. The discovery that daily dialysis and hemodiafiltration, which increase the clearance of uremic toxins including urea, improve longevity in CKD patients, calls into question the idea that urea is just a helpless bystander [25-26]. Additionally, there is mounting evidence of urea toxicity. Urea has been shown to have an effect on cellular processes both indirectly (by altering serum or tissue compounds) and directly (by increasing oxidative stress) [27], which reduces the tight junctions of intestinal cells and impairs adipocytes' ability to absorb glucose [28], as well as endothelial dysfunction [29-30]. Patients with CRF have an increased in urea and creatinine concentration because kidneys become less effective in removing nitrogenous wastes from the blood, which leads to an accumulation of these substance. Other factors, such as a rise in urea and creatinine from consuming too much protein, shock, gastrointestinal bleeding, etc., could also be to blame [31]. In this investigation, it was shown that patients'

hemoglobin concentrations were significantly lower than those of the control group. It is symptoms of anemia in CKD. Numerous investigations revealed that the most frequent side effect of advanced chronic renal illness was anemia. This outcome was in agreement with earlier research [32-34]. In a longterm study of generally healthy males, GFR, as estimated by urine creatinine clearance, decreased at a rate of approximately 0.75 ml/min year [35] Even among living kidney donors who have undergone comprehensive examination for excellent health, this aging-related reduction in GFR is still noticeable [36]. The same reduction in GFR with age is visible among isolated indigenous cultures with low incidence of cardiovascular disease [37].

According to the study's findings, patients with CKD have significantly higher levels of (GDF) than those in the healthy group. These results were in line with those reported by Nalado et al. in 2020 [38] who discovered that GDF-15 levels were considerably greater in CRF patients with IDA compared to CKD patients without IDA. These results were also in line with those reported by other researchers [39]. In their dialysis patients, Li et al., [40] found an increase in GDF-15 levels, but they were unable to demonstrate a connection between GDF-15 and iron indices finding that was similarly observed by our cohort of participants. Actually, there are a number of plausible mechanisms that could explain why IDA patients have high GDF-15 levels. Firstly, in CKD patients with iron insufficiency, elevated hepcidin levels may be suppressed by GDF-15, which rises as a key mediator in a negative feedback loop. Another theory is that iron sequestration in macrophages caused by iron deficiency could independently lead to Induction of GDF-15 in erythroid progenitor cells [41]. Our study supports the findings of Yilmaz et al., [39], who found that GDF-15 was a reliable indicator of functional IDA in CKD and haemodialysis patients. Patients with end-stage renal illness had much higher GDF15 levels than healthy people did, and GDF15 was closely related to the vintage of the dialysis solution [42] given its strong correlation with cardiovascular disease and overall mortality from all causes, it is not surprising that GDF15 was recommended as an independent serum marker of mortality in patients with chronic kidney disease (CKD) and hemodialysis [43-46]. Its expression is tightly controlled, and among other things, hypoxia, oxidative stress, and inflammation are among the conditions that frequently cause GDF15 to be activated [47]. It's interesting to note that GDF15 is expressed by the kidney itself in response to various insults, such as ischemia and toxic damage [48-49]. There are not many studies in people connecting GDF15 to kidney disease. According to Nair et al., the progression of CKD and tubulo-interstitial GDF15 expression are both linked with circulating GDF15 levels. Because it was discovered to be distinct from other risk factors, the authors hypothesize that GDF15 isn't just a risk factor but also plays a role in the development of CKD [50].

Additionally, the present study demonstrates a favorable connection between GDF and BMI in CKD. The only two biomarkers significantly elevated in obese patients were GDF15 and TG levels. We have been unable to show that TG and obesity had a comparable incremental response connection. The absence of a correlation among TG or blood sugar levels and GDF15 shows that these variables have no bearing on circulating GDF15 levels in obesity. This might suggest that morphological rather than metabolic changes in the patient are what are causing increased GDF15 and could be investigated further in disease-related experimental models. These results contradict some studies linking GDF15 to TG, HbA1c in type 2 diabetes, and older people [51-52]. Our research has some flaws. First, the cross-sectional study approach provides it challenging to draw conclusions about the relationship between Hb, GDF-15 levels, and the risk of anemia. Hepcidin has been linked to the anti-inflammatory cytokine Growth Differentiation Factor-15, which has been proposed as a key regulator of hepcidin [53]. Conditions of inflammation and oxidative stress can encourage macrophages to secrete GDF-15 [54]. Additionally, in anemic patients, a very strong positive correlation between hepcidin and GDF-15 has been noted [55]. A growing body of research suggests that erythroblasts produce GDF-15 in response to anemia [56], which in turn suppresses hepcidin production and lowers iron storage. Additionally, in anemic patients, a significant positive association between hepcidin and GDF-15 has been noted [55]. New research suggests that erythroblasts release GDF-15 in response to anemia [56], which reduces the production of hepcidin and lowers iron storage [57-58]. There is considerable debate around GDF-15's contribution to the development of IDA. Studies revealing a connection (or lack thereof) between blood iron parameters and GDF-15 expression in IDA patients, however, will help to clarify the examination, care, and observation of IDA in CKD patients [59]. A straightforward regression analysis revealed a GDF-15 and a negative connection levels and GFR as well as a clinically meaningful connection kidney disorders and GDF-15 levels. According to Kim et alresearch .'s from 2019 [60], Plasma GDF-15 levels were significantly greater in older CKD patients. and were inversely correlated with eGFR. According to our findings, plasma GDF-15 may serve as a valuable marker for identifying renal impairment in elderly individuals. In patients with IgA nephropathy, Ham et al. (1178) described comparable trends in patients with idiopathic membranous nephropathy, while Na et al., [61] shown that plasma GDF-15 has an inverse association with eGFR and is connected to poor renal outcomes. In type 1 diabetics with nephropathy, higher levels of GDF-15 predicted a speedier loss of renal function [62] and the need for dialysis in those with light chain amyloidosis [63]. The GDF-15 concentration closely corresponds with intrarenal expression of GDF-15 mRNA, as shown by Viji et al., [64], and higher GDF-15 is significantly linked to an renal function decline is more likely to occur in CKD patients. Although various theories have been put forth, it is still unknown how elevated GDF-15 levels might indicate the presence of renal problems and indicate how the disease will progress. Previous research has shown that GDF-15 levels rise following organ failure, particularly kidney impairment. According to Simonson et al., [65], proximal tubule damage in a mouse model is positively correlated with urine levels of GDF-15. In mouse models of kidney or lung injury, Zimmers et al., [66] showed that GDF-15 expression was induced, indicating the GDF-15 may be an early mediator of organ injury. GDF-15 loss inside a lipopolysaccharide-induced renal injury model exacerbates renal damage, according to Abulizi et al., [67]. Other researchers showed that the genetic deletion of GDF-15 worsened damage to the renal interstitium and and tubules in diabetic mice [68]. These results lead us to the conclusion that GDF-15 expression rises very early in renal injury to guard against tissue damage and can therefore predict disease by contrasting this rise with the severity of tissue harm. To fully comprehend the precise

underlying mechanisms at play, additional research is required.

CONCLUSIONS

Based on the findings of our investigation, a strong correlation exists between CKD and anemia. The study helps to clarify how anemia, defined as low hemoglobin along with elevated urea and creatinine levels, increases the risk of death in CKD patients. However, it is necessary to treat anemia. Mortality was higher in those with CKD and increased levels of GDF-15 in the blood. A higher rate of heart failure was likewise linked to elevated GDF-15 levels. The mechanisms relating these circulating biomarkers to CVD in CKD patients require more study. The GDF is adversely regulated by hemoglobin. Therefore, there is a link between GDF-15 levels and the likelihood of anemia in CKD patients. Additionally, in CRF patients, there is a favorable association between GDF and BMI. Therefore, a rise in BMI is a significant risk factor for the development of chronic renal failure. In CKD patients, there is a substantial clinical correlation between GDF and renal diseases, with a negative correlation shown between GDF and GFR. There is a strong clinical association between GDF and renal problems in CRF patients, with a negative correlation shown between GDF and GFR. Anemia caused by a drop in hemoglobin (Hb) and an increase in GDF in the early stages of kidney disease. The GDF is a good biomarker for predicting renal disease and anemia at the outset of the disease, as a result of what we have suggested.

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