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Research Article

GDF-15 As Prediction Biomarker for Cardiorenal Disease

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Abstract

Background: Cardiovascular disease (CVD) leading to renal dysfunction and vice-versa is termed as cardiorenal syndrome (CRS).
Objectives: The present study was designed to investigate early prediction and diagnosis of the CVD in addition to estimate some of biochemical markers and correlate between Hb concentration and kidney function test and GDF 15.
Methods: The study was conducted in General Hospitals Al Sader General Teaching n the province of Al-Najaf al-Ashraf. The population of this study consisted of 75 Iraqi adults who underwent health examinations between june to January 2023. Subjects ages younger than range between (42-80) years and those with a history of CVD. The study cases are determined the age, CBC, kidney function test (urea and creatinine) and (fasting glucose and random blood sugar) in patient with CVD. Also, this study determined the level of GDF in patient with CVD and control group.
Result: A total of 75 patients diagnosed as CVD admitted to our hospital were enrolled in the present study that consisting of 50 patients and 25 controls were examined. The median age was 59.92 $\pm$ 2.877 years; 100% were male, The result showed significant increase in hb and RBC 10^6/µl count, in patients with CVD comparison with healthy group. Patients with a higher level of WBC count were older, had a higher level of Neutrophil 10^3/µl, had a history of CVD (myocardial infarction and percutaneous coronary intervention or coronary artery); and had a higher rate of Creatinine (mg/dl), uremia, and hyperglycemia. Adults with CVD and higher circulating GDF-15 concentrations experienced greater mortality. Elevated GDF-15 concentration was also associated with an increased rate of heart failure. Further work is needed to elucidate the mechanisms linking these circulating biomarkers with CVD in patients with CKD. hemoglobin positively regulates the GDF. So that, there is relationship between GDF15 levels, and the risk of anemia in patient with kediny disease. GDF increase in early stage of cardiovascular disease that related to increase in Hb. So, that we suggested that the GDF is a good biomarker for predict the cardiovascular disease with high hb at disease onset.

1. Introduction

Recurrent worldwide non- transmissible cardiovascular disease (CVD) constitutes one of the biggest contributors of mortality worldwide suffering. Worldwide, occurrences related to CVD are increasing in frequency. The primary contributory factor of CVD is atherosclerosis [1]. The most common cause other mortality worldwide is still cardiovascular (CV) illnesses, which include peripheral artery disease (PAD), heart attack, ischemic coronary syndrome, stroke, and a host of other cardiac and vascular disorders [2].

Latest study has demonstrated that cardiac biomarkers are more accurate than algorithms relying just on conventional risk variables in predicting cardiovascular disease risk. 4,5 Before identified as macrophages detrimental cytokine 1 (MIC-1), development and differentiation factor 15 (GDF-15) serves as a distinct component of the transforming growth factor-2 β (TGF-β) relatives that has been linked to autoimmune conditions. explanations through an assortment of diseases, including malignancies and cardiovascular conditions [3–7].

Renal cardiovascular disease, often referred to simply as cardiovascular renal syndrome, serves as the main phrase for any disease about the cardiovascular system or kidneys which negatively affects another tissue and eventually results with a breakdown of both [8]. Immediate heart failure resulting in a reduction within the rates of glomerular filtration was a manifestation of the condition known as type 1 cardiorenal dysfunction. The past study has suggested that the primary root cause of poor kidney performance in cardiorenal syndromes subtypes two and two is a reduction in heart rate associated with lower perfusion of the kidneys.

Nevertheless, elevated cerebral arterial volumes may be an even more significant cause, according to new research [9]. Volumes overloading due to renal failure, aberrant ventricular activity in context of metabolic abnormalities (e.g., acidemia), and neurohormonal abnormalities associated with renal illness are heightened causes of categories of three and four cardiorenal disorders [10]. Individuals with infection, system-wide lupus erythematosus (SLE), diabetic mellitus, compensating a condition called with neuroblastoma are susceptible to type 5 cardiorenal illness; these conditions can all result in kidney as well as heart damage [11].

This research aimed to anticipate and identify cardiovascular disease (CVD) individuals who had developed CRS and to additionally calculate certain the biological indicators that can assist classify various types of CRS or suggest the start or efficacy of therapy.

2. Methods

2.1. Study population

At the region of El-Najaf el-Ashraf, the research was carried out at General Hospitals Al Sader General Teaching. The current study included 75 adult Iraqis who were examined for health issues throughout June 2023 and January 2023. Individuals lacking levels of hemoglobin, individuals having liver disease, and smokers were also eliminated, as was individuals with ages that fell within forty-two and eighty years old alongside those who had previous instances of CVD (ischemic coronary disease, congestive heart failure, ventricular arrhythmia or aortic aneurysm, and hemorrhage). Admitted to insurance questionnaires and information on health coverage reimbursements were used to gather the subjects' medical histories. Ultimately, a sample of 75 individuals, including twenty-five controls and 50 patients with cardiovascular disease (CvD), were analyzed.

2.2. Collection of Blood Sample

Blood samples were drawn from vein by sterilized synergies with 5 milliliters. The sample put in the labeled tube. Blood was left at room temperature for 10 minutes for clotting, centrifuged 6000 rpm for 15 minutes, and then serum was separated and freezing at -80 ºC until time for performed the laboratory analysis for study.

2.3. Laboratory analyse

Complete Blood Count (CBC)

During the medical examination upon entry into the cohort after June 2023, a blood sample was drawn of all subjects in an EDTA tube for measurement of the complete blood cell counts: Hb, RBC, WBC (total and subtypes) and platelet counts. The storage process of blood samples was described previously [12].

Kideny Fuction Test

Colorimetric method was used to determination of urea concentration in the serum Specific kit for measuring human urea and creatinine concentrations in serum was supplied by Biolabo SA, France.

Fasting And Random Blood Sugar

Colorimetric reaction was uesd to determine the concentration of fasting blood sugar in the serum. The level of fasting blood sugar in serum was supplied by Biolabo SA, France.

GDF-15 concentration

Concentration of GDF-15 was routinely measured by an established available enzyme linked immunosorbent assay kit. The detection limit was 400 ng/L, and the intra and inter-assay imprecisions were $< 0.9\%$ and $< 2.3\%$, respectively. All GDF-15 measurements were performed by investigators that were not aware of patients' characteristics and outcomes.

Statistical Analysis

The SPSS software was employed for statistically evaluating the data (SPSS, Version 26). The test for significance was employed, or descriptive calculations of averages or the standard deviation were performed comparing patients alongside the control subgroups. To determine the correlation among marker and factors, Pearson correlation coefficients were calculated. The data visualizations were created with the Microsoft Office 2016's EXELL implementation. Every one of these variables was statistically tested at $P<0.05$ significance.

3. Results

3.1. Patient characteristics

A total of 75 patients diagnosed as CVD admitted to our hospital were enrolled in the present study that consisting of 50 patients and 25 controls were examined. The median age was 59.92 ± 2.877 years; 100 % were male, the median Hb level was 14.538 ± 0.5362 g/dl and RBC 10^6/µl count 8.923 ± 0.6787. As illustrated in same table, there is nonsignificantly difference in Platelet 10^3/µl in patients with CvD (284.62 ± 21.361) when comparison to control. Patients with a higher level of WBC count were older, had a higher level of total cholesterol (Neutrophil 10^3/µl), had a history of CVD (myocardial infarction and percutaneous coronary intervention or coronary artery); and had a higher rate of Creatinine (mg/dl), uremia, and hyperglycemia. The baseline characteristics of the two groups were shown in Table 1.

Table 1: Baseline clinical and laboratory characteristics of the study patients and control

PARAMETERS	PATIENT (MEAN±SE)	CONTROL ((MEAN±SE)
Age (year)	59.92 ± 2.877*	21.6 ± 0.67
HB (g/dl)	14.538 ± 0.5362*	12.09 ± 0.3057
RBC 10^6 /µl	8.923 ± 0.6787*	5.1 ± 0.2413
Platelet 10^3 /µl	284.62 ± 21.361	276 ± 15.131
WBC 10^3 /µl	9.846 ± 0.71*	5.7 ± 0.2797
Neutrophil 10^3 /µl	73.415 ± 2.2252*	47.15 ± 1.7016
Lymphocyte 10^3 /µl	24.315 ± 2.2857	20.78 ± 0.9438
Urea (mg/dl)	44.554 ± 4.7648*	24.95 ± 0.9645
Creatinine (mg/dl)	1.2569 ± 0.15627*	0.581 ± 0.02238
RBS (mg/dl)	188.9546 ± 20.99516*	127.1 ± 2.31637
FG (mg/dl)	143.4615 ± 5.80408	69.1 ± 2.9229
GDF15	71.47624 ± 5.63173	39.16317 ± 7.785839

* P< 0.05 statistically significant with control group

3.2. GDF15 level

The figure 1 shown 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 CVD comparison with healthy group. The enrolled patients were divided into two groups upon the levels of serum Hb (G1: Hb <14 g/dl, G2: HB14–18 g/dl). The result represented the significant increase in GDF15 in this patients that suffered from high Hb compared to CVD patient with normal range of Hb.

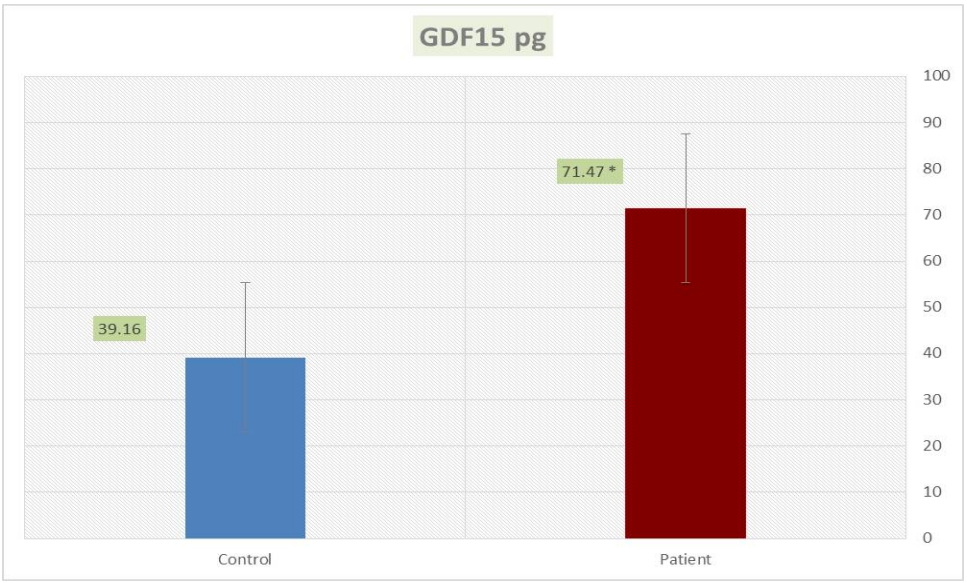

Figure 1: Comparison of the GDF 15 (pg) between Groups of Patients with CVD and healthy group

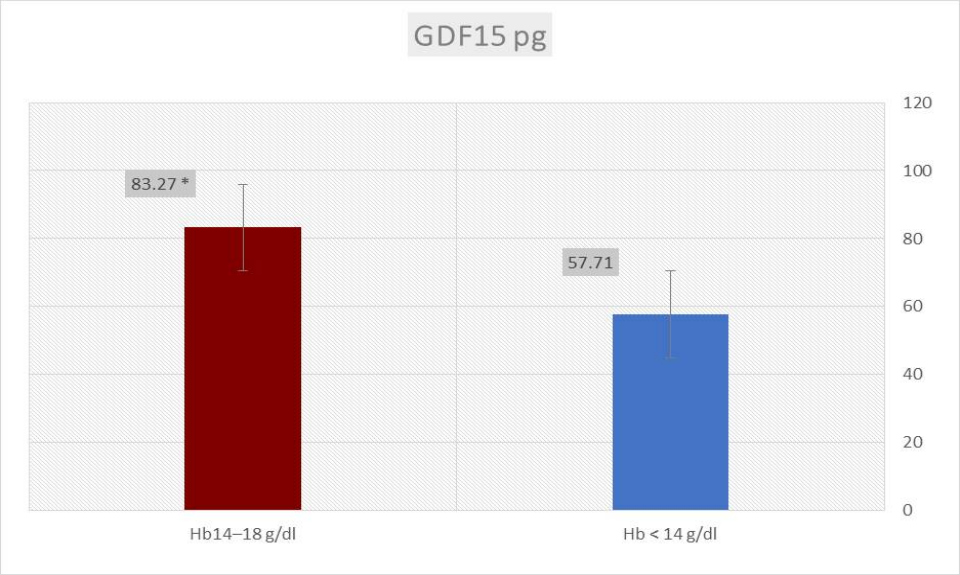

Figure 2: Comparison of the GDF 15 (pg) between two groups divided upon the levels of serum Hb

3.3. Correlations of serum GDF-15 levels with other clinical biochemical factors

Results of the association and linear regression among the Patients with CVD revealed in Table 2, Increasing levels of GDF-15 at presentation were associated with increased Hb, lymphocyte and hyperglycemia. By multiple regression analysis that included all patients' characteristics shown in Table 2, used the natural logarithm of GDF-15 as the dependent variable.

Table 2: Growth differentiation factor-15 is associated with Hb in patients with cardiovascular disease

Correlations	Pearson Correlation	P<0.05
Age (year)	0.42	0.152
HB (g/dl)	0.659 *	0.014
RBC 10^6 /µl	-0.281	0.352
Platelet 10^3 /µl	-0.218	0.474
WBC 10^3 /µl	-0.453	0.120
Neutrophil 10^3 /µl	-0.214	0.482
Lymphocyte 10^3 /µl	.561*	0.046
Urea (mg/dl)	0.404	0.170
Creatinine (mg/dl)	0.437	0.136
RBS (mg/dl)	.611*	0.026
FG (mg/dl)	0.484	0.094

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

4. Discussion

The results of the latest research, individuals with Cardiovascular had significantly higher levels of hemoglobin and Erythrocyte (hematopoietic characteristics) than those in the healthy group. High haemoglobin variation within everyone is associated with higher mortality from all causes [13]. Increased haemoglobin variation has been linked to an elevated likelihood of hypertensive within everyone, according to additional research [14]. Given that cardiovascular disease (CVD) is the primary cause worldwide of death [1] and that one of the primary indicators of risk for Cardiovascular is high blood pressure [15].

Subsequently seems sense to believe such increased haemoglobin fluctuation could possibly raise the likelihood from Cardiovascular. Actually, haemoglobin variation was a reflection Both the presence of inflammation as well as recurrent impoverished stressors, whose are believed to increase the possibility of cardiovascular diseases (CVDs) by inducing ventricular overgrowth and coronary artery disease accordingly [16, 17].

Following correcting for years of age, our findings were comparable overall a previous investigation [18] along with shown a beneficial relationship among the amount of hemoglobin along with renowned cardiac risk variables like body mass index high blood pressure, fasted hyperglycemia, cholesterol levels in general, along with cigarette use. It has been established which higher levels of haemoglobin or pcv cause circulation become more viscous, which increases nerve resistance overall lowers circulation overall oxygenation [19].

In comparison against the controls, the current research demonstrated a substantial rise among number of white blood cells in participants. These findings corresponded via the research conducted by [20] which suggested greater levels overall white blood cells, or lymphocytes, monocyte number, or neutrophil populations significantly predictive of a greater likelihood of cardiovascular disease [20]. It was recently suggested that some white blood cell variants, including macrophage [21] lymphoid [22], and neutrophils [23], may be more accurate indicators of the risk of cardiovascular illness (CVD) then white blood cell altogether. Though the results of the previous research have been conflicting, they additionally demonstrated separate connections between the likelihood of Cardiovascular as well as differentiation is

important, specifically the total number of neutrophils, monocytes, and lymphocytes. Just neutrophil were linked to coronary artery disease according to a 2004 systematic review [24] that had been subsequently validated in investigations [25, 26].

Historically, cells were once thought to being either biomarkers or mediators for cardiovascular illness [27]. Neutrophils are cells reflect the inflammatory that infected situation inside the individual in question and are thus predictive of an increased likelihood for heart disease. These are quickly drawn to inflammatory regions, whereby what they do best was generating reactive oxygen molecules, antibody then perforin (also announcement, and internalization to effectively battle infections. It is obvious that these characteristics are helpful in ensuring that infections were cleared. Nevertheless, there is a chance that those damaging traits might harm tissues that are healthy [28].

Investigations indicate a correlation between CVD mortality and kidney function indicators, including BUN, creatinine levels, particularly glomerular filtration rates [29, 30]. In comparison to different kidney-related indicators, concentrations of BUN are regularly observed to be elevated among individuals having Cardiovascular during studies on patients, rendering it an accurate gauge for Cardiovascular mortality [31, 32]. According with individuals who had decreased BUN, as it persons who had greater BUN exhibited a greater likelihood of CVD overall all-cause mortality [33].

According to the earlier study, the quantities of creatinine, urea, and ostonecine were significantly higher in the people with cardiovascular conditions condition versus the unaffected condition. Researchers also found that ostentation as well as creatinine levels among people with heart disease were related to aging. The research showed the kidney's operation is impacted by heart failure and stroke and also that individuals with these conditions had elevated levels of ostentation, a component of bones indicator. First of all Additionally, Saygitov et al. found that a higher blood nitrogen urea concentration beginning at moment before admittance were connected with a mortality risk that's over four times greater [34].

For most Cardiovascular individuals, increased Urea is linked to poor morbidity and death. Individuals are two times more likely to die from CVD events if they had excessive blood sugar levels upon admission. A very simple regular testing called Urea may identify people at increased risk having ACS (acute coronary syndrome) and place them under careful observation for any unfavorable vascular events [35]. both creatinine and blood elevations have been observed in ACS people; approximately one third of these individuals had elevated levels both combination of these two markers. When prognostic value with each of these variables was compared, it was shown which creatinine is not as good as an indicator of Acute coronary syndrome survival as Urea [36].

The present investigation's results demonstrated that, as compared with the normal category, individuals with Cardiovascular had significantly higher (GDF) levels. These results were in accordance with those of [37], who discovered that certain forms of cardiovascular disease (CV) had been linked to concentrations of development differentiating protein 15 (GDF-15), a cytokine released in the face of cell damage including inflammatory. presently uncertain, therefore, whether it predicts outcomes when applied to various forms of atherosclerotic cardiovascular disease (ASCVD) [37].

Circulation biomarkers of proteins have the potential for better evaluation, direct action, evaluate prediction, as well as aid in the management of heart disease) illnesses. [38]. Beneath normal circumstances, development differentiating hormone Fifteen (GDF-15), an element major the transforming growth factor beta superfamily, is only faintly recognized by a great deal of tissues. GDF-15 is markedly increased in people with illness in the aftermath of oxidative, related to machinery, deprived of oxygen, or inflammation stressors. [39] As a result, the company-15 was extensively investigated as an early biomarker for a number of illnesses, such as cancer, Type II diabetes mellitus, atrial fibrillation, heart failure (HF), and ischemic heart disease [40]. Higher GDF-15 values in atherosclerosis cardiovascular diseases (cardiovascular disease) revealed connected with heart failure, heart disease load, or atherosclerosis indicators in groundbreaking research. [41, 42].

The results we obtained are consistent alongside those of [43], who found that circulatory biomarkers of proteins may help in evaluation as well as evaluation. Development differentiating aspect-15 (GDF-15) serves as an indicator of inflammatory processes along with oxidative stress, respectively, which has been linked to a bad outcome in cardiovascular conditions [43]. But as a result of a vascular damage, which includes hypertension overabundance myocardial infarction, coronary artery disease, or atherosclerosis, GDF-15 may rise noticeably [44–46].

Over last 10 years, a growing body of research indicates the existence of GDF-15 may be a useful predictive indicator for individuals suffering from the condition known as acute coronary syndrome [47–49]. Increased GDF-15 values were also linked to an increased risk of cardiac failure. More research must be conducted comprehend the pathways that connect those biomarkers found in circulation to heart failure in individuals with chronic kidney disease. The hemoglobin, negatively regulates protein Function [50].

Multiple investigations indicate protein GDF-15 rises upon exposure to an array vary in stimuli, that include cytokines associated with inflammation or reactive oxygen species, among others [51–53]. Furthermore, GDF-15 has significant levels of expression in responses to a variety of mediators as well as growth factors such as TNF-, angiotensin-2, M-CSF, TGF-, and IL-1 (interleukin-1) [54–56].

Additionally, the cancer regulator enzyme p53 produces GDF-15, which inhibits the growth of tissues [57]. Furthermore, it was previously documented that pro-inflammatory compounds generated by GDF-15, including IL-1b, TNF-α, and CRP, regulate p53 receptors within the GDF-15 promoters to cause GDF-15 production in the cells of macrophages [58].

Young People experiencing CKD who had greater circulation GDF-15 amounts also experienced elevated death rates. Increased GDF, which is-15 concentrations were also linked to an increased risk coronary heart disease. More research is needed to determine the processes relating those circulation indicators to cardiovascular risk in people with persistent kidney disease [50].

Furthermore, elevated GDF, which stands-15 concentrations have been linked to hormone shortage in men patients with cardiovascular disease, thus lends credence to the theory that GDF-15 may influence Computer-aided design by upregulating in the presence of low testosterone [59, 60]. Additional studies suggested that this particular biomarker participates along the GH signalling system by correlating a decreased stimulation about growth hormone (also known as GH) with greater concentrations of GDF-15 in rat cardiomyocytes in Following this discovery, the identical researchers studied youngsters who had inherited heart defects as well as discovered that, in comparison to unaffected controls as well as youngsters with heart illness and typical development, youngsters alongside concurrent the heart illnesses and breakdown to flourish had substantially greater amounts of GDH-15 in their the blood plasma [61].

The present research additionally shows both GDF15 with (hemoglobin, lymphocytes, RBS) for Cardiovascular have a beneficial association. The waist-to-height proportion, their ages, arterial blood pressure, lipids, creatinine levels, insulin, blood sugar, hemoglobin that has been glycated (HbA1c), the C peptides all have been highly correlated significantly elevated GDF, which is-15 concentrations. In obese individuals, GDF, which is-15 was independently predicted by years of age, insulin resistance, glucose levels, as well as creatine [62]. Endothelial failure is linked to both elevated GDF-15 nor elevated insulin resistance. Failure of endothelial cells is linked to an elevated

likelihood of cardiovascular diseases including can cause damage to the cardiovascular system, inflammatory disorders, as well as metabolic disruption [63]. Accordingly, there is a beneficial relationship between circulating GDF-15 levels and Crp, triglycerides, glucose, HbA1c, overweight or obese status, and body composition [64].

5. Conclusions

The study extra likelihood of cardiovascular disease has been linked to increasing GDF-15 concentrations. Increased hemoglobin quantity, uremia, increased hyperglycemia are linked to GDF, which is-15, which offers additional predictive significance above established risk variables. To clarify the processes relating those biomarkers of circulation to CRS, which stands more research is required.Additionally, the present investigation has discovered a high correlation between GDF15 and neutrophiles counts in patients suffering from cardiovascular illness (CVD).

Article Information

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Informed Consent: Informed consent was obtained from all participants involved in the study.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author.

Clinical Trial Registration: Not applicable.

Reporting Guidelines Statement: This observational study was conducted in accordance with the STROBE reporting guidelines.

Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

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