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Evaluation of Growth Differentiation Factor-15 levels in Rheumatoid Arthritis Iraqi Patients with and without diabetes

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Abstract

Background: The underlying cause due to rheumatoid arthritis (RA) depends heavily based on macrophages. Autocrine growth differentiation factor -15 (GDF-15)regulates the activation of macrophages. Objective: The purpose of this research was to look at serum GDF-15 concentrations as a possible marker of RA disease activity. Methods: This research enrolled 50 patients with RA as well as 50 healthy controls with identical demographics. The patient group was further subdivided equally based on the prevalence of diabetes disease. The concentrations The GDF-15 was measured using an ELISA, as well CRP; in addition, ESR levels were determined. Other parameters (lipid profile and glucose) were measured using colourimetric methods. Results: In contrast to the control group, the measurement of GDF-15 in the serum of RA people who are afflicted and without diabetes was significantly higher ($P< 0.05$). A negative relationship between GDF-15 using ESR($r=-0.491$; $P<0.05$), CRP) $r=-0.465$; $P<0.05$), in addition to TG ($r=-0.428$; $P<0.05$) was found. The receiver operating characteristic curve reveals that this marker has good sensitivity and specificity in RA patients with diabetes. Conclusion: An increase in levels of GDF-15 might be stabilising and counteracting dysregulated inflammatory processes via a compensatory mechanism.

Keywords

Growth Differentiation Factor-15, Rheumatoid Arthritis, Diabetes Mellitus Type 2, Inflammation.

Among the many forms of arthritis, rheumatoid arthritis (RA) is among the most autoimmune, a systemic illness primarily affecting synovial joints. The infiltration of immune cells characterises RA into the joint, and autoantibodies are a defining feature of the disease. These autoantibodies can potentially form immune complexes in the joint, attracting immune cells (1, 2), which leads to gradual, symmetrical swelling of the compromised joints, which leads to the breakdown of cartilage, bone loss, and impairment. A select number of joints are initially affected, but as the disease progresses, Many joints are impacted, extra-articular the signs are prevalent. Two- to three-fold more women than men suffer from this. Frequent than men, and RA diagnoses' The 60s are the decade with the highest median age. (3). RA damages cartilage, bone, cardiovascular, pulmonary, and endocrine systems (4).

Immunopathology of rheumatoid arthritis is characterized by a complex interaction between the adaptive

and innate immune systems, as well as responses mediated by synovial cells (5). Rheumatoid arthritis is a chronic, systemic, inflammatory disorder with the primary treatment goals of disease control and pain relief (6). RA is an autoimmune disease that affects women disproportionately, suggesting that female hormone variations contribute to disease progression (7). RA is also considered a disease with extra-articular manifestations, including rheumatoid nodules, pulmonary involvement, and vasculitis (8). Symmetrical chronic synovitis affects tiny peripheral joints but can affect nearly all joints with a synovial membrane (9).

The RA affects approximately five people in the thousands and can cause significant impairment due to joint injury. Understanding the aetiology of the disease, best practices for measuring success, and cutting-edge therapies, such as the significance of early RA treatment and diagnosis, have advanced significantly over the past two decades. In up to 90% of patients, identification and therapy at an early stage of RA can either stop the growth of joint deterioration entirely or greatly slow it down, thereby controlling long-term damage disability (10) and maximising cost-effectiveness (11).

Aside from its more common names, Other names for growth and differentiation factor 15 (GDF-15) include macrophage inhibitory cytokine-1 (MIC-1), prostate-derived factor (PDF), Bone morphogenetic protein in the placenta, and placental transforming growth factor-beta (PTGF-beta). Differentiated growth factor-15 (GDF-15) is connected with the TGF-β superfamily of growth factors. A cysteine knot, consisting of seven conserved cysteine residues, is a characteristic feature of the Superfamily of the TGF-β. Orthologous GDF-15 molecules have the least species-wide sequence conservation of all members of the superfamily (12).

GDF-15 is synthesised as a propeptide of about 40 kDa. At cleavage, the N-terminus is split off and made available to the body as a dimeric active protein that is disulfide-linked of 40 kDa molecular weight. GDF-15 communicates in the placenta, kidney, lung, macrophages, and T-cells are examples of immune system cells expressing various GDF-15; this is also true for other organs and tissues(12).

The expression of GDF-15 rises with increasing years, and several markers, including chemical reactions involving oxygen, protein glycation, inflammation, and hormone shifts, that associated with biological age. The production of GDF-15 is prompted due to these stressors by the transcription factors p53 or early growth response protein-1 (EGR-1). Earlier studies have shown that the cytokine known as GDF-15 is one that suppresses inflammation. Enhanced GDF15 expression in healthy people decreases hunger and inflammation via enhancing insulin sensitivity. Increased GDF15 serum levels may result from a reduction of sensitivity in central and peripheral GDF15 receptors due to the over-expression of GDF15 in chronic metabolic and inflammatory diseases. [(13),(14),(15)].

GDF-15 in the serum of people who have rheumatoid arthritis have been demonstrated to be higher, which has been linked to enhanced disease activity. (12),(16). Clarification is needed about GDF-15 subsets and their associations with RA risk in the diabetic population of Iraq.

Methods

Subjects

The research being presented here is a case-control study that recruited 100 subjects where 50 of them were patients with RA collected from the Department of Joint Diseases/ Al-Yarmouk Medical Hospital in which specialised doctors confirmed the presence of rheumatoid arthritis in the patient (RA) according to the standards specified by the College of Rheumatology, American and European League Against Rheumatism (ACR/EULAR) (17). As a control group, we enrolled fifty individuals who were in good health.

Of some patients, eight were male, and 42 were women, whereas 22 males and 28 healthy females were in the control group. The disease period ranged from (2-7) years—the Ethics Committee of the Institutional Review Board of Ethnic Research Group of Baghdad University's Science College. The participation of each person in this investigation was granted after receiving their informed consent.

Consistent with these requirements, the group of patients were subdivided into two distinct groups of diabetes being present and active: RA and DM (G1) group, which contains 25 patients; RA without DM (G2) group, which includes 25 patients in addition to the control group 50 patients. The patient's ages ranged from (30-70) years, as may be seen in (Table 1).

Table 1: Description of the patients and control groups.

Description/ Group	Controls	Patients of RA with DM (G1)	Patients of RA without DM(G2)
Number	50	25	25
Gender (male/ female)	(21/24)	(3/22)	(5/20)
Age range (year)	(30-60)	(53-70)	(30-67)

Collection of samples

Each participant gave a venous blood sample of three millilitres collected in a gel tube and was left for 10 min, then immediately centrifuged, and the serum was kept until analysis at -20 °C.

GDF-15 concentration was measured.

The levels of GDF-15 were tested using an ELISA kit manufactured by MyBioSource Company in the United States of America. ELISA stands for enzyme-linked immunosorbent assay.

GDF-15 could be detected at concentrations as low as 23.0 pg/mL. The coefficient of variation (CV) for the GDF-15 assay was 8% within an assay and 10% between different assays.

Biochemical analysis

The C-reactive protein (CRP) was measured using a kit from Boditech (Korea) by Cobas c111 (Roche Diagnostics, Germany). The Biochemistry Analyzer (Bio system-BTS, Spanish) was used to measure all other biochemical markers (lipid profile and glucose).

The depth of red blood cells, which had sunk by the end of the first hour, was utilised in the calculation of ESR. This was done at the end of the first hour.

Data examination

Version 22.0 of the SPSS software was used. (provided by SPSS, USA) for our statistical study. For continuous variables that followed normal distributions, both the mean and the standard deviation (SD) were provided as their respective values. An analysis of variance (ANOVA) was performed with the goal of determining the nature of the link that exists between the blood level of GDF-15, the activity of RA, and the other parameters. The Pearson correlation coefficient was also utilised in order to express the degree of association that exists between GDF-15 and the other variables. When the P value was less than 0.05, the statistical findings were regarded as significant. The curve of receiver operating characteristic (ROC) was utilised to forecast GDF-15's potential as a RA biomarker.

Results

The study's sample comprised 50 RA patients and 50 healthy control participants aged between (30-70 years) and weights (60-90 Kg). Table 2 displays the mean ± SD for the patients and control groups. The average (IQR) disease duration for RA patients was five years.

The obtained results indicated the presence of significant (P< 0.001) higher levels in (age, CRP, ESR, TC, TG, LDL-C, LDL, glucose and GDF-15) when comparing patients with healthy people. While mean levels of weight, and HDL-C, showed nonsignificant differences (P>0.05).

Table 2: The mean (±SD) level of the characteristics of the patients and the Participants from the control group.

Parameters	Patients group (N=50)	Control group (N=38)	P value
Age (Years)	56.3 ± 8.31	41.7 ± 9.17	0.001
Weight (kg)	83.4±9.01	81.9±8.51	0.351
CRP(mg/l)	6.80± 3.69	0.73± 0.39	0.001
ESR (mm/h)	25.3 ± 9.42	11.5 ± 5.50	0.001
TC (mg/dl)	262.9 ± 74.7	148.02 ± 50.2	0.001
TG (mg/dl)	218.1 ± 75.00	94.55 ± 23.28	0.001
HDL-C (mg/dl)	42.16 ± 9.58	45.31 ± 12.53	0.184
LDL-C (mg/dl)	183.46 ± 85.46	83.83 ± 50.86	0.001
RBS (mg/dl)	122.4±45.8	90.5±12.6	0.001
GDF-15(pg/ml)	185.6 ± 93.3	136.3 ± 59.5	0.004

BMI (kg/m^2)	31.0 ± 2.95	26.9 ± 2.90	0.000

Table 3 represents the description of the patient group when it is split into two groups based on the existence of diabetes in each category RA and DM (G1) group and the RA without DM (G2) group.

When looking at the outcomes shown in Table 3, the results of RA and DM (G1) and RA without DM (G2) relative to the control group revealed higher levels significantly (P< 0.001) in age, CRP, ESR, LDL-C, HDL-C, TC, TG, BMI, RBS, and GDF-15.

When comparing the G1 and G2 groups, there were insignificant statistical (P>0.05) differences except that of age and RBS, which showed a significant (P<0.05) increase in G1.

Table 3: The mean (±SD) level of parameters of (G1), (G2), and Control groups.

Parameter	Control group (n=38)	group (G1) (n=25)	group(G2) (n=25)	P value (G1 with control) groups	P value (G2 with control) groups	P value (G1 with G2) groups
Age (Years)	41.7 ± 9.17	59.7±6.28	52.9±8.81	0.001	0.001	0.005
Weight (kg)	74.9±9.43	83.3±10.1	82.4±7.4	0.171	0.336	0.735
CRP (mg/L)	0.73 ± 0.39	6.75±3.38	6.84±4.05	0.001	0.001	0.903
ESR (mm/h)	11.5 ± 5.50	25.6±8.69	24.9±10.26	0.001	0.001	0.738
TC (mg/dl)	148.02 ± 50.2	255.3±84.8	270.5±63.7	0.001	0.001	0.413
TG (mg/dl)	94.55 ± 23.28	217.3±74.8	218.9±76.7	0.001	0.001	0.926
HDL-C (mg/dl)	45.55 ±12.53	34.7±7.35	37.3±8.11	0.001	0.003	0.433
LDL-C (mg/dl)	87.23 ± 52.4	194.5±88.04	172.3±78.5	0.001	0.001	0.269
RBS (mg/dl)	90.5±12.6	151.1±49.5	93.8±11.2	0.001	0.621	0.001
GDF-15 (pg/ml)	136.3± 52.5	202.6± 86.1	153.1 ±76.6	0.001	0.024	0.119
BMI (kg/m^2)	26.9 ± 2.9	31.4 ± 3.2	30.6 ± 2.6	0.000	0.000	0.323

We looked at how other factors correlated with GDF-15 concentrations in the blood. There had a substantial negative impact correlation between serum GDF-15 with ESR in RA without DM (G2) group (r=-0.491, P<0.05) and with TG (r=-0.428, P<0.05) (Fig 2) in RA without DM (G2) group, as well with CRP (r=-0.465, P<0.05) in RA and DM (G1) group, and with BMI (r=-0.337, p<0.05) in control group (Fig 3) On the other hand, as indicated in Table 4, There was no significant relationship between GDF-15 and RBS and the remaining parameters. This was the case for all of the variables.

Table 4: Correlation of GDF-15 in (G1, G2 and control) groups with other parameters.

Parameters	GDF-15					
	Control group		G1 group		G2 group	
	r	p	r	P	r	p
Age (Years)	-0.002	0.991	0.07	0.74	0.009	0.965
BMI (kg/m^2)	-0.337	0.039	0.029	0.892	0.085	0.684
CRP(mg/L)	0.201	0.227	-0.465**	0.019**	0.271	0.19
ESR (mm/h)	0.8	0.632	-0.218	0.295	-0.491**	0.013**
TC (mg/dl)	-0.178	0.286	-0.228	0.272	0.028	0.894
TG (mg/dl)	-0.139	0.406	-0.118	0.573	-0.428*	0.033*
HDL (mg/dl)	0.16	0.338	-0.262	0.205	-0.027	0.898
LDL (mg/dl)	-0.202	0.225	-0.12	0.567	0.29	0.16
RBS (mg/dl)	0.035	0.835	-0.117	0.578	0.014	0.948

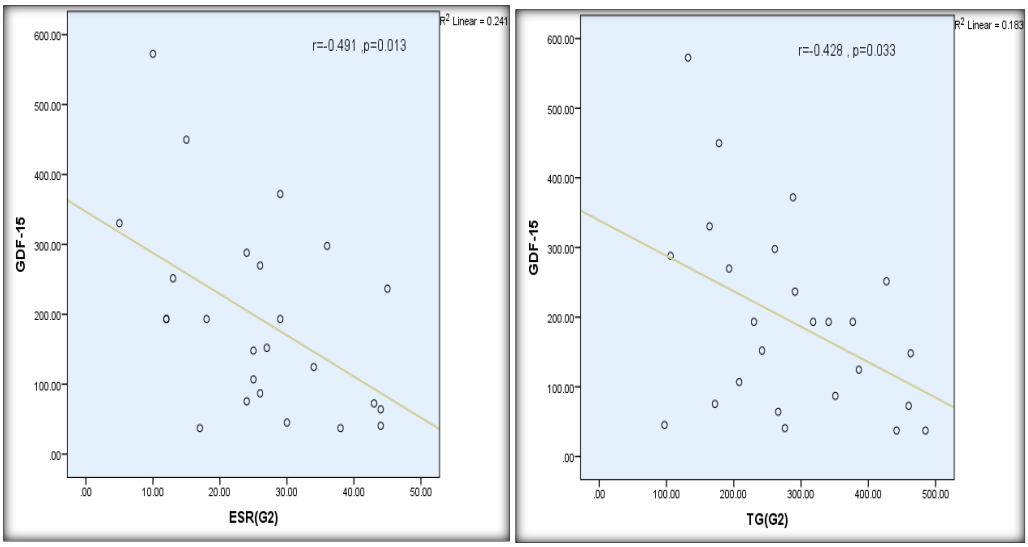

Figure 2: The significant Pearson correlation of GDF-15 with ESR and TG in the G2 group.

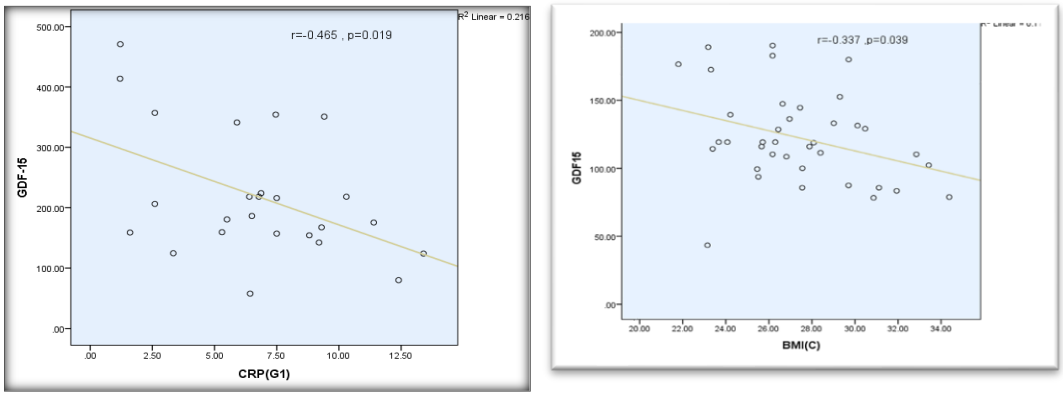

Figure 3: The significant Pearson correlation between GDF-15 and CRP in the G1 group.

To investigate whether or not serum GDF-15 may act as a marker for RA in either of the groups, a receiver operating characteristic (ROC) curve was constructed G1and G2, which revealed that this marker has good sensitivity and specificity in RA patients with diabetes, as shown in (Table 5) and (Fig.4 A and B).

Table 5: The values of Area under the curve, Cut off deal, sensitivity and spasticity.

Groups	Area under curve (AUC)	Cut off value (pg/ml)	Sensitivity	Spasticity
G1	0.917	153.44	0.88	0.84
G2	0.633	191.7	0.52	1.00

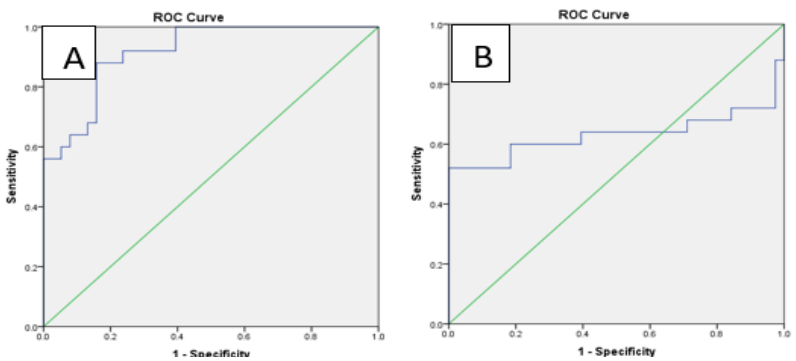

Figure 4: The receiver operating characteristic (ROC) curve of serum GDF-15 in the A: G1 and B: G2 groups.

Discussion

According to our study, Those suffering from RA exhibited higher serum GDF-15 levels than controls that were healthy. The research uncovered a link between serum GDF-15 concentrations, C-reactive protein and total cholesterol levels, as well as erythrocyte sedimentation rate.

Patients with rheumatoid arthritis in Iran were surveyed to assess serum GDF-15 levels.; they found an increase in this marker compared to the control, and they suggested GDF-15 as an indicator of disease activity levels (18).

In a separate investigation, the researchers in Turkey looked at the concentrations of serum GDF-15 in patients with RA. They found that the concentrations of serum GDF-15 in patients with RA were considerably greater than in control people(19). In patients with RA who have an active form of the disease, serum levels of GDF-15 were shown to be significantly greater than in those with less active disease activity. There was a correlation between high concentrations of GDF-15 in the serum and elevated concentrations of C-reactive protein (CRP). The score used to measure the Biological activity of rheumatoid arthritis (DAS28) was also connected with these elevated levels. Score Relative to the Disease Activity (DAS; 28 represents the number of joints assessed here)(20). According to the findings, GDF-15 might play a part in the aetiology of RA, including joint degeneration (21). Plasma concentrations of GDF-15 were substantially greater in individuals diagnosed with RA in the Chinese Han population than in healthy controls (22).

In a separate investigation including individuals with RA, the researchers concluded that GDF-15 might Play an essential role in the course of the disease, collaborative effort, and atherosclerosis (21). Autoimmune disorders are caused by immune cells attacking host tissues due to prolonged abnormal immune responses against self-antigens. Elevated GDF-15 levels are frequently seen in RA patients. They are associated with symptoms including ESR carotid intima-media thickness, number of achy joints upon waking, morning stiffness, and overall soreness. Type 1 diabetes (T1D) has also been linked to GDF-15 elevation in beta cells, and GDF-15 has been proposed for use as a biomarker for type 1 diabetes (12).

High insulin resistance is linked to systemic inflammation in rheumatoid arthritis, which is brought on by pro-inflammatory cytokines, including IL-6 and TNF-α (tumour necrosis factor-alpha). Those diagnosed with RA have an increased risk of developing type 2 diabetes. (23).

Rheumatoid arthritis is a persistent inflammatory condition in which macrophages play a significant role in the pathogenesis of the disease. Macrophage activation is autoregulated by the growth differentiation factor-15. Diseases of inflammation and cancer, health problems like atherosclerosis, pulmonary thromboembolism, and lupus and systemic sclerosis have benefited clinically by measuring GDF-15 serum levels. Cardiovascular illness, metabolic disorders, inflammation, and cancer have all been linked to GDF-15 (18).

Rheumatoid factor is a well-established test for diagnosing and monitoring rheumatoid arthritis prognosis (RA). There have been reports of rheumatoid factor in the serum of patients with different diseases, for example, diabetes mellitus, which has been linked to pro-inflammatory cytokines, including TNF-α. These cytokines play a crucial part in developing chronic inflammatory and autoimmune diseases, such as RA (24).

C-reactive protein levels tend to be abnormally high in rheumatoid arthritis patients. Although many patients with RA have normal CRP values, as shown by retrospective and real-world observational research, suggests that CRP levels only represent one indicator of disease activity and could be evaluated in conjunction with other measurements. Additionally, RA patients' initial serum CRP levels are impacted by various variables. Further, it has been demonstrated that surplus fat, female hormone levels, food quality and stress influence CRP levels in RA patients. Depending on the sort of drug and way of doing things, CRP levels often fall when pharmacological therapies for RA diminish systemic inflammation (25). A slower response to inflammatory stimulation than CRP, elevated ESR is a proxy for acute-phase protein levels and, in contrast to CRP, implies long-lasting, chronic inflammation (26).

Compared to the general public, RA patients have significantly higher cardiovascular (CV) morbidity and mortality rates. However, People with active RA decreased concentrations of low-density lipoprotein (LDL) and total cholesterol, as found in a study by Harles Schoeman et al. (2015). The amount and activity of various HDL-associated proteins are altered in patients with active RA, affecting HDL-C composition. This results in creating more pro-oxidant, proatherogenic HDL –C particles. Patients with RA who are being treated for active RA may experience significant changes in their lipid metabolism, including elevated levels of circulating cholesterol (27).

Conclusion

The negative correlation between GDF-15 with ESR and CRP leads to the conclusion that increased GDF-15 might stabilise and counter dysregulated inflammatory processes via a compensatory mechanism.

According to ROC analysis, GDF-15 concentrations may be a biomarker for predicting RA disease activity in diabetic patients.

Conflicts of interest

There are no competing interests, as the authors have stated.

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