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ORIGINAL ARTICLE

Study of Nepheroblastoma Overexpressed Protein (NOV/CCN3) as a Biomarker in Serum of Iraqi Patients with Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune condition that is chronic, inflammatory, and can affect any joint in the body. Rheumatoid arthritis is defined by symmetric inflammation of synovial joints, which can eventually lead to the erosion of cartilage and bone .The objective of this study was to measure CCN3, CRP, I.R, Insulin .F.G, and Lipid profiles in patients with Rheumatoid arthritis. The current study comprised a total of 120 participants, who were separated into two groups. Group1 contained 70 Rheumatoid arthritis patients, and group2 controls 50; the samples were extracted from women and man, the levels of CCN3, CRP, I.R .F.G, Insulin, Cholesterol, TG, VLDL, LDL, and HDL were evaluated. The levels of PTX3 and Insulin were determined using an enzyme-linked immunosorbent assay (ELISA), and the stories of F.G, Cholesterol, TG, CRP, VLDL, LDL, and HDL, were assayed using a spectrophotometer. The result of CCN3 shows a high significant change among two groups' patients RA and control. Systole, Diastole, and LDL values have non-significant change in their levels in RA patients. Triglyceride, Cholesterol, HDL, VLDL, CRP, Insulin, F.G, and I.R values have a significant change in their levels in patients RA.
Conclusion: According to the presented results CCN3, CRP, I.R .F.G, Insulin, T.G, Cholesterol, VLDL, and HDL all have an effect on RA patients. RA patients are not affected by their systole, diastole, or LDL levels.

INTRODUCTION

Rheumatoid arthritis, also known simply as RA, is a debilitating autoimmune condition that can last for years. RA is characterized by an abnormally high level of cytokines that promote inflammation, such as interleukin (IL)-1; these cytokines gradually cause joint damage and swelling over time (1). It is estimated that 0.1–2.0 percent of the world's population is afflicted with this condition. Even though there have been some recent advancements in treatment, there is still no known cure for rheumatoid arthritis (RA), which has a poorly understood cause(2). Because it can affect numerous organ systems, such as the cardiovascular, pulmonary, ophthalmic, and cutaneous systems, as well as the hematologic system, the risk of multiple related problems is increased. This condition is linked to reduced physical function, a decline in quality of life, and an increase in the risk of morbidity and mortality, particularly as a result of the complications of cardiovascular disease (3).

It most frequently presents itself as polyarticular pain that has a symmetric distribution and mostly impacts the hands and the feet. Not only are these joints painful, but they are also frequently swollen and hot to the touch. Stiffness first thing in the morning that lasts for more than half an hour is usual. Untreated rheumatoid arthritis can result in joint abnormalities, as well as irreparable bone and cartilage destruction, which can lead to disability and a decline in quality of life (4). Although RA primarily affects the joints, it can also cause discomfort, damage to bones and cartilage, and even pulmonary fibrosis. Additionally, it can have adverse effects on the eyes, heart, lungs, and skin (5). The condition is difficult to diagnose since there are more than one hundred different types of arthritis, and among the many ailments that affect the joints, numerous symptoms are the same. This makes it difficult to determine which disorder a patient is suffering from. Blood tests such as the erythrocyte sedimentation rate (ESR), which measures the levels of inflammation in the body, C-reactive protein (CRP), and complete blood count (CBC), as well as joint scans and X-rays, are some of the diagnostic methods that can be used for inflammatory arthritis. Other methods include imaging procedures such as magnetic resonance imaging (MRI) and ultrasound. Because of the significant amount of time that passes between the onset of the disease and the opportunity to identify particular biomarkers, the diagnosis of inflammatory arthritis is a difficult problem to solve (6-7). It is more effective to avoid inflammatory arthritis than it is to treat it, as making changes to one's lifestyle, losing weight, and eating foods that are rich in antioxidants are all extremely successful in preventing or delaying the beginning of inflammatory arthritis (8). Drug therapies are regarded to be the primary contributor in lowering symptoms and slowing disease development, as well as controlling the disease activity associated with RA (5).

When it comes to the treatment of inflammatory arthritis, the primary focus is on pain management, specifically the application of heating and ice packs with the purpose of providing solace. Medication such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are additional frequent methods that are used against inflammatory arthritis. However, other practical forms of treatment for inflammatory arthritis include physical therapy and occupational therapy (9). In severe cases where drugs continue to be ineffective, surgery to replace the affected joint with an artificial one might be undertaken. This procedure is most commonly performed on the knees and hips (10). Inflammatory arthritis is also commonly treated using physical therapy, which consists of strengthening the muscles around the afflicted joint. This approach is utilized in the treatment of some individuals (11).

MATERIALS AND METHODS

Patients' selection: The study was conducted in the Biochemistry lab for the period from November 2021 to January 2022, after obtaining consent from the patients and ethical approval from the relevant institutional review board. We studied 70 RA patients and 50 controls. A 5 ml of venous blood has been obtained, after centrifugation, and then examined parameters were evaluated. CCN3 and Insulin levels were calculated using the enzyme-linked immune sorbent assay (ELISA) method. This method involves connecting an antibody or antigen to an assay enzyme. CRP, FBG, Cholesterol, TG, and HDL concentrations were calculated using a spectrophotometer and the Cobas c111 analyzer device.

Inclusion Conditions: Diagnosed using screening markers, such as lipid profile, insulin resistance (IR), FBG, and BP, patients with metabolic syndrome were shown to be clinically abnormal.

Exclusion Criteria: Diabetes mellitus, cardiovascular disease, and thyroid disease were all eliminated from the study based on history and clinical examination.

Statistical analyses: The statistical analysis tool was used to examine the data (SPSS 25). For normal parametric distribution data, the T-test was utilized with 0.05 alpha levels.

RESULT AND DISCUSSION

The result mean ±SE of patients, and control [(46.02 ± 1.3)(28.3 ± 0.5)] respectively ,the result showed a high a significant change between two groups in the age (P< 0.05) as shown in Table (1)

Alanzy AK, et al. (12) and Castañeda S, et al. (13), it revealed from the data that there was no difference in the age of patients compared to the control group.

Body mass index result was presented in Table (2).The results show mean ±SE of patients and control of BMI [(29.33 ±0.72) (22.91±0.31)] respectively, where the result indicates a huge significant difference among two groups (P<0.01).

The composition of a person's body has an effect on those who suffer from RA. A sedentary lifestyle reduces muscle mass and increases body fat1–4; the prevalence of obesity among RA patients; and aging are all factors that contribute to the loss of lean body mass in RA patients. RA patients are more than 60% more likely to have a BMI (body mass index) that is higher than the average (above 25 kg/m2). (14).

There was non- significant difference in systole results (P>0.05). The mean ±SE of patients and control were [(10.09 ±1.10) (8.39 ±0.10)] respectively.

According to the Van den Oever IA, et al. (15), there were non-significant in systole between patients RA and controls, supporting our findings.

The mean ±SE of Diastole in patient's and control were [(12.60 ±0.15) (12.03 ±0.07)] respectively, the result indicates a non- significant change between two groups in the Diastole (P>0.05) as shown in Table (3).

Van den Oever IA, et al in their study (15), also found there were non-significant differences in systole between patients and controls, supporting our findings.

Table (1) Comparison between control and patients groups in Age.

Group	Mean ± SE
Control	28.3 ± 0.5
Patients	46.02 ± 1.3
T-test	10.92* *
P-value	0.000
* (P≤0.05)	

Table (2) Comparison between control and patients groups in BMI.

Group	Mean ± SE
	BMI (kg/m^2)
Control	22.91 ±0.31
Patients	29.33 ±0.72
T-test	1.956 **
P-value	0.0001
Highly Significant (P≤0.01)	

Table (3) Comparison between control and patients groups in Blood pressure.

Group	Mean ± SE	
	Systole	Diastole
Control	8.39 ±0.10	12.03 ±0.07
Patients	10.09 ±1.10	12.60 ±0.15
T-test	2.909 NS	0.901 NS
P-value	0.249	0.0771
*significant differences at (P<0.05) NS: Non-Significant.		

The results of CCN3 showed mean ± SE of patients and control [(813.12 ±10.72) (693.64 ±7.05)] respectively, where the result showed a high significant change among two groups in the CCN3 (P< 0.01) as shown in Table (4).

A study conducted in 2020, found CCN3 is an important factor in the pathogenesis of numerous disorders, including those affecting the cardiovascular system and the central nervous system. However, the part that CCN3 plays in the progression of RA has not yet been analyzed in detail. Collecting the sera of RA patients as well as healthy controls allowed researchers to evaluate the possibility that CCN3 has a role in the progression of RA. In patients with RA, the mean level of CCN3 was 4288 pg/ml, with a range of 1395-9233 pg/ml; in healthy controls, the mean level of CCN3 was 2506 pg/ml, with a range of 1409-4691 pg/ml. In addition to this, the amount of CCN3 that was deposited in joint tissues that had been embedded in paraffin was also measured. We detected a significant accumulation of CCN3 in the joint tissues of RA patients, but we did not find any evidence of this in the joint tissues taken from OA patients who served as a control. In patients with RA, the blood CCN3 level has the potential to be a sensitive measure for the disease activity. Additionally, CCN3 was found to be related with inflammatory cytokines as well as anti-CCP antibody in RA patients (16).

The mean ±SE of CRP in patients and control were [(19.47 ±3.33) (3.13 ±0.16)] respectively, the result indicates a significant change between two groups in the CRP (P<0.01) as shown in Table (4).

C-reactive protein (CRP) is commonly measured as a sign of systemic inflammation in rheumatoid arthritis (RA) (RA). However, it is also an immunological regulator that plays a significant role in inflammatory pathways linked with RA and promotes atherogenic consequences. Comorbidities connected to systemic inflammation are widespread in RA, and CRP has been associated with the risk for cardiovascular disease, diabetes, metabolic syndrome, pulmonary illnesses, and depression. The link between systemic inflammation, CRP, and comorbidities in RA is complex (17).

CRP, in general, plays a significant part in both the host's defense systems against pathogenic pathogens and the inflammatory response. When CRP binds to immunoglobulin Fc gamma receptors (FcR), this stimulates the production of proinflammatory cytokines, which in turn leads to an inflammatory feedback loop that is amplified. It is produced mostly by hepatocytes in response to stimulation by IL-6, but CRP has also been shown to be expressed by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. This is due to the fact that IL-6 is a pro-inflammatory cytokine. In individuals diagnosed with rheumatoid arthritis (n = 197;(p< 0.0001), a substantial association was shown to exist between serum CRP levels and tissue inflammation scores derived from knee synovium biopsy samples. CRP levels have been proven to have a strong correlation with IL-6 levels in both the serum and synovial fluid of patients diagnosed with rheumatoid arthritis (RA). CRP is not only a sign of inflammation or infection; it also functions as an immunological regulator. There has been debate regarding the direct role that CRP plays in inflammation and infection; however, the discovery that different CRP isoforms each have their own unique set of biological properties has provided a potential explanation for the seemingly contradictory observations that have been made. An explanation for the observations that seem to contradict each other . Hepatocytes are responsible for the synthesis of CRP, which is then secreted into the circulation as pentameric CRP (pCRP), which is also referred to as native CRP. It is believed that pCRP has a role in immunological regulation. pCRP is able to irreversibly dissociate into monomeric CRP (mCRP) via a conformationally changed intermediate when it is bound to cell membranes or liposomes. mCRP is a proinflammatory isoform that is able to activate platelets, leucocytes, and endothelial cells as well as bind complement component 1q to activate complement. In comparison to pCRP, mCRP has a low solubility and is thought to be tissue bound; nonetheless, transmission through microparticles and ligand complexes has been hypothesized. Depending on its structural form, CRP interacts with a wide variety of leucocytes and endothelial cells, stimulating the release of proinflammatory cytokines such as IL-6, IL-1, and TNF-; up-regulating adhesion molecules; increasing the release of monocyte chemoattractant protein-1 to recruit monocytes; inhibiting the production of nitric oxide; and activating platelets; these interactions ultimately result in the induction of proinflammatory (17).

Dessie, G.et al (18), noted in their study. In RA patients, a high amount of systemic inflammation was suggested by elevated hs-CRP values.

According to the findings presented in the Contreras-Haro B, et al (19). Serum levels of found hs-CRP were found to be low in both groups; however, they were found to be considerably lower in patients who were receiving anti-IL-6R (0.04 mg/dL vs. 0.16 mg/dL; p 0.001) The number of patients in the anti-IL-6R group who had very low levels of hsCRP (values of less than 0.1 mg/dL) was 81 percent, while the percentage in the JAKi group was just 42.9 percent.

Table (4) Comparison between control and patients groups in CRP and CCN3.

Group	Mean ± SE	
	CRP	CCN3
Control	3.13 ±0.16	693.64 ±7.05
Patients	19.47 ±3.33	813.12 ±10.72
T-test	8.757 **	29.921 **
P-value	0.0003	0.0001
** (P≤0.01).		

There was significant difference in Insulin Resistance (IR) results (P<0.05). The mean ±SE of patients RA and control were [(0.239 ± 0.016) (0.285 ± 0.011)] respectively. As showni in Table (5).

According to the by Corrado A, et al (20). Anti-TNF α-agents may play a key role in reducing the impact of lipid dysregulation and glucose dysregulation in RA patients. TNF-inhibition could be a useful method for preventing metabolic syndrome and lowering cardiovascular risk.

Table (5) Comparison between control and patients groups in IR.

Group	Mean ± SE of I.R
Control	0.285 ± 0.011
Patients	0.239 ± 0.016
T-test	0.0473 *
P-value	0.0469
* (P≤0.05)	

Table (6) Comparison between control and patients groups in Insulin.

Group	Mean ± SE
Control	2.3 ±0.15
Patients	0.99 ± 0.04
T-test	9.5* *
P-value	0.000
* (P≤0.05).	

Table (7) Comparison between control and patients groups inF.G.

Group	Mean ± SE
Control	87.1 ±1.1
Patients	95.4 ±3.2
T-test	2.1 *
P-value	0.035
* (P≤0.05).	

The results of Insulin Resistance (IR) where presented as mean±SE in mean patients RA and control [(0.239 ± 0.016) (0.285 ± 0.011)] respectively, as shown in Table (6)

In their study by Shahin D, et al. (21). The patients' serum insulin levels were greater than those of the control group.

The results of Fasting serum glucose where presented as mean ±SE in mean patients and control [(95.4 ±3.2) (87.1 ±1.1)] respectively, as shown in Table (7).

According to the by Shahin D, et al (21). The patients revealed higher fasting serum glucose levels than those of the control group.

The results revealed a high significant difference (P≤0.01), mean±SE between Patients RA and control [(143.18 ±8.04) (96.37 ±3.80)] respectively. As shown in Table (8).

A study conceded in 2021 found that the Triglyceride of the concentration was patients group non-significantly than in the healthy control group (P >0.05) (15).

The level of Triglyceride greater was non- significantly in patients with RA when compared to the control group in research by Shahin D, et al. (21).

There was significant difference in Cholesterols results ((P≤0.01). The mean ±SE of patients RA and control were [(186.29 ±5.14) (160.31 ±2.39)] respectively. As shown in Table (8).

In a study conducted by Van den Oever IA et al., the level of Cholesterols was considerably higher in RA patients compared to the control group (15).

A study conceded in 2021 found that the Cholesterols of the concentration was patients group significantly than in the healthy control group (P <0.05) (21).

The mean ±SE of HDL in Patients RA and control were [(71.31 ±3.43) (56.44 ±1.62)] respectively, the result indicates a significant change between studied groups in the HDL (P≤0.01) as shown in Table (8).

The level of HDL was significantly greater in patients with RA when compared to the control group in research by Van den Oever IA, et al. (15).

A study conceded in 2021 found that the H DL of the concentration was patients group significantly than in the healthy control group (P <0.05)(21).

The mean ±SE of patients and control were [(92.49 ±4.13) (84.64 ±3.13)] respectively. There was no significant difference in LDL results (P>0.05).As shown in Table (8).

Van den Oever IA, et al. (15). Research the effect of antiTNF medication on body composition and insulin resistance in rheumatoid arthritis patients. They detected a statistically significant difference between the patients and the controls. (P<0.05).

A study conceded in 2021, found that the LDL of the concentration was patients RA groups non-significantly than in the healthy control group (P >0.05)(21).

The results revealed a high significant difference (P≤0.01), mean ± SE between Patients RA and control in VLDL [(28.71 ±1.62) (19.26 ±0.76)] respectively. As shown in Table (8).

In their study by Shah SA, et al (22). There was no significant relationship found between VLDL-cholesterol and inflammatory markers.

Table (7) Comparison between control and patients groups in Lipidprofile

Group	Mean ± SE (mg/dl)				
	Triglyceride	Cholesterol	HDL	LDL	VLDL
Control	96.37 ±3.80	160.31 ±2.39	56.44 ±1.62	84.64 ±3.13	19.26 ±0.76
Patients	143.18 ±8.04	186.29 ±5.14	71.31 ±3.43	92.49 ±4.13	28.71 ±1.62
T-test	21.889 **	13.984 **	9.354 **	11.834 NS	4.407 **
P-value	0.0001	0.0004	0.0021	0.191	0.0001
** (P≤0.01), NS: Non-Significant.					

The receiver operating characteristics curve (ROC): ROC is a statistical study that is used to determine the optimal specificity and sensitivity for a diagnostic test by plotting the connection between sensitivity and specificity. 1. Specificity (23).

ROC test for CNN3 markers showed very clear cut off value with 82.9% sensitivity and 82% specificity that indicates CNN3 considered as a good diagnostic marker. As shown in charts (1).

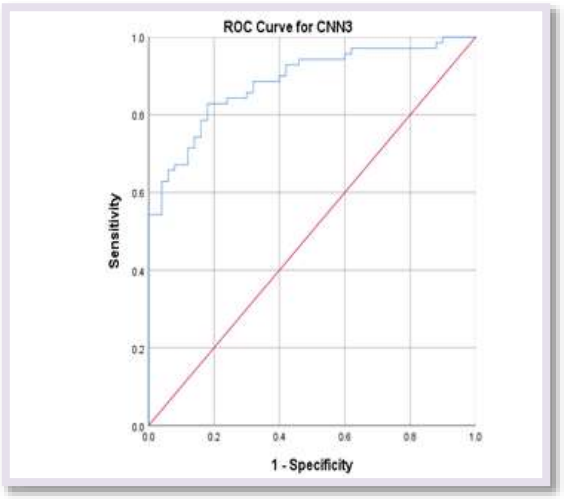

Chart 1: ROC curve for CNN3.

CONCLUSION

The result of CCN3 shows a high significant change among two groups' patients RA and control. In our study, the high concentration of CCN3 in patients compared to healthy people showed that it can be considered as a marker in the diagnosis of the disease RA.

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