Original Article

Circulating Serum Caveolin-1 and Interleukin-37 as Predictive Biomarkers in Rheumatoid Arthritis Patients

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Abstract

Background: The immune system mistakenly attacks healthy tissues in rheumatoid arthritis (RA), causing a cascade of symptoms such as joint pain, swelling, stiffness, and even functional damage. In this study, we aimed to predict RA by investigating the circulating serum levels of Caveolin-1 (CAV1) and Interleukin-37 (IL-37). **Methods:** The current case-control study was conducted on 46 volunteers (13 men and 33 women) who experiencing RA and divided into two groups: 26 patients in Active RA State (7 men and 19 women) and 20 patients in Remission (Stable) RA State (6 men and 14 women) and corresponded with 30 apparently healthy group (12 men and 18 women) aged 25 to 70 years. Demographics, glucose, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), urea, creatinine, rheumatoid factor (RF), c-reactive protein (CRP), CAV1, and IL-37 levels were compared between groups. **Results:** In comparison to the healthy group, RA patients (both in active and remission states) had significantly higher levels of serum RF, CRP, and IL-37, also a significant low level of CAV1 ($p<0.01$). The only metrics with which CAV1 and IL-37 showed a positive association were RF and CRP; however, no significant correlations were found with the other parameters ($p>0.05$). Predicting biomarkers for RA patients may be easier using RF, CRP, CAV1, and IL-37, according to the results of area under curve (AUC) of the receiver operating characteristic (ROC). **Conclusion:** The correlation between Cav-1 and IL-37 was significantly inverse. These results provide credence to the idea that CAV1 and IL-37 could be a part in early diagnosis of RA.

Keywords: Caveolin-1, Interleukin-37, Rheumatoid Arthritis, Autoimmune, Inflammation.

Introduction

The healthy cells were mistakenly attacked by immune system in autoimmune diseases because it cannot tell the difference between its own cells and foreign ones.[1] The more than eighty distinct types of autoimmune diseases impact a wide range of body systems. Symptoms of autoimmune diseases can range from mild to severe, depending on the individual. Genetics and environmental factors could be potential contributors to the symptoms.[2] Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation that deteriorates peripheral joints and leading to permanent deformity.[3] Genetic susceptibility, self-tolerance dysregulation, immunological dysregulation brought on by external triggers, and subsequent synovial cell change are some of the hypothesized etiologies of RA.[4] Although the detection of several convincing causal elements, RA etiology is immensely complicated, and has not been fully understood yet.[5] When someone has RA, the cells that make-up the synovium's intimal lining layer multiply out of control, creating lesion tissue.[6] In synovial hyperplasia, there are primarily two distinct kinds of cells involved. Type A synoviocytes are terminally featured cells that are dispersed unevenly throughout the synovial membrane and have a finite ability to replicate.[7]

Type B synoviocytes, also known as fibroblast-like synoviocytes (FLSs), are stimulated to produce chemokines,

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growth factors, and proinflammatory cytokines by Type A synoviocytes.[8] It is believed that FLSs, as specialized cells, contribute to the development of RA by causing damage to joints and ongoing inflammation.[9] Joints are broken down and osteoclasts are formed when pannus tissue expresses FLSs, which release proteolytic enzymes, aggrecanases, and cathepsins.[10] In terms of the joint environment, FLSs promote the inflammatory cells influx into joint region through chemoattractants. Inflammatory cell retention and recruitment, pannus hyperplasia, and bone deterioration are all ways in which joint processes contribute to the advancement of RA.[11] One possible solution to retrieve an equilibrium between pro- and anti-inflammatory cytokines is to target individual cytokines or the signaling pathways that cause them to be produced. We must prioritize the discovery of a crucial molecular mechanism that might lead to slow down RA evolution.[12]

Caveolin-1 (CAV1), also known as caveolin or VIP21, is a transmembrane protein of 21–24 kDa that serves as the primary core protein of caveolae, which are vesicular frequently encountered in the cellular membranes.[13] Involved in vesicular transportation and signaling transmission, caveolae are created as a consequence of a specific buildup of glycol-sphingolipids, CAV1, and cholesterol.[14] CAV1 was the first caveolin family member to be discovered in cells altered by the Rous sarcoma virus as a tyrosine-phosphorylated protein. It was later determined to be a constitutional element of caveolae and transport vesicles originating from the trans-Golgi network.[15,16] It›s been suggested that CAV1 acts as a framework to serve as a foundation for the routes› particular controlled activity.[17] CAV1 may play crucial regulatory roles in endocytosis, signal transduction, cholesterol and molecular transportations, and transcytosis membrane trafficking.[18] Beside its primary function as a therapeutic target, it has been associated with two processes that have been studied extensively for their mechano-transduction functions: the modulation of focal adhesions and integrin-mediated actin reconfiguration.[19,20] Based on the cellular environment, CAV1 may either suppress or cause inflammation in conditions involving inflammatory diseases.[21]

Interleukin-37 (IL-37), an anti-inflammatory cytokine, blocks the activity of both innate and adaptive immunity by suppressing the molecules and pathways that promote inflammation.[22-24] In inflammations or some autoimmune disorders, such as RA, IL-37 is stimulated as a natural immune response.[25] Several tissues, including the bone marrow, thymus, liver, uterus, lymph nodes, testis, lung, colon, and placenta,[26] also different inflammatory cells like natural killer cells, monocytes, keratinocytes, and activated B cells secrete IL-37.[27,28] Lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), transforming growth factor-β1 (TGF-β1), toll-like receptors (TLRs), IL-18, and agonists are among the inflammatory stimuli that activate IL-37.[29,30] By binding extracellularly to membrane receptors and forming intracellular complexes, IL-37 can take part in the control of signaling pathways and perform its anti-inflammatory function.[31] When IL-37 binds to nuclear DNA, it can move into nucleus where it modulates genes transcription, which reduces the generation of cytokines and chemokines that promote inflammation.[32] As IL-37 is correlated to the inflammatory onset, autoimmune, metabolic, and cancer problems, it could be a potential target for therapeutic interventions.[33-36]

Therefore, the purpose of the present study was to examine CAV1 with IL-37 serum levels in RA patients in Basrah Province, Iraq, in the hopes of gaining insight that may support in the early detection, prevention, and treatment of RA.

Materials and Methods

Subjects and Principles

IL-37 and CAV1 serum levels in RA patients were studied in this case-control clinical study. Patients were seen by the teaching hospitals (Al-Fayhaa and Al-Zubayr) in Basrah Province in Iraq between October 2022 and February 2023. We randomly assigned 46 RA patients (13 males and 33 females) to one of two groups: those in an active RA state (7 males and 19 women) and those in remission (stable) (6 men and 14 women). In a matched set of 30, 12 males and 18 female healthy controls served as a counterpoint to these patients. The Al-Fayhaa and Al-Zubayr teaching hospitals' rheumatology departments used the 2010 ACR/EULAR categorization criteria to classify RA patients.[37] Results were consistent with a diagnosis of RA based on RA disease activity score version-28 (DAS28).

For patients in the active period group, the DAS28 is greater than 3.2, while for patients in the stable period group, it is less than 3.2.[22] The participants in this research had to be rheumatoid arthritis (RA) sufferers aged 25 to 70. Exclusion criteria for this study included a history of intra-articular corticosteroid injection in the knee within the past six months, erosive osteoarthritis, chronic liver and kidney diseases, other autoimmune diseases, pregnancy, cancer, biological treatments, acute coronary syndrome, and current infection.[7,14] The healthy control group, they were healthy people without RA (even in the family history), with no radiographic osteoarthritis, no indication of chronic inflammatory disease, and no indicators or symptoms suggesting any connective tissue disease.[26,27] For at least three months, each participant's clinical conditions were stable. When the subjects were visited, a structured interview was carried out to collect demographic information. A common self-administered questionnaire is employed to gather information on a person's age, the length of their RA, their health behaviors (such as smoking, drinking alcohol, and eating), their medical records, and their medication lists.

Sampling Procedures

Following 12 hours fasting and thirty minutes of relaxation in the supine posture, all samples were obtained in morning time (10:00 to 11:00 AM). Each participant had 10 milliliters of fresh venous blood drawn and left to clot at room temperature for 20 minutes in an untreated tube. After that, the serum was isolated by centrifuging the sample at 402xg for twenty minutes. While every single sample

was used immediately for the variable estimation, the remaining was kept in freezing at -80°C till it was needed.

Determinations of Clinical Parameters

The serum levels of glucose, urea, and creatinine were measured using a UV-Vis Spectrophotometer (UV-EMC-LAB, Duisburg, Germany). Immunonephelometry assay was used to assess rheumatoid factor (RF) and C-reactive protein (CRP). The levels of serum insulin, CAV1, and IL-37 were determined using an enzyme-linked immunosorbent assay (ELISA) conducted in Human/Germany. The sandwich ELISA technique was employed, and a standard curve was utilized to quantify the quantity of each biomarker.[18,31]

Calculations of BMI and HOMA-IR

Body mass index (BMI) was calculated using the formula: BMI (Kg/m^2) = weight (Kg) / height (m^2).

Homeostatic Model Assessment for Insulin resistance (HOMA-IR) equation was utilized to calculate (IR):[38] HOMA-IR = fasting insulin (μU/mL) X fasting glucose (mg/dL) / 405.

Statistical Analysis

The version 26 of the Statistical Package for the Social Sciences (SPSS) program was utilized for statistical analysis which developed by IBM Corporation, based in Armonk, NY, USA. The data had a normal distribution, and the variance analysis was employed to compare groups before conducting Dunnett's t-test to ascertain statistical significance. The receiver operating characteristics (ROC) curve, which determine sensitivities, specificities, and 95% confidence interval (95% CI), was created by graphing 1-specificity on the x-axis, and sensitivity on the y-axis versus, and calculating the area under curve (AUC). Correlations were created using Pearson correlation. A p-value of less than 0.05 was considered statistically significant, while a p-value of less than 0.01 was considered highly significant. An AUC value close to 0 or 1 suggested a strong diagnostic value.

Ethical Approval

The research's protocol was conducted in accordance with the Declaration of Helsinki, and received approval from the Ethics and Behavioral Research Committee (Scientific Committee) of the Department of Basic Sciences at the College of Nursing, University of Basrah, located in the Province of Basrah, Iraq. Upon receiving a thorough explanation of the processes, all participants provided their informed consent by completing consent forms.

Results

Non-significant variations were seen in both of age and gender between people with RA in active and remission states, and healthy controls. The average age for the three groups was 51.42 ± 11.46, 50.92 ± 9.18, and 52.71 ± 10.36 years, respectively. All the attributes of the participants who participated in this investigation are documented in Table 1. The findings demonstrated that individuals with rheumatoid arthritis (both in active and remission states) did not exhibit a statistically significant alteration ($p>0.05$) in their BMI, urea, glucose, HOMA-IR, insulin, creatinine levels when compared to the group of healthy individuals, as presented in Table 2. However, the data from Table 2 indicated that patients with rheumatoid arthritis (both active and in remission) showed a substantial elevation ($p<0.01$) in serum levels of RF, CRP, and IL-37 indicators, also a significant decline ($p<0.01$) in CAV1 level in comparison with healthy controls.

The obtained area under the curve (AUC) data suggests that RF, CRP, CAV1, and IL-37 have the potential to be highly predictive biomarkers in both Active RA participants (AUC = 1.000, 1.000, 0.0001, 1.000, respectively) and Remission RA subjects (AUC = 1.000, 1.000, 0.007, 1.000, respectively). In Figure 1, it was shown that BMI, glucose, insulin, HOMA-IR, urea, and creatinine were not effective predictive biomarkers in patients with Active RA (AUC = 0.592, 0.431, 0.455, 0.443, 0.476, and 0.450, respectively) or Remission RA (AUC = 0.624, 0.576, 0.448, 0.488, 0.419, and 0.492, respectively).

Table 1: Present Study Demographics.

Parameter		RA Subjects		Healthy Controls
		Active RA	Remission RA	
Total Number of Subjects		**26**	**20**	**30**
Gender Ratio (Men/Women)		7/19	6/14	12/18
Age (Years) (Mean ± SD)		51.42 ± 11.46	50.92 ± 9.18	52.71 ± 10.36
DAS28 (Mean ± SD)		6.91 ± 1.62	1.98 ± 0.86	0
Duration of RA (Years) (Mean ± SD)		11.56 ± 3.25	7.33 ± 1.62	0
Morning Stiffness Time (min)		84.33 ± 20.12	31.55 ± 16.26	0
Tenderness Joints (three or more joints) (case, %)		23, 88.46%	13, 65%	0, 0%
Swellings Joints (three or more joints) (cases, %)		18, 69.23%	2, 10%	0, 0%
Erosion or Osteoporosis Joints (by X-Ray) (case, %)		17, 65.38%	5, 25%	0, 0%
Educational Background	Learned	18	16	24
	Illiterate	8	4	6
Smoking Habits	Positive	0	0	0
	Negative	26	20	30
Food Habits	Vegetarian	21	17	19
	Non-Vegetarian	5	3	11
Employment Status	Employed	10	8	14
	Not Employed	16	12	16
Demographic Area	Urban	20	11	22
	Rural	6	9	8

The results from Table 3 indicate that there were strong and statistically significant positive associations ($p<0.01$) between the CAV1 level and the RF, CRP, and IL-37 in both Active and Remission RA individuals. In addition, IL-37 exhibited a strong and statistically significant positive connection ($p<0.01$) with RF, CRP, and CAV1. In contrast, CAV1 and IL-37 exhibited insignificant negative correlations ($p>0.05$) with BMI, urea, glucose, HOMA-IR, and insignificant positive correlations ($p>0.05$) with insulin and creatinine in participants with Active RA. CAV1 and IL-37 exhibited insignificant negative associations ($p>0.05$) with insulin, glucose, HOMA-IR, and insignificant positive correlations ($p>0.05$) with creatinine and BMI in participants with Remission RA. In Remission RA individuals, CAV1 had a no significant inverse ($p>0.05$) correlation with urea, while IL-37 displayed a no significant ($p>0.05$) direct connection with urea.

Table 2: Serum Biomarkers Levels in RA Subjects and Healthy Group.

Marker	RA Patients										Healthy Controls
	Active RA					Remission RA					
	Mean ± SD	SE	Range	95% CI		Mean ± SD	SE	Range	95% CI		Mean ± SD
				Lower	Upper				Lower	Upper	
BMI (kg/m^2)	21.00 ± 1.53	0.3	18.50 – 23.50	20.38	21.62	21.25 ± 1.72	0.38	18.49 – 24.00	20.44	22.05	20.53 ± 1.14
Glucose (mg/dL)	83.10 ± 4.59	0.90	75.60 – 90.60	81.25	84.95	86.25 ± 6.51	1.46	75.80 – 96.70	83.20	89.30	84.55 ± 6.16
Insulin (µU/mL)	12.00 ± 1.53	0.30	9.50 – 14.50	11.38	12.62	11.95 ± 1.31	0.29	9.70 – 13.90	11.33	12.56	12.32 ± 2.02
HOMA-IR	2.46 ± 0.36	0.70	1.80 – 3.00	2.32	2.61	2.55 ± 0.34	0.76	1.90 – 3.30	2.39	2.71	2.60 ± 0.62
Urea (mg/dL)	35.25 ± 5.35	1.05	26.50 – 44.00	33.09	37.41	34.25 ± 5.32	1.19	25.70 – 42.80	31.76	36.74	35.70 ± 3.52
Creatinine (mg/dL)	1.03 ± 0.15	0.03	0.78 – 1.28	0.97	1.09	1.06 ± 0.18	0.04	0.77 – 1.34	0.97	1.14	1.06 ± 0.18
RF (IU/mL)	209.20 ± 19.89**	3.90	176.70 – 241.70	201.17	217.23	148.37 ± 14.20**	3.16	125.66 – 171.07	141.75	154.98	11.27 ± 2.11
CRP (mg/dL)	29.53 ± 5.20**	1.02	21.03 – 38.03	27.43	31.63	23.34 ± 4.79**	1.07	15.64 – 31.03	21.09	25.58	2.13 ± 0.97
CAV1 (ng/mL)	6.07 ± 0.92**	0.18	4.57 – 7.57	5.70	6.44	10.04 ± 0.95**	0.21	8.52 – 11.56	9.60	10.48	14.57 ± 2.02
IL-37 (pg/mL)	90.70 ± 14.61**	2.87	66.82 – 114.57	84.79	96.60	59.69 ± 15.80**	3.53	34.32 – 85.05	52.29	67.08	20.15 ± 4.84

The data is presented in the format of mean ± standard deviation (SD), with SE representing the standard error. The range refers to the extent between the highest and lowest values in a collection. The 95% confidence interval (lower and upper) is the range of values within which we can be 95% confident that the true value lies. The level of significance is determined by an asterisk (*). When comparing a patient value to a control value, the p-value is considered insignificant when it is greater than 0.05. Conversely, the p-value is considered significant when it is less than 0.05 (*), and highly significant when it is less than 0.01 (**).

Table 3: Correlations Coefficient of CAV1 and IL-37 vs. other Parameters in RA Subjects.

Parameters	Active RA Subjects		Remission RA Subjects	
	Correlation Coefficient (r)		Correlation Coefficient (r)	
	CAV1 (ng/mL)	IL-37 (pg/mL)	CAV1 (ng/mL)	IL-37 (pg/mL)
BMI (kg/m^2)	-0.166	-0.143	0.326	0.235
Glucose (mg/dL)	-0.129	-0.104	-0.284	-0.230
Insulin (µU/mL)	0.004	0.013	-0.218	-0.167
HOMA-IR	-0.078	-0.061	-0.344	-0.263
Urea (mg/dL)	-0.151	-0.210	-0.047	0.039
Creatinine (mg/dL)	0.318	0.329	0.233	0.141
RF (IU/mL)	0.970**	0.975**	0.958**	0.917**
CRP (mg/dL)	0.986**	0.971**	0.955**	0.917**
CAV1 (ng/mL)	1	0.992**	1	0.973**
IL-37 (pg/mL)	0.992**	1	0.973**	1

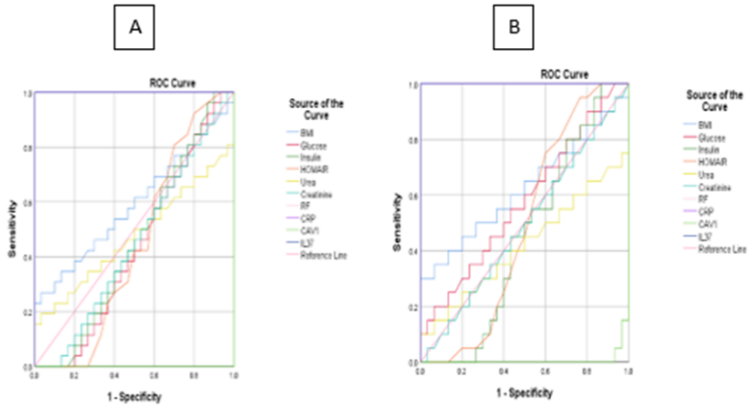

Figure 1: BMI, Glucose, Insulin, HOMA-IR, Urea, Creatinine, RF, CRP, CAV1, and IL-37 ROC Curve for RA and Healthy Control Subjects. A: Active RA. B: Remission RA.

Assessed utilizing Pearson Correlation. The level of significance is determined by an asterisk (*). When comparing a patient value to a control value, the p-value is considered not significant if it is greater than 0.05. Conversely, the p-value is considered significant if it is less than 0.05 (*), and highly significant if it is less than 0.01 (**).

Discussion

This research, conducted in Basrah Province in Southern Iraq, is the first known study to investigate the correlation between various blood biomarker levels in individuals with RA. Based on the statistics, both the patients and the healthy controls in the current study were non-smokers. In addition, as indicated in Table 1, both the healthy control group and the patient volunteers were primarily from urban areas and had respectable jobs and educational backgrounds. The main differences between urban and rural settings include those relating to eating habits, genetics, social contacts, mental health, pollution, environment, and other elements that are rapidly becoming more prevalent in metropolitan areas.[39]

RA, an inflammatory disorder, is characterized by the immune system attacking the body's tissues, resulting in joint soreness, stiffness, swelling, and loss of function. It can attack any joint but is more prevalent in the fingers and wrist. It impacts females more frequently than males.[40] The majority of elderly persons experience it, and it frequently begins in middle age. The condition may only manifest for a brief period, or the symptoms may appear and disappear. The serious type can persist for a lifetime. The risk of RA may be influenced by hormones, genes, and environment. The localized and inflammatory mechanisms that result in RA's mortality and morbidity harm soft tissue, bones, internal organs, and blood vessels as well as cartilage and other tissues.[41]

Our data analysis showed no statistically significant disparity in glucose, insulin, HOMA-IR, urea, and creatinine levels between patients with rheumatoid arthritis (RA) and individuals without the condition.[42] However, our investigation revealed a substantial significant disparity in CRP and RF levels between patients with RA and healthy individuals. Elevated levels of CRP and RF may indicate the presence of a highly detrimental medical disease that is causing inflammation.[43]

Caveolin-1 (CAV1) is an essential protein that engages in cell communication by binding to many signaling molecules.[44] The reduced level of CAV1 in RA subjects in our study may be attributed to oxidative damage and inflammation. Inflammation could increase IL-37 levels, resulting in the overproduction of microRNA-192 (miR-192). This overproduction suppresses RA-FLSs enhancement by declining CAV1 which resulting a significant raising in cell death and reducing in cell proliferation.[45] One research has illustrated that CAV1 enhances cell viability and growth in several diseases. Consequently, CAV1 could facilitate miR-192 growth-regulating effect in RA-FLSs.[41] Furthermore, RUNX2, a specific transcription factor involved in bone formation, has an essential function in modulating extracellular matrix (ECM) proteins production/release which predominantly found in cartilage.[46] RA patients have raised levels of RUNX2 as a result of increased levels of ECM. Therefore, this could be an additional potential cause for the declining of CAV1 levels in RA in comparison to healthy controls in our study. Moreover, low levels of CAV1 which were observed in our study in comparison to healthy controls might be due higher CD26 levels, a 110 kDa cell surface glycoprotein. It is worth noting that CAV1 acts as a co-activated ligand for CD26. When CAV1 binds to CD26, it leads to NF-κB activation and T-cells growth. Both of these process is crucial for inflammation enhancement and subsequent tissue damage.[47] Remarkably, an increased influx of leukocytes induced by CAV1 synthesis can exacerbate inflammation. Considering that the source of different potential Toll-like receptor (TLR) ligands are the inflamed joint and its surroundings, it is potentially that CAV1 is also responsible for the pro-inflammatory cytokine production in FLSs.[48]

Interleukin-37 (IL-37) belongs to IL-1 family and functions by inhibiting function and production of cytokines that cause inflammation. The elevated IL-37 levels in individuals with RA in this study may be attributed to the presence of inflammation. IL-37 may serve like a pivotal natural suppressor in RA. It has been recognized as it plays two distinct roles, one within cells and one outside of cells.[49] Furthermore, studies have shown that IL-37 inhibits the synthesis of many pro-inflammatory cytokines. Insufficient levels of IL-37 are likely responsible for the uncontrolled inflammation observed in RA.[50] The notion is substantiated by the discovery that the pro-inflammatory cytokines exert a significant impact on the serum level of IL-37, which was low in RA patients in remission compared to those who were actively experiencing symptoms. IL-12 has been demonstrated to have both exacerbating and inhibitory effects in experimental arthritis. The progression of RA is believed to involve IL-7 as a crucial mediator. Hence, it's reasonable to propose that IL-37 could act as a negative feedback mechanism to decline elevated pro-inflammatory cytokines levels in RA subjects.[51]

High concentration of IL-37 has the potential to effectively diminish joint inflammation and its severity. Additionally, the autoreactive T lymphocytes in the synovium of RA subjects were activated by dendritic cells (DCs) which leading to a prolonged inflammatory response. The findings of this study demonstrate that elevated IL-37 levels in RA subjects may restrict DCs function and decline adaptive immunological response. The DNA integration into the nucleus inhibits macrophage and DCs activation, resulting in T cells tolerance and cytotoxicity prevention which collectively limit inflammatory responses.[52] Moreover, RA subjects who exhibit elevated IL-37 levels can benefit from its anti-inflammatory properties due to CD4+T Th1 cells predominance in synovial region. It secretes cytokines that have a strong pro-inflammatory effect, such as IL-18 which can stimulate the IFN-γ production, leading to RA inflammation development.[53] Several researches have explained that IL-37 may has an ability to inhibit IL-18 signaling pathways

and reduce the IFN-γ levels. As a result, the inflammatory response in RA is decreased.[54]

Conclusion

Our findings indicate that Cav-1 and IL-37 show potential as biomarkers that provide valuable information for the early prediction of RA. Although detecting RA patients is crucial and time-sensitive, it cannot prevent the onset of autoimmune disease. However, it can increase the chances of early treatment. Additional investigation into the importance of diagnosing and treating RA is necessary due to the pressing nature of the condition.

Recommendations

Further researches are required in this area to understand the function of the investigated clinical biomarkers in the physiology and pathophysiology of the development of RA. Other studies should be conducted on patients with different conditions to see their effects on RA patients such as smoking, oxidant/antioxidant status, and study the genetic expression of some proteins and mutations.

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