Role of '14_3_3 Eta Protein' in Rheumatoid Arthritis

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Abstract: Background: Rheumatoid arthritis (RA) is a common, chronic, inflammatory, autoimmune disease of unknown etiology, associated with articular, extra-articular and systemic effects. It is affecting approximately 1% of the world population **Objectives:** This study is designed to measure the serum levels of 14_3_3 eta protein in patient with rheumatoid arthritis in order to detect its value as a diagnostic and disease severity marker. **Patients and Methods**: We conducted our study on 30 RA patients, and 30 normal healthy individuals served as a control group. The patient and control groups were subjected to full history taking, thorough clinical examination, laboratory investigations, and plain x-ray of the clinically affected joints. **Results:** Significantly higher plasma levels of 14_3_3 eta protein in patients compared to the controls. Statistically significant difference between groups according to ESR and CRP. Positive correlation and significant between marker 14-3-3 Eta protein with ESR, CRP, RF, Anti CCP, Modified DAS score and Larsen Radiological score. RF, AntiCCP and 14-3-3eta indices were significant predictors with sensitivity of (73.3%, 76.6% and 86.67% respectively) this makes 14-3-3 eta protein being the most significant predictor. **Conclusion:** Serum levels of 14_3_3 eta protein was measured in all patients and controls using ELISA technique.

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1. Introduction

Rheumatoid arthritis (RA) is a common, chronic, inflammatory, autoimmune disease of unknown etiology, associated with articular, extra-articular and systemic effects. It is affecting approximately 1% of the world population [(1)].

The synovium, or membrane present in the synovial joints that lines the joint capsules and creates synovial fluid for the joints in the hands and feet, is the first structure affected. The subsequent inflammatory changes lead to cartilage and bone destruction [(2)].

The first symptom of RA is most often starts in the small joints of the fingers and toes. As the arthritis becomes worse, the pain spreads to joints in the ankles, elbows, hips, knees, and shoulders. The symptoms of RA most often begin slowly over weeks to a few months associated with fatigue, joint pain and stiffness, most likely in the morning. Over time, the symptoms can change or become more severe where the extra- articular manifestations develop affecting mainly cardiac and respiratory systems [(3)].

If the disease is diagnosed early before significant joint erosion occurs, treatment can prevent irreversible joint damage. However, early diagnosis is difficult for several reasons: joint symptoms and signs are limited, physical findings to suggest synovitis may be absent, and laboratory test results may be seronegative in some patients. Classification criteria for rheumatoid arthritis from the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) include serology tests for rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody, but 28% to 44% of patients with early disease test negative for both markers [(4)].

Therefore there is desperate need for development of a new biomarker that have predictive capacity for RA. A major unmet need is the assessment of risk for structural progression in RA, particularly in early disease and achieving early remission and prevention of structural damage [(5)].

It is has been believed that (14-3-3 proteins) are the hope in this field. The 14-3-3 family of conserved regulatory proteins consists of seven isoforms. Under normal circumstances, these proteins exist as intracellular adapters that can either homo- or hetero-dimerise to form a cuplike structure known as the amphipathic groove, which allows them to interact with more than 200 intracellular proteins to modulate their activities. Interactions include an array of biological processes, such as protein trafficking and cellular signaling [(6)].

One isoform of theses 14-3-3 family of proteins is the 14-3-3 eta protein. This isoform has been found highly expressed extracellularly in the joints of patients with erosive RA. Additionally, it strongly correlated with MMP-1 and MMP3 in synovial fluid and serum which further characterizes its biological expression and association with rheumatologic disease processes [(5)].

Since RA is an autoimmune disease, the elevation of extracellular 14-3-3η elicits the production of autoantibodies to the native protein,

which will posses the diagnosticutility as early diagnosis coupled with an effective treatment strategy is key to improving outcomes in RA. Accordingly, it has been reported than 60% of patients were positive for 14-3-3η, 32% for RF,44% for ACPA [(5)].

As ACPA and RF are often used together to inform an RA diagnosis, there is incremental benefit of adding 14-3-3η to each of the markers. When rheumatoid factor (RF) was added to (ACPA) diagnostic capture increased from 59% to 72% and this increased further to 78% when 14-3-3η was added. Combined testing of 14-3-3eta with established markers will help physicians with more definitive diagnostic information and help facilitate early treatment with disease modifying anti-rheumatic drug [(5)].

Aim of the work

This study is designed to measure the serum levels of 14_3_3 eta protein in patient with rheumatoid arthritis in order to detect its value as a diagnostic and disease severity marker.

2. Patients and Methods

This study was conducted on 30 RA patients diagnosed according to the American College of Rheumatology (ACR) new classification criteria. 30 healthy individuals matched for age and sex who served as a control group.

Patients were recruited from Physical Medicine, Rheumatology, and Rehabilitation department of Ain Shams University.

All patients were informed about our research work and signed consents before participating in this study.

Exclusion criteria:

- Other autoimmune diseases e.g Degenerative arthritis, as osteoarthritis, Other Seronegative spondyloarthropathies as Ankylosing spondyloarthritis, Reiter's disease and enteropathic arthropathy, Psoriatic arthritis
- Infections
- Osteoporosis
- Malignancy

Methods:

All patients were subjected to the following:

I- Full medical history taking with special emphysis on:

i- Personal history: including name, age, sex, marital state, occupation, residence, menstrual history and special habits of medical importance.

ii- History of medications: including steroids, non-steroidal anti-inflammatory (NSAIDs) and disease modifying antirheumatic drugs (DMARDs). The dose, the duration of intake, drug sensitivity and any intolerable side effects were recorded.

iii- Past history: As regards previous admission to hospital, surgeries, blood transfusion, other rheumatologic diseases, rheumatic fever and tuberculosis.

iv- Family history: As regard similar condition in the same family, history of diabetes mellitus and/or hypertension.

v- Analysis of the complaint of patients and history of the present illness with special emphasis on:

- Onset, course and duration of the disease (with special attention to skin, nails and joint lesion).
- Constitutional symptoms: as fatigue, fever, malaise, weight loss and illness.
- Articular symptoms: as pain, tenderness, hotness, redness, swellings, range of motion and deformity.

II- Clinical examination:

General examination:

- Vital signs: Pulse, Blood pressure, Temperature, Respiratory rate.
- Examination of mouth for oral ulcers.
- Examination of neck for cervical lymph nodes, thyroid swelling or scar of previous operation.
- Examination of skin for: subcutaneous nodules, skin rash, palpable purpura, digital gangrene or ulcers.
- Examination of the extremities for Raynaud's phenomenon and oedema.
- Eye examination**:** for conjunctivitis, scleritis, episcleritis, uveitis, iritis, corneal opacities, dryness and fundus examination.
- Examination of lymph nodes, for enlargement in different groups of lymph nodes.

Articular examination:

Inspection:

i. Skin overlying the joint for redness, scars of previous surgeries, dilated veins, discoloration.

ii. Joint swelling that may be due to bony thickening, synovial membrane thickening or joint effusion.

iii. Distribution of inflamed joints (symmetrical or not, mono or polyarticular (joint number), small or large joints.

iv. Joint deformity in both hands and feet:

- For hands and wrists: swan neck deformity, boutonniere, radial or ulnar deviation.
- For feet: hammer toe, bunion, hallux valgus, loss of foot arches, overriding of toes.
- For elbow: flexion deformity.
- For knee: genu valgus, varus and flexion deformity.

III- Assessment of disease activity:

Modified Disease Activity28 (DAS28):

A) Number of tender joints (28 joint count).

B) Number of Swollen joints (28 joint count).

C) Patient's Global Assessment (PGA) of disease activity on visual analogue scale.

D) Acute Phase Response: ESR

IV- Laboratory investigations as:

a) Routine laboratory investigations:

- Complete blood count (CBC).
- Erythrocyte Sedimentation Rate (ESR).
- C-Reactive Protein (CRP).
- Fasting blood sugar.
- Liver enzyme tests.
- Kidney function tests.
- Serum uric acid.
- Rheumatoid factor (RF).
- Anti cyclic citrullinated peptide (anti CCP Ab).
- Serum levels of 14_3_3 eta protein.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. So, the p-value was considered significant as the following: Probability (P-value) P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant, P-value >0.05 was considered insignificant.

3. Results

Table (1): Comparison between patients and control according to laboratory data

Parameter	Patient group No. = 30		Control group No. = 30		t -test	P -value	ig.
	Range	Mean ± SD	Range	Mean ± SD			
ESR(mm/h)	10 – 96	32.93±22.39	11 – 24	17.15±4.49	-3.712‡	< 0.001	HS
CRP(mg/dl)	1.3 – 12	5.1 ± 2.11	1.5 – 6.3	3.58 ± 1.64	3.086•	< 0.001	HS
Hb(mg/dl)	9.9 – 15	12.31 ± 1.39	9.5 – 15	12.01 ± 1.73	0.741•	>0.05	NS
WBCs(×103/ml)	2.4 – 14.2	7.31 ± 2.87	5.6 – 9.1	7.24 ± 1.27	0.113•	>0.05	NS
Platelet(×103/ml)	167 – 460	274.10 ± 92.15	43 – 385	261.43 ± 78.27	0.574•	>0.05	NS
AST (IU/L)	8 – 37	19.43 ± 7.11	10 – 26	16.80 ± 5.18	1.640•	>0.05	NS
ALT(IU/L)	13 – 32	18.85 ± 4.71	11 – 26	16.93 ± 5.23	1.489•	>0.05	NS
Urea(mg/dl)	2 – 35	10.33 ± 7.82	4.1 – 18.1	9.65 ± 4.03	0.419•	>0.05	NS
Creatinine(mg/dl)	0.6 – 1.1	0.75 ± 0.13	0.6 – 1.1	0.80 ± 0.16	-1.183•	>0.05	NS
FBS(mg/dl)	65 – 103	83.83 ± 12.94	60 – 93	77.93 ± 10.66	1.928•	>0.05	NS
Total Ca(mg/dl)	7.5 – 10	8.98 ± 0.63	8.5 – 10.2	9.26 ± 0.62	-1.775•	>0.05	NS
Ionized Ca(mg/dl)	2.9 – 5.8	4.82 ± 0.76	3.2 – 6	4.95 ± 0.74	0.682•	>0.05	NS
Serum uric acid(mg/dl)	2.1 – 7.1	4.41 ± 1.46	2.8 – 7.5	5.11 ± 1.62	-1.758•	>0.05	NS
RF(IU/ml)	1.3 – 128	3.03±2.34	1.5 – 6.1	3.35±1.43	-2.005‡	<0.05	S
Anti CCP(IU/ml)	0.3 – 405	28.24±75.47	0.1 – 5	3.03±2.34	2.744‡	< 0.001	HS
14-3-3 eta protein(ng/ml)	1.6 – 12.5	6.82±2.53	0 – 11	3.36±2.68	-3.525‡	< 0.001	HS

t-Independent sample t-test; p-value >0.05 NS

Table (2): Correlation between marker 14-3-3 Eta protein with all parameters, using Pearson Correlation Coefficient in patients group.

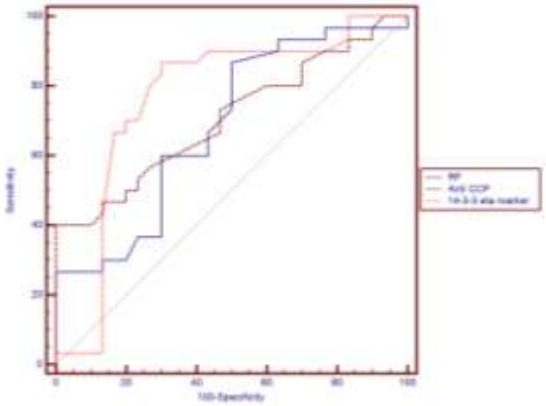
Parameters	14-3-3 eta protien		
	r	P-value	Sig.
Age (years)	-0.224	0.234	NS
Disease duration (months)	0.164	0.385	NS
ESR(mm/h)	**0.381***	<0.05	S
CRP(mg/dl)	**0.496****	< 0.001	HS
Modified DAS-28	**0.707****	< 0.001	HS
Hemoglobin(mg/dl)	0.129	0.495	NS
WBCs(×103/ml)	0.107	0.226	NS
Platelet(×103/ml)	0.119	0.303	NS
AST (IU/L)	-0.149	0.431	NS
ALT(IU/L)	-0.254	0.176	NS
Urea(mg/dl)	0.166	0.380	NS
Creatinine(mg/dl)	-0.012	0.949	NS
FBS(mg/dl)	-0.030	0.875	NS
Total Ca(mg/dl)	-0.223	0.236	NS
Ionized Ca(mg/dl)	0.012	0.949	NS
Serum uric acid(mg/dl)	0.097	0.609	NS
RF(IU/ml)	**0.520****	< 0.001	HS
Anti CCP(IU/ml)	**0.521****	< 0.001	HS
Larsen Radiological score	**0.841****	< 0.001	HS

r-Pearson Correlation Coefficient p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

Positive correlation and significant between marker 14-3-3 Eta protein with disease duration, WBC (x103/mL), Platelets (x103/mL), ESR (mm/hr), CRP (mg/dL), RF, Anti CCP, Modified DAS score and Larsen Radiological score.

Receiver operator characteristics (ROC) curves were constructed for CRP, ESR, RF, Anti CCP and Marker 14-3-3 Eta protein as predictors of activity of rheumatic in included patients. CRP, ESR, RF, Anti CCP and ETA indices were significant predictors as denoted by the significantly large area under the

curves (AUCs); with Marker 14-3-3 Eta protein being the most significant predictor.



Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
RF	0.640	>2.9	73.3	56.7	62.9	68.0
Anti CCP	0.796	>4.1	76.67	70.00	71.9	75.0
14-3-3 eta marker	0.818	>3.9	86.67	83.33	83.9	86.2

Figure (1): Receiver-operating characteristic (ROC) curve for prediction of activity of rheumatic using the CRP, ESR, RF, Anti CCP and Marker 14-3-3 Eta protein (ng/ml).

4. Discussion

Rheumatoid arthritis (RA) is a common, chronic, inflammatory, autoimmune disease of unknown etiology, associated with articular, extra-articular and systemic effects. It is affecting approximately 1% of the world population [(1)].

If the disease is diagnosed early before significant joint erosion occurs, treatment can prevent irreversible joint damage. However, early diagnosis is difficult for several reasons: joint symptoms and signs are limited, physical findings to suggest synovitis may be absent, and laboratory test results may be seronegative in some patients. Classification criteria for rheumatoid arthritis from the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) include serology tests for (RF) and (Anti-CCP), but 28% to 44% of patients with early disease test negative for both markers [(4)].

Therefore, RA identification in the early stages is essential to prevent erosion and to stop the progression of radiologic changes. In this context, the attention paid to the identification of biomarkers with a diagnostic role in the early stages of the disease is still a subject of great interest [(7)].

It is has been believed that (14-3-3 proteins) are the hope in this field 14-3-3 eta protein belongs to the family of 14-3-3 proteins that consists of 7 isoforms, it is localized intracellularly, being externalized in the inflammatory process where it can be citrullinated. The 14-3-3 proteins act like chaperonins [(8)]. It has been demonstrated that soluble biomarker, 14_3_3ε, was present at significantly higher levels in the synovial fluid and serum of patients with arthritis compared to healthy individuals and that serum levels correlated strongly with the matrix metalloproteinases (MMP) MMP-1 and MMP-3 [(6)].

This study is designed to measure the serum levels of 14_3_3 eta protein in patient with rheumatoid arthritis in order to detect its value as a diagnostic and disease severity marker.

Our study included 30 patients, 24 females (80%) and 6 males (20%). The study also included 30 healthy individuals who served as the control group 25 of them were females (83.3%) and 5 were males (16.7%). In this study, the RA was more prevalent in females compared to males (80% of our patients were female) the increased number of female patients in our studied group as well as ***Mohamed et al.*** [(9)]***; Hirata et al.*** [(10)] is 82 % and 86% respectively because RA is 2.5 times more common in females than males [(11)].

The age of our RA patients ranged from 32-55 years with a mean± SD of 39.5±5.0 years and our results come in accordance with ***Mohamed et al.*** [(9)] who reported a mean±SD 44.32±8.44. On the other hand, ***Hirata et al.*** [(10)] reported a mean± SD of 57.3 ± 14.7 years. The onset of RA can occur at any age but peak incidence occurs during the fourth and fifth decades [(11)].

In our study, the disease duration of our 30 RA patients ranged from 6-60 months with a mean±SD of 25.14±13.69 months, this is similar to ***Marian et al.*** [(12)] who reported a disease duration with a minimum of 2.5 and maximum 5 years (30-60 months), but disagreed with ***Novikov et al.*** [(13)] who reported disease duration ranged from 5–20 months as they were studying serum 14-3-3 eta in early RA.

In our study, the serum 14-3-3 eta is elevated in all 30 RA patients, it ranged from 1.6 to 12.5 ng/ml with a mean±SD 6.82±2.53ng/ml. There was a highly significant difference between patients and controls as regard serum 14-3-3 eta levels (P<0.001) while ***Mohamed et al.*** [(9)] reported that Serum 14-3-3 η levels in patients with RA (mean &SD 2.72±1.75 ng/ml) were significantly higher (P< 0.0001) as compared to healthy control, and this suggested that Serum 14-3-3η is expressed at significantly higher levels, these levels were three to five times higher than corresponding levels in the serum of matched donors [(6)].

Regarding disease activity by modified DAS-28 (which was calculated by using ESR values), it showed group values ranged from 3.2– 8.2 with a mean±SD of 6.17 ± 1.13. Among our patient one of them (3.3%) had mild disease activity (DAS-28 >2.6 to ≤ 3.2), 3 patients (16.7%) had moderate disease activity (DAS-28 >3.2 to ≤ 5.1), and 24 of them

(80%) had severe disease activity (DAS-28 >5.1), this is similar to ***Abd Alhamid*** [14] where modified DAS-28 values ranged from 2.9-8.9 with a mean±SD of 6.5±1.6, and there were 2 patients (6.7%) with mild RA disease activity, 2 patients (6.7%) had moderate RA activity, and 26 patients (86.7%) had severe activity of RA. This was not in agreement with ***Singh et al.*** [15] whom 4.5% of their studied 200 RA patients were in remission, 2.5% had mild disease activity, 31% had moderate disease activity, and 62% had severe disease activity, this difference may be due to large number of their studied patients (200 patients).

A highly significant positive correlation between serum 14-3-3η levels and DAS28 in our patients (P <0.0001) was reported in our study, This data matching with ***Mohamed et al.*** [9] which stated that there was significant positive correlation between serum 14-3-3η levels and DAS28 in RA patients & particularly in early RA (P <0.0001) and not with established RA as they where treated by both anti-TNF and standard DMARD therapies, which denote the relation between serum 14-3-3 eta and the severity of the disease.

As regard the laboratory results, in our study the ESR levels in the RA patients ranged from 10-96 mm/hr with a mean± SD of 32.93±22.39 mm/hr. The CRP levels in the RA patients ranged from 1.3-12mg/dL with a mean±SD of 5.1±2.11 mg/dL. There was highly significant difference between patients and controls as regard ESR and CRP(p<0.001). That come in accordance with ***Abd Alhamid*** [14] who reported highly significant differences between patients and control regarding CRP and ESR levels (p<0.001). Although ESR and CRP are nonspecific for the diagnosis of RA, but they are important auxiliary markers for the activity of RA [16].

Our study showed significant positive correlation between serum 14-3-3 η levels and ESR, CRP (p<0.05, p<0.001) respectively. This is in accordance to ***Mohamed et al.*** [9] who registered significant positive correlations between serum 14-3-3 η levels and ESR, CRP (P=0.004, P=0.032) respectively. In the early period of the disease, high CRP levels lead to the consideration that a progressive and erosive disease is present ***Neto et al.*** [17] therefore, elevated serum 14-3-3 eta indicate disease progressiveness.

Among our 30 RA patients, RF was negative in 22 of them (73.3%) and positive in 8 of them (26.7%) with mean±SD of 3.03±2.34 U/ml, and anti-ccp Ab was negative in 21 patients(70%) and positive in 9 patients (30.0%) it's mean±SD among them was 28.24±75.47 U/ml, this disagreed with ***Abd Alhamid*** [14] who reported that 21of their patients (70.0%) were RF positive, and anti-ccp Ab was positive in 20 patients (66.7%) it's mean±SD among them was 145.24±100.55 U/ml,this differences in our value may related to that most of our patient were under DMARDs and anti-TNF treatment. This was confirmed in a study that analysed changes in RF and antiCCP levels with Infliximab and Methotrexate treatment in RA**,** which determined a decrease in RF levels, greater declines in anti-CCP antibody levels with treatment in RA [18]**.**

As regard antibodies test, There was a significant difference of RF and AntiCCP between the patients and controls (p<0.05, (P<0.001), ***Mohamed et al.*** [9] reported RF and Anti-CCP levels in patient with RA were significantly higher (P<0.001) as compared to all controls. The difference in RF value between previous studies may refere to the seronegativity in RF value in our study, 22 of our patients (73.3%) were negative.

Our study revealed significant positive correlation between serum 14-3-3 eta and Anti-CCP, RF (P<0.001). This is in accordance to ***Mohamed et al.*** [9] that reported positive correlation between serum 14-3-3 η and titers of ACPA and RF (P=0.001 & P=0.034 respectively). Previous studies by ***Forslind et al.*** [19] on the possible predictive value of antibodies to citrullinated proteins for x ray changes have provided that anti-CCP positive patients had significantly higher Larsen score (p=0.008) Another study investigated that the Anti-CCP antibody assay has a similar diagnostic sensitivity to that of RF in early RA, but is better as a predictor of the disease course over 3 years [20]**.** This boosts the result of our study that presence of anti-CCP and serum 14-3-3 eta are associated with joint destruction.

Scored radiographs can be used as an outcome measure to assess the severity and progression of RA [21]. Among our 30 RA patients larsen values ranged from 1-50 with a mean± SD of 9.33 ±9.90. Highly significant positive correlation between, serum 14-3-3 eta and larsen score (P<0.0001) was scored in our study.. This comes in accordance to a study by ***Hirata et al.*** [10] who found that there was positive correlation between the serum levels of 14_3_3 eta protein (ng/mL) and radiographic joint damage progression in their RA patients. The higher the 14-3-3ε baseline levels the stronger the association with radiographic progression between baseline and each of the follow-up evaluations (r approximately 0.19, p<0.001). Similarly, the higher the decrease in 14-3-3ε titers between baseline and 18 months, the lesser the radiographic progression from 18 to 30 months (r = –0.14, p = 0.018). In another study for analysis of serum 14-3-3η expression in relation to joint damage and progression revealed significantly higher levels of 14-3-3η in patients who already had radiographic evidence of damage at study baseline, as well as in

those who developed progression by the end of the follow-up period. The stimulation of monocytes from THP-1 cell line with 14-3-3 eta in concentration similar to those found in the serum found in the serum of patients with RA resulted in the induction of pro-inflammatory cytokines, interleukin (IL)-1β, IL-6, TNF-α, and joint degradation factors such as MMP-9 and RANKL [(8)].

There was no statistical significant differences between the RA patient and control groups as regards Hg levels, WBC and levels,Urea, Creatinine, serum uric acid, total and ionized serum Ca levels.

ROC curve analysis comparing patient with RA with all control demonstrated a significant AUC of 0.764 at a cutoff of >3.9 ng/ml, the ROC curve yielded a sensitivity of 86.67% a specificity of 70% a PPV of 74.3, and an NPV of 84.0 denoting high diagnostic accuracy and implicating strong ability of 14_3_3 eta protein to differentiate between the patients and controls. This in accordance with ***Mohamed et al.*** [(9)] where the ROC curve yielded a sensitivity of 87.7%, a specificity of 97.6%.

In our study, we found that in our RA patients 86% of patients were positive for 14-3-3 eta, 26.6% for RF and 30%for ACPA. This come in accordance with ***Marotta et al.*** [(22)] who stated that in early RA cohort, 60%of patients were positive for 14-3-3 eta, 32% for RF, 44% for ACPA.

14-3-3-eta protein complements to RF marker, so like which study demonstrated that 14-3-3η is an RA specific marker that complements both RF and ACPA, increasing their diagnostic value [(22)].

In a project conducted on 619 subjects, 14-3-3-eta protein sensitivity and specificity for RA was 77% and 93%, respectively, in the early stages of the disease, the determination of protein 14-3-3-eta along with RF and Anti-CCP increases the diagnostic rate from 72%(RF + Anti-CCP)to 78% (RF + Anti-CCP + 14-3-3-eta). One of the advantages of 14-3-3η as an RA marker is that it can improve identification rates of early RA. Maksymowych and colleagues found that adding 14-3-3η (cutoff ≥0.19 ng/ml) to RF and CCP antibody testing increased diagnostic sensitivity for early RA patients [(8)].

Conclusion

Patients with RA had elevated levels of serum 14_3_3 eta protein compared to controls. We found that serum 14_3_3 eta protein concentrations significantly correlated with disease severity scales, laboratory data (acute phase reactants) and radiological findings. 14_3_3 eta protein measurement may not only serve as a diagnostic biomarker for RA, and has the potential to contribute to the fundamental processes underlying the pathogenesis of RA,but also it may serve as a biomarker for disease progression, activity and severity. So, our data stated that addition of 14-3-3η as a serological for RA is of great value.

4/21/2019

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