Serum Level of 14-3-3η (Eta) Protein as a Diagnostic Marker for Rheumatoid Arthritis and Potential Correlation with Disease Activity

Abstract

Background: New markers are needed for early diagnosis of Rheumatoid Arthritis as Seronegativity in both early and established RA remains a major limitation of both anticitrullinated protein antibodies (ACPA) and rheumatoid factor (RF). The 14-3-3η protein may represent a novel biomarker for the detection of RA.

Aim of the work: to study serum14-3-3η as a prospective RA-specific marker that complements both RF and ACPA and increasing their diagnostic value.

Methods: RA patients (92 patients; 57 with early RA & 35 with established RA) were included and control group (74 subjects; 18 patients with PsA,14 patients with SLE &42 healthy subject). All demographic, clinical data &serological data(disease activity score in 28 joints (DAS28) and ESR, CRP, RF and ACPA were recorded. serum14-3-3η levels were estimated for all.

Results: serum 14-3-3 η levels in patients with RA (mean &SD 2.72±1.75ng/ml) were significantly higher (P<0.0001) as compared to healthy individuals [0.09±0.09 ng/ml] and all controls [0.14±0.21ng/ml)]. For serum 14-3-3 η diagnostic accuracy in RA; ROC curve analysis comparing patient with RA with all control showed a significant AUC (P < 0.0001) and at a cutoff of ≥ 0.39 ng/ml, the ROC curve yielded a sensitivity of 90.2%, a specificity of 94.6%, a PPV of 0.98, and an NPV of 0.73. There were no significant differences in14-3-3 η serum levels between the early and established RA groups (2.73±1.79 Vs 2.70±1.69ng/ml). There was significant positive correlation between serum 14-3-3η levels and DAS28 in RA patients & particularly in early RA (P <0.0001).

Conclusion: 14-3-3η is an RA specific marker that complement bothRF and ACPA, and of great value as a serological marker for early RA.

Keywords: Serum14-3-3η; RA diagnosis; Disease activity

Research Article

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that affects about 1.5% of the community. It is induced by multiple pathophysiological factors and reveals high heterogeneity among patients accompanying the course of the disease. If untreated, RA results in severe joint destruction leading to impaired physical function and workplace disability [1,2]. It is now widely affirmed that identification of RA at an early stage, evaluation of disease severity at diagnosis, and implementation of an efficient treatment strategy can significantly improve a patient's prognosis [3]. In recognition of this, RA classification criteria were established in 2010 focusing on defining the disease by its earliest features [4]. Seronegativity in both early and settled RA remains a major hindrance of both anticitrullinated protein antibodies (ACPA) and rheumatoid factor (RF) highlighting the need for new complementary markers that will improve diagnostic sensitivity [5,6]. Development of novel RA markers is required to allow classification of patients into different risk groups properly. The current markers estimate only for around thirty percent of the total diversity in predicting disease outcome [7]. The 14-3-3η protein is a novel biomarker for RA detection [1]. There are seven is forms of the 14-3-3 intracellular proteins family. They share about 50% amino acid similarity among each other and interact with a lot of intracellular proteins, thereby controlling an array of biological processes including protein synthesis, cellular metabolism, protein trafficking, and cytoskeleton transport [8]. Overall isomers, only 14-3-3η was present in synovial fluid with high levels (at least 5-fold greater than its level in matched sera) implicating the joint as the likely source of 14-3-3η [9,10]. In the extracellular environment, soluble 14-3-3η possesses ligand activity, preferentially activating cells of the innate immune system [8]. Soluble 14-3-3η acts through signaling cascades as the extracellular kinase and P38 pathway, this leads to up regulation of some proinflammatory cytokines, such as interleukin6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), Matrix metallopeptidase 9 (MMP-9) and receptor activator of nuclear factor-κB ligand (RANKL) [11]. Serum levels of 14-3-3η favor to be high in RA patients, but not in another disorder as osteoarthritis, osteoporosis, gout, psoriasis, Crohn's disease, ulcerative colitis,

type 1 diabetes, systemic lupus erythematosus, primary Sjogren's syndrome, scleroderma, and multiple sclerosis [12,13]. Early diagnosis of RA can minimize irreversible joint damage [14].

Aim of the Work

Is to evaluate the diagnostic benefit of serum 14-3-3η as a diagnostic marker for RA (early and established) by comparing its presence in RA versus the non-RA patient's using a 14-3-3η quantitative ELISA, and to detect to what degree it will enhance diagnostic utility when combined with standard clinical and serological variables in early RA. Also, we try to explore possible correlation with disease activity.

Subjects And Methods

Patients with RA and controls

Demographic evaluation of all participants was done (Table 1), besides clinical assessment of the early and established cohorts with RA (Table 2). Serum 14-3-3η levels were measured for 92 patients with RA classified according to the (ACR) American College of Rheumatology 2010 criteria (4) with mean age 44.32±8.44years & female /male ratio 8.2/1. For comparison to the established RA group, serum 14-3-3η levels were analyzed from a total of 74 controls. 42 presumed healthy subjects and 32 patients with arthritis other than RA; 14 patients with systemic lupus erythematosus and 18 patients with psoriatic arthropathy. For evaluation of the 14-3-3η expression in early RA, serum levels were measured in 57 patients who had a mean disease duration 1.17±0.47 years. All demographic & clinical data, Disease Activity Score in 28 joints (DAS28) and Serological assessment including ESR, CRP, RF and ACPA were recorded. Patients and controls were collected from the outpatient clinic of Rheumatology in SAUDI GERMAN HOSPITAL, Jeddah; KSA. All participants signed informed consent forms to participate in the study. Also, Ethics Board approval was obtained before the work.

Assay of serum 14-3-3 η

Determination of serum 14-3-3η levels was done using the quantitative 14-3-3-η ELISA kits. The 14-3-3η ELISA assay has strong analytical action as determined by high sensitivity, assay accuracy and lack of significant cross-reactivity with other is forms. Also, it is characterized by an absence of affect by potential interfering substances such as RF and various therapeutics used in RA, and absence of sample drift over time. The assay sample and buffer were incubated together in a pre-coated plate for one hour. After the incubation period; the wells were decanted and washed five times. The wells were then incubated with a substrate for horseradish peroxidase (HRP) enzyme. The product of the enzyme-substrate reaction formed a blue colored complex. Finally, a stop solution was added to stop the reaction, which turned the solution yellow, the strength of the color was measured spectrophotometrically. A standard curve was plotted relating the intensity of color to the concentration of standards [15].

Table 1: Demographic & serological data of studied groups.

Groups(No.) Parameters	Rheumatoid arthritis(92)	Controls(74)	PsA(18)	SLE(14)	Healthy control (42)	P value
Gender (Female %)	89.13(82)	86.49%(64)	83.33%(15)	92.86%(13)	85.71%(36)	NS
Age (Years) Mean ±SD	44.32±8.44	41.55±6.75	45.16±8.49	40.52±5.28	40.52±5.89	NS
RF(IU/ml) Mean± SD	78.73±80.61	12.52±15.07	14.58±19.46	20.09±22.45	9.12±7.36	<0.0001
ACPA (U/ml) mean± SD	186.84±258.05	3.59±6.31	4.06±5.15	4.98±10.70	2.95±4.72	<0.0001
14-3-3η (ng/ml) Mean± SD	2.72±1.75	0.14±0.210.19±0.38	0.19±0.38	0.17±0.16	0.09±0.09	<0.0001

ACPA: Anticitrullinated Protein Antibodies; RF: Rheumatoid Factor; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; Psa: Psoriatic Arthritis, Ng= Nanogram, U/Ml= Unit/Mille, IU/Ml= International Unit

Table 2: Demographic & serological data of RA patient group.

Parameters	Early RA, n = 57, mean± SD	Established RA, n = 35 mean± SD	P value
Age	44.94±8.64	43.31±8.13	NS
Gender(Female/Male)	50/7	32/3	NS
Disease duration	1.17±0.47	7.06±2.58	<0.0001
RF(IU/ml)	76.74±80.37	81.98±82.08	NS
ACPA (U/ml)	209.67±256.11	149.12±260.64	NS
14-3-3η (ng/ml)	2.73±1.79	2.70±1.69	NS
DAS 28	3.63±1.23	3.10±0.78	0.027
CRP(mg/L)	26.71±32.54	7.06±8.71	0.001
ESR (mm/hour)	47.56±25.70	31.54±10.33	0.001

RA: Rheumatoid Arthritis; DAS28: Disease Activity Score, 28-Joint Count; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; RF: Rheumatoid Factor; ACPA: Anticitrullinated Protein Antibodies

Statistical methods

Statistical analysis was performed using SPSS version 21.0 (SPSS Inc., Chicago, IL). Data are expressed as mean value ± SD. Differences among groups in clinical & serological data were compared by one-way ANOVA test for normally distributed values. Correlations between variables were estimated by the Spearman rank- order correlation. Descriptive statistics were used to express clinical and serological measurements according to disease category and healthy controls. Mean & SD of 14-3-3 η serum expression differences between the RA and control groups were tested for statistically significant differences using t. test. For comparing more than two groups, the one-way ANOVA method was used to determine if there is statistical significance across the groups or not. Receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic utility of 14-3-3 η as estimated by the area under the curve (AUC), and the corresponding positive and negative predictive values (PPV; NPV). The additional diagnostic value increased by assessment of 14-3-3 η in early and established RA (in addition to RF or ACPA alone and together). Further, sensitivity and specificity of RF, ACPA, and RF and/or ACPA with and without the inclusion of 14-3-3 η was calculated for both the groups with early and established RA concerning the healthy controls and all controls (healthy plus disease controls). We compared patients who were 14-3-3 η positive and negative for disease activity using t.test. The relationship between 14-3-3 η and other serological markers was assessed using the Spearman's rank correlation coefficient procedure for non-normally distributed data and Pearson's product-moment correlation for normally distributed variables. Differences between groups were considered to be statistically significant when P< 0.05.

Results

Compared to control group

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 individuals [0.09 ±0.09 ng/ml] and all controls [0.14±0.21ng/ml). RF and ACPA levels in patient with RA were significantly higher (P<0.0001) as compared to all controls. There was the insignificant difference between RA patients and all controls as regard to age and gender distribution. Although levels of serum 14-3-3 η in PsA and SLE patients were numerically higher than healthy individuals control group but it was insignificant(P>0.05). ROC curve analysis comparing patient with RA with all control demonstrated a significant (p < 0.0001) AUC of 0.988 (95% CI, 0.977–0.999; Figure 1). At a cutoff of ≥ 0.39 ng/ml, the ROC curve yielded a sensitivity of 90.2%, a specificity of 94.6%, a PPV of 0.98, and an NPV of 0.73(Figure 1).

Among patients' groups

There were no significant differences in14-3-3 η serum levels between the early and established RA groups (2.73±1.79 Vs 2.70±1.69ng/ml). Early RA had significantly higher levels of CRP, ESR, and DAS28 (P=0.001, P= 0.001& P=0.027 respectively) compared to established RA. There were no significant differences in RF and ACPA levels between the early and established RA groups. In both early and established RA, patients with positive (or higher levels) serum 14-3-3 η had insignificantly higher DAS28 (3.55±1.21 Vs 3.10±0.98, P>0.05) compared to negative (or higher levels) patients. Furthermore, RF and ACPA levels in patients with positive (or higher levels) serum 14-3-3η were significantly higher (220.30±269.26 Vs 13.80±31.85, & 89.33±82.92 Vs 24.32±33.51 P= 0.004 respectively) compared to negative one. As expected early RA had significant short disease duration and insignificant ages compared to established RA.ROC curve analysis comparing early RA with healthy controls demonstrated a significant (P< 0.0001) AUC of 0.999 (95% CI, 0.997–1.00). At a cutoff of ≥ 0.39 ng/ml, the ROC curve yielded a sensitivity of 87.7%, a specificity of 97.6%, a PPV of 0.98, and an NPV of 0.85. ROC curve analysis comparing established RA with healthy controls demonstrated a significant (P< 0.0001) AUC of 0.990 (95% CI, 0.976–1.00). At a cutoff of ≥ 0.39 ng/ml, the ROC curve yielded a sensitivity of 91.4%, a specificity of 97.6%, a PPV of 0.96, and an NPV of 0.93.

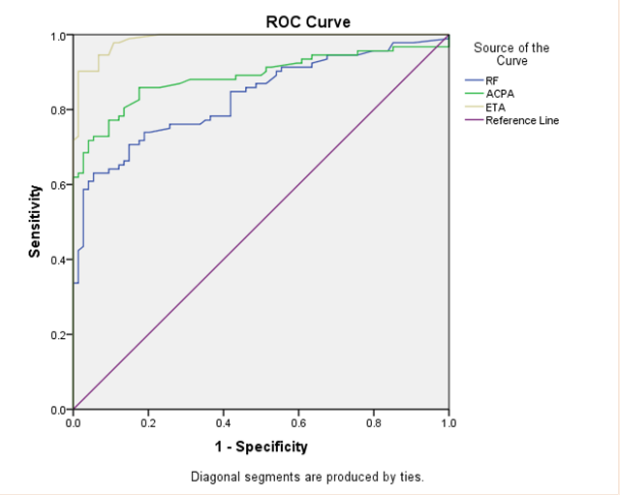

Figure 1: Receiver operating characteristic curves (ROC) of 14-3-3η, RF and ACPA for RA diagnosis.

Correlations of serum 14-3-3 η with clinical & serological measures in RA patients

The correlation presented in Tables 3A&B showed the relationship between the levels of 14-3-3 η and clinical and serological variables in both the early and established RA cohorts, Serum 14-3-3 η correlated positively with the titers of ACPA and RF (P=0.001 & P=0.034 respectively). Also, there were significant positive correlations between serum 14-3-3 η levels and CRP, ESR and DAS28 (P=0.032, P=0.004 and P<0.0001, respectively). As expected, a significant correlation between ACPA and RF was observed in both the early and established RA. Of the 57 patients assessed with early RA, 37(64.9%), 39(68.4%), and 47(82.5%) were positive for RF, ACPA, and 14-3-3 η, respectively. As expected in a cohort with advanced RA, the proportion of patients with positivity in all three markers was greater in the cohort with established RA (RF 25 (71.4%), ACPA 30(85.7%) and 14-3-3 η 30(85.7%). When assessing the cohort with early & established RA, The hopeful benefit of adding 14-3-3 η to each of the markers was assessed; adding 14-3-3 η to RF and/or ACPA increased diagnostic detection for RA (Table 4).

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Table 3: Complementary between diagnostic markers (RF, ACPA, 14-3-3η) in patients with early and established RA

Diagnostic Markers	Early RA, n=57	Incremental Benefit	Established RA, n=35	Incremental Benefit
RF	37(64.9%)	-----	25(71.4%)	-----
ACPA	39(68.4%)	-----	30(85.7%)	-----
14-3-3 η	47(82.5%)	------	30(85.7%)	-----
RF and /or ACPA	39(68.4)	2	30(85.7%)	5
RF and/or 14-3-3 η	47(82.5%)	10	30(85.7%)	5
ACPA and/or 14-3-3 η	49(85.9%)	11	32(91.4%)	2
RF and/or ACPA and/or 14-3-3η	50 (87.7%)	11	32(91.4%)	2

RF: Rheumatoid Factor; ACPA: Anticitrullinated Protein Antibodies; RA: Rheumatoid ArthritiS

Table 4a: Correlation coefficients (r) of 14-3-3η with clinical and serological measures in patients with early RA (Spearman's rank correlation).

Variables	DAS28	RF	ACPA	14-3-3	CRP	ESR
DAS28	------					
RF	<0.0001	--------				
ACPA	<0.0001	<0.0001	-------			
14-3-3	<0.0001	0.01	<0.0001	-------		
CRP	<0.0001	<0.0001	<0.0001	0.038	--------	
ESR	<0.0001	0.002	0.001	0.02	<0.0001	--------

RA: Rheumatoid Arthritis; DAS28: Disease Activity Score, 28-Joint Count; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; RF: Rheumatoid Factor; ACPA: Anticitrullinated Protein Antibodies

Table 4b: Correlation coefficients (r) of 14-3-3η with clinical and serological measures in patients with established RA (Spearman's rank correlation).

Variables	DAS28	RF	ACPA	14-3-3	CRP	ESR
DAS28						
RF	0.026	-------				
ACCP	0.027	0.012	------			
14-3-3	NS	NS	0.002	------		
CRP	<0.0001	NS	0.043	NS	------	
ESR	0.03	0.034	NS	NS	0.05	-----

RA: Rheumatoid Arthritis; DAS28: Disease Activity Score, 28-Joint Count; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; RF: Rheumatoid Factor; ACPA: Anticitrullinated Protein Antibodies

Discussion

Both ACPA and RF markers are included in the ACR/EULAR classification criteria for RA [4], and studies show that the combined use of these markers provides greater sensitivity than the use of either alone [16,17]. Despite this increased sensitivity, patients who develop erosive RA may remain negative for both markers [18]. Thus, other markers for RA have been sought. Serum 14-3-3η is expressed at significantly higher levels than the other isoforms in the synovial fluid of patients with arthritis and that these levels were three to five times higher than corresponding levels in the serum of matched donors, citing the joint as the likely source of serum 14-3-3η [8]. In agreement with these data, our study showed that serum 14-3-3η levels were significantly higher in RA patients than all control subjects which is matched with a recent study showed that 14-3-3η is significantly different between patients with early RA and other autoimmune disorders, and healthy controls [14] & also with another study which reported that 14-3-3η is an RA-specific marker that complements

both RF and ACPA, increasing their diagnostic value [19,20]. We found that by the addition of serum 14-3-3η to both RF and ACPA markers; the detection sensitivity in subjects with early RA was increased by 19.3% & 12.3% respectively; of the 57 subjects with early RA, 43 (75.4%) patients were positive for RF or ACPA, and 47 (85.9%) were 14-3-3η positive. Seven (50%) of the 14 patients who were seronegative for RF and ACPA were 14-3-3η positive and also we reported that using serum 14-3-3η assessment for the detection of early RA had the upper hand over either RF or ACPA by 17.6% and 17.5 %, respectively (Table 3) which was matched with a studies demonstrated that serum 14-3-3 η assessment enhanced the detection of RA over either RF or ACPA by 32% and 22%, respectively, in patients with early RA [14] and with a previous study stated that in an early RA cohort, 60% of patients were positive for 14-3-3η, 32% for RF, 44% for ACPA and 72% for at least one of those three markers [20]. Further, of the 35 patients with established RA, only 3 (42.9%) of the 7 patients who were seronegative for RF and ACPA were 14-3-3η– positive (Table 4). So, 14-3-3η has a clinical utilization further than RF and ACPA in patients with early RA only, and we stated that the testing of 14-3-3η together with RF and ACPA might assist in identifying those patients who require an early referral to a rheumatologist and14-3-3η confirms joint-specific inflammation in the absence of traditional serological markers as it was reported that a positive association between 14-3-3η and MMPs suggested that 14-3-3η may have a role in the pathogenesis of RA [20]. 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 [14]. For the diagnosis of RA, the benefit of increased sensitivity allows earlier detection and treatment in the course of disease, which can minimize irreversible joint damage. Furthermore, a separate study indicated that 14-3-3η serum concentration is correlated with the presence of joint damage [11]. ROC curve analysis comparing patient with RA with all control demonstrated a significant ($p < 0.0001$) AUC of 0.988 (95% CI, 0.977–0.999; Figure 1). At a cutoff of ≥ 0.39 ng/ml, the ROC curve yielded a sensitivity of 90.2%, a specificity of 94.6%, a PPV of 0.98, and an NPV of 0.73 (Figure 1) but when applying ROC curve analysis comparing early RA with healthy controls demonstrated a significant ($p < 0.0001$) AUC of 0.999 (95% CI, 0.997–1.00). At a cutoff of ≥ 0.39 ng/ml. the ROC curve yielded a sensitivity of 87.7%, a specificity of 97.6%, a PPV of 0.98, and an NPV of 0.85 meaning that 14-3-3η is more specific in early RA with high NPV. On the hand, the role of ACPA in the diagnosis of RA is now well established, largely based on prospective data indicating that it has a PPV of about 95% for the development of RA in populations of patients with undifferentiated arthritis, though its NPV is only about 60–70% [21,22]. SO, our data stated that addition of 14-3-3η as a serological for early RA is of great value. We also reported 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 since it was previously reported that 14-3-3η is modifiable by both anti-TNF and standard DMARD therapies [23,24]. Also we found significantly positive correlation between serum 14-3-3η levels and other serological markers (RF, ACPA, CRP and ESR) (Tables 4a-4b). These data matching with other studies which stated that serum 14-3-3η correlate with disease activity (DAS28) and with titters of CRP and noted a modest correlation with ACPA and RF in the early RA cohort, and also in the established RA cohort [11] and with Previously reported that 14-3-3η concentrations are 5-fold higher in synovial fluid than in matched serum [8]. On the other hand, a previously shown that serum 14-3-3η expression is not strongly correlated with standard clinical and serological measures in both early and established RA [25]. In vitro data show that the soluble extracellular form of 14-3-3η activates several proinflammatory signaling cascades relevant to RA [11]. Serum 14-3-3η has also been described as a potent inducer of MMP-9 in vitro, and levels of 14-3-3η correlate with MMP expression in serum and synovial fluid of patients with RA, suggesting that it may play a role in the joint damage cascade [8-11]. Several RA-relevant transcripts were shown to be up regulated by 14-3-3η and included pro-inflammatory cytokines, interleukin (IL)-1β, IL-6, TNF-α, and joint degradation factors such as MMP-9 and receptor activator of nuclear factor kappa-B ligand (RANKL) [11]. The main limitations of our study are the small sample size for both early & established RA and the lake of radiographic progression scoring system. Although, there are a group of patients with undifferentiated arthropathy who are negative for both RF and ACPA & not fulfill the criteria for diagnosis RA in need for testing serum 14-3-3ηfor early detection of RA which will be of great benefit. Finally we recommended ongoing evaluation of the diagnostic utility of 14-3-3 η biomarker as an early marker for RA diagnosis which can provide earlier therapy with DMRD to prevent joint affection and reduce the economic and personal costs of RA. We can conclude that 14-3-3η is a RA specific marker that complements both RF and ACPA, and increasing their diagnostic value. We can conclude that 14-3-3η is an RA specific marker that helps the diagnosis of rheumatoid arthritis and its activity with complements of both RF and ACPA.

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