# Serum and synovial fluid 14-3-3η protein in patients with primary knee osteoarthritis compared with rheumatoid arthritis: relation to functional status and radiographic damage

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**Aim of the work**
The aim of the present work was to examine the association between 14-3-3η protein levels in both serum and synovial fluid (SF) with radiographic damage and physical function in patients with primary knee osteoarthritis (OA) compared with rheumatoid arthritis (RA) patients.

**Patients and methods**
This is a cross-sectional study that involved two groups: group 1 included 50 primary knee OA patients, and group 2 included 50 RA patients. All study patients were assessed for serum and SF levels of 14-3-3η protein that was measured through ELISA technique. Functional assessment of OA patients was done using Western Ontario and McMaster Osteoarthritis index (WOMAC). Radiological assessment was evaluated using Kellgren–Lawrence (KL) grading scale.

**Results**
The mean age of OA patients was 51.7 ± 10.4 years, disease duration was 24.8 ± 5.2 months, and mean WOMAC and KL grading scores were 18.5 ± 6.5 and 2.0 ± 0.99, respectively. Serum and SF 14-3-3η protein was significantly higher among RA compared with OA (1.5 ± 0.51 and 3.6 ± 1.1 ng/ml vs. 0.24 ± 0.03 and 0.24 ± 0.03, $P = 0.004$ and 0.018, respectively). There were no significant differences in serum and SF 14-3-3η protein between male and female OA patients ($P = 0.99$ and 0.87, respectively). A significant correlation was found between serum levels of 14-3-3η and erythrocyte sedimentation rate ($r = 0.49$, $P = 0.014$). The correlations between 14-3-3η protein in OA patients with WOMAC and KL grading scale were weak and not significant ($P > 0.05$).

**Conclusions**
14-3-3η protein levels were significantly lower in OA patients compared with RA patients. Although 14-3-3η levels were significantly correlated with inflammation, there was no correlation with functional status or radiological damage in knee OA patients.

**Keywords:**
osteoarthritis, Western Ontario and McMaster Osteoarthritis index, Kellgren–Lawrence grading scale, rheumatoid arthritis, 14-3-3η protein

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## Introduction

Osteoarthritis (OA) is the most common degenerative joint disease known worldwide, it affects about 10% of men and 18% of women over 60 years. One old study stated that the global increase in life expectancy will make OA a leading cause of disability by the year 2020 and the single greatest cause by 2030 [1]. OA generally can be subcategorized into primary (idiopathic) and secondary OA. The knees are the most commonly affected joints by OA in the body, and account for high morbidity and disabilities of the total burden of the disease [2].

Understanding the pathogenesis of the disease and identification of risk factors can help in early detection and prevention of OA progression. Multiple disciplines are involved in the pathogenesis of OA, including genetic, biologic, and biomedical components [3]. Several biomarkers are involved in pathogenesis of OA, of particular interest is matrix metalloproteinase (MMP) and interleukin (IL) [4,5]. As the ultimate goal for OA management is to alleviate pain, improve functional status, and limit joint destruction, identification of biomarkers associated specifically with mechanistic joint damage would more fully inform the profile of patients who are at higher risk of radiographic progression. Monitoring of such biomarkers would be useful in guiding effective treatment strategies targeted toward minimizing joint

damage, decreasing the resulting disability, and thereby improving patient outcomes [6].

14-3-3 proteins are polypeptides that regulate intracellular signaling pathways [7,8]. The isoform, 14-3-3 eta (η) protein family, is an intracellular protein involved in numerous cell processes, including regulating the proliferation, differentiation, and apoptosis of cells [8,9]. Extracellular 14-3-3η has been demonstrated to stimulate the expression of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and MMP [9]. Previous studies have implicated that the serum14-3-3η protein participates in the process of inflammation in rheumatoid arthritis (RA) and is significantly higher in RA patients compared with patients with other inflammatory arthritis and healthy controls [7,10]. Serum 14-3-3η levels improve the diagnostic utility of patients with RA and also form a prognostic biomarker for radiographic damage and progression [10]. 14-3-3η protein was detected in serum and synovial fluid (SF) of patients with RA [11].

14-3-3η protein is an intracellular protein and is pathologically expressed in the extracellular space. The mechanism by which this protein is released into SF is well known. It is suggested that 14-3-3η may be released from cells via exosomes and that dendritic cells release this protein. Kilani *et al.* [9] observed that fibroblast MMP-1 expression increased in a dose-dependent fashion, suggesting that the high level of MMP-1 seen in inflamed joints might be due MMP-1 stimulatory effect of 14-3-3η protein.

The potential use of 14-3-3η protein as a marker for measuring not only functional status but also the articular cartilage damage in patients with primary knee osteoarthritis (KOA) has not been studied yet. Therefore, this study aimed to examine the serum and SF level of 14-3-3η protein in patients with primary KOA compared with RA. Additionally, the association between 14-3-3η protein in both serum and SF with radiographic damage and physical function in KOA patients was investigated.

## Patients and methods

This study was carried out at the outpatient rheumatology clinic, Assiut University Hospitals, Assiut, Egypt. Fifty OA patients aged greater than equal to 18 years fulfilling the American College of Rheumatology (ACR) guidelines for primary KOA were enrolled [12]. Fifty adult RA patients, diagnosed according to the 2010 American College of Rheumatology classification criteria, were enrolled as a patient control group [13]. Patients with any other arthritis or connective tissue diseases were excluded. All patients provided informed consent to participate in the study. This study was approved by the local ethical committee of the faculty and is consistent with the Declaration of Helsinki 1995.

Full medical history was taken from the patients, including sociodemographic data such as age, sex, disease duration, and comorbidities such as diabetes mellitus and hypertension. The BMI was calculated. The clinical assessment included examination of both knees for signs of inflammation, swelling, redness, and tenderness. Functional assessment was done using Western Ontario and McMaster Osteoarthritis index (WOMAC) [14]. It includes three subscales measuring stiffness, pain, and physical function [15]. The WOMAC form was translated and explained to the patients and they were asked to answer the questionnaire. Patients with KOA were subjected to a complete blood count, erythrocyte sedimentation rate (ESR) (mm/first hour) assessments.

Measurement of 14-3-3η protein was done on both serum and SF samples. Serum and SF samples were stored at −20°C and thawed prior to further analysis. Serum and SF 14-3-3η protein levels were measured by quantitative 14-3-3η ELISA JOINTstat supplied by Augurex Life Sciences Corp., The value of 14-3-3η was considered positive at a level greater than equal to 0.19 ng/ml [16].

Plain radiography knees (anteroposterior weight-bearing, lateral, and skyline views) were assessed using Kellgren–Lawrence (KL) scale [17], where grade I represents doubtful joint space narrowing; grade II: definite narrowing and osteophytes; grade III: some sclerosis and possible deformity of bone contour; and grade IV: severe sclerosis and definite deformity of bone contour [18].

### Statistical analysis

Analysis was complete using STATA15 (STATA Corp., 220 - 887 Great Northern Way Vancouver, BC, V5T 4T5). Variables were presented as mean and SD or SEM, median (interquartile range), or frequencies and percentages. The relationship between variables was investigated by Spearman's rank correlation coefficient. Two multivariate linear regression analyses were measured. The dependent variables were WOMAC and KL scores, while serum and SF 14-3-3η protein along with other clinical and laboratory parameters were tested as the predictors in the multiple regression models. A *P* value of less than 0.05 was considered significant in all analyses.

## Results

Of the 50 patients with KOA, 25 (50%) were females, the demographic and clinical characteristics are presented in Table 1. The mean age was 51.7 ± 10.4 years and the mean disease duration was 24.8 ± 5.2 months. Fifty RA patients, 44 (88%) of them were female, mean age of 37.7 ± 13 years, and mean disease duration of 9.6 ± 8 months, were included as a patient control group.

The relation between serum and SF 14-3-3η protein and WOMAC and KL scores is presented in Table 2. The SF 14-3-3η protein significantly correlated with the ESR ($r$ = 0.49, $P$ = 0.014). KL score significantly correlated with the disease's duration. In the multivariate regression analysis, after adjusting for age, disease duration, BMI, and ESR, serum 14-3-3η protein was not significantly related to both WOMAC and KL scale. Similar results of SF 14-3-3η protein were detected with WOMAC and with KL scale.

The mean serum and SF 14-3-3η protein expression was significantly higher in RA patients compared with OA (Fig. 1). Serum and SF 14-3-3η protein expression was comparable between male and female OA patients (0.24 ± 0.14 vs. 0.24 ± 0.17, $P$ = 0.990 and 0.23 ± 0.13 vs. 0.24 ± 0.18 ng/ml, $P$ = 0.871, respectively) (Fig. 2).

Fig. 3 shows an example of radiographic picture in a female patient with KOA (18-months duration OA) and KL grading scale I (left) and KOA in a female patient with 3 year duration and KL grading scale III (right).

**Table 1 Clinical and demographic characteristics of primary knee osteoarthritis patients**

| Variables | KOA ($n$=50) | RA ($n$=50) | $P$ |
|---|---|---|---|
| Age (years) | 51.7±10.4 | 37.7±13 | <0.001 |
| Sex (females) | 25 (50) | 44 (88) | 0.26 |
| BMI | 25.1±4.1 | 23.4±3.6 | 0.09 |
| Disease duration (months) | 24.8±5.2 | 9.6±8 | **<0.001** |
| Diabetes mellitus | 8 (16) | 9 (18) | 0.29 |
| Hypertension | 12 (24) | 11 (22) | 0.28 |
| ESR (first hour) | 27.3±21.5 | 50.6±29.2 | **0.001** |
| Hemoglobin (g/dl) | 13±1.1 | 10.7±2.1 | **<0.001** |
| WBCs (×10³/mm³) | 7.1±3 | 6.6±1.9 | 0.42 |
| PLT (×10³/mm³) | 235.5±58.3 | 310±108 | **0.003** |
| WOMAC scale | | | |
| Pain | 5.1±2.4 | - | - |
| Stiffness | 3.5±1.9 | - | - |
| Physical function | 9.8±5.1 | - | - |
| Total score | 18.5±6.5 | - | - |
| KL grading scale | 2±0.99 | - | - |
| 14-3-3η protein (ng/ml)# | | | |
| Serum | 0.24±0.03 | 1.5±0.51 | 0.004 |
| Synovial fluid | 0.24±0.03 | 3.6±1.1 | 0.018 |

Values are presented as mean±SD or $n$ (%) or as mean±SEM. ESR, erythrocyte sedimentation rate; KL, Kellgren and Lawrence; KOA, knee osteoarthritis; PLT, platelet; WBCs, white blood cells; WOMAC, Western Ontario and McMaster Osteoarthritis index. Bold values are significant at $P$ value less than 0.05.

**Table 2 Correlations between serum and synovial fluid 14-3-3η protein and clinical, laboratory, and radiographic parameters in primary knee osteoarthritis patients**

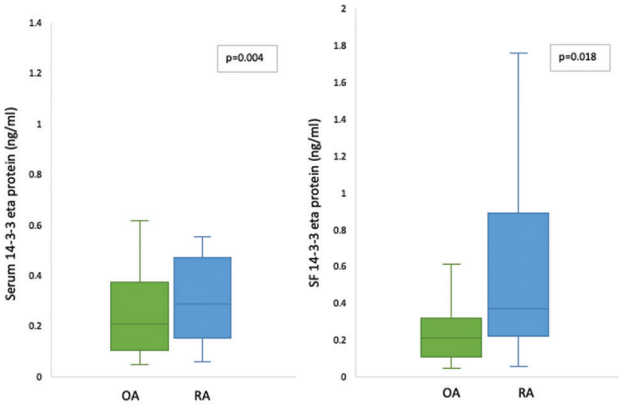
| | Primary KOA patients ($n$=50) | |
|---|---|---|
| Variables $r$ ($P$) | Serum 14-3-3η | SF 14-3-3η |
| Age | −0.14 (0.52) | −0.06 (0.75) |
| BMI | −0.24 (0.25) | −0.33 (0.11) |
| Disease duration | 0.02 (0.09) | 0.18 (0.37) |
| ESR (first hour) | 0.34 (0.09) | 0.49 **(0.014)** |
| WOMAC | | |
| Pain | 0.15 (0.49) | −0.042 (0.84) |
| Stiffness | 0.12 (0.56) | −0.02 (0.94) |
| Physical function | −0.01 (0.98) | −0.16 (0.44) |
| Total score | 0.09 (0.69) | −0.15 (0.48) |
| KL scale | −0.35 (0.09) | 0.02 (0.93) |

ESR, erythrocyte sedimentation rate; KL, Kellgren-Lawrence; KOA, knee osteoarthritis; SF, synovial fluid; WOMAC, Western Ontario and McMaster Osteoarthritis index. Bold values are significant at $P$ less than 0.05.

## Discussion

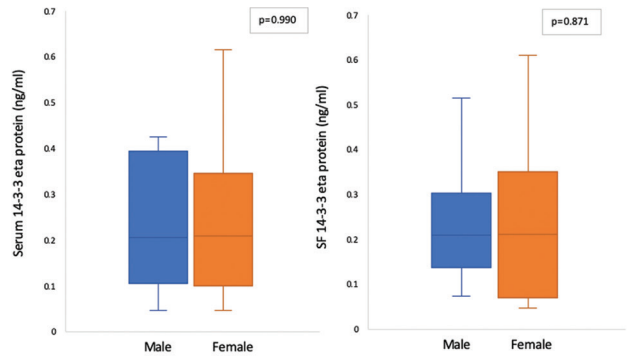
OA is a common cause of musculoskeletal disability. The main pathological change of OA is progressive articular cartilage degeneration, however, synovitis is another major factor in the development of OA [2,19]. OA is usually diagnosed according to the combination of symptoms, but researchers proposed that synovitis is the main cause of pain and edema in OA patients [20,21]. Therapeutic interventions have traditionally focused on symptom management, however, there is potential for pharmacologic modification of the disease process, such as disease-modifying antiosteoarthritic drugs (DMOADs) and targeted gene therapy in OA [22].

**Figure 1**



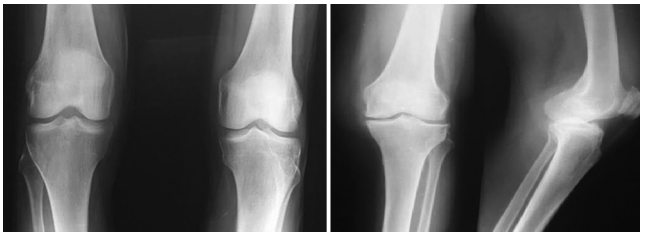

Serum and synovial fluid (SF) protein in patients with primary knee osteoarthritis (OA) and rheumatoid arthritis (RA).

**Figure 2**




Serum and synovial fluid (SF) protein in male and female patients with primary knee osteoarthritis (OA).

**Figure 3**



Plain radiography (AP and/or lateral views) with knee osteoarthritis (OA) in a female (60 years old with disease duration 18 months) and KL grading scale I (left) and KOA in a female patient (60 years old with 3-year duration) and KL grading scale III (right). KOA, knee osteoarthritis

In OA, the synovial membrane secretes SF and its components, such as TNF and ILs [9]. Moreover, 14-3-3 proteins in SF are secreted by the synovial membrane macrophages or chondrocytes or result from a diffusion process from abnormally elevated plasma levels. This family is predominantly found intracellularly, and involved in a wide range of cellular processes [10]. In the current work, 14-3-3η protein in the serum and SF of KOA patients was compared with RA and its association with functional status and radiographical damage was focused upon.

In alignment with previous studies, this work confirmed that 14-3-3η protein is a novel marker that is expressed at a high level in patients with RA compared with OA [11,23–25]. Othman *et al.* [23] showed that serum 14-3-3 levels were significantly higher among RA patients compared with OA and controls [26]. Hussin *et al.* [25] reported that serum level of 14-3-3η was significantly higher in RA compared with healthy patients. The serum 14-3-3 protein levels in this work were similar to the serum 14-3-3η protein level among primary OA patients and healthy controls of another study [23].

Of note, Trimova *et al.* [27] provided a novel mechanism for 14-3-3η-level increase in the RA SF. They showed that macrophages from the synovial membrane of RA patients, but not from OA, showed dense and widespread cytoplasmic staining for the 14-3-3η protein. Moreover, RA macrophages highly express 14-3-3η that is secreted in the SF. The 14-3-3η protein distinguished patients with RA from healthy controls and OA due to its ability to upregulate the levels of proinflammatory cytokines, which are closely associated with inflammatory progression in RA [9,16,28].

In accordance with previous studies, there was a significant correlation between 14-3-3η protein and the inflammatory marker (ESR) [23,29,30], but in contrast to other studies [9,28,31]. 14-3-3η isoform has the ability to induce factors linked to inflammation and radiographic damage [10].

In the present study, both serum and synovial 14-3-3η levels were not significantly correlated with knee radiographic damage or functional status. Other studies have shown a correlation between serum and SF 14-3-3η levels and radiographic damage at baseline and the radiographic progression in a prospective study for RA patients [11]. This can be due to differences in the inflammatory mediators involved in the structural changes in RA and OA. While the inflammatory cytokines such as TNF-α and ILs are the main players in patients with RA [5,32], MMP and oxidative stress are involved in the radiographic damage in OA [4,33]. In a previous experimental study, there was a significant correlation between the 14-3-3η level in the SF and the presence of either patellar osteophytes or lateral or medial (or both) condylar periarticular osteophytes. 14-3-3η protein was one of the reasons for the high levels of MMP-1 and MMP-3 observed [34]. 14-3-3-η protein was significantly high in juvenile idiopathic arthritis patients and could discriminate juvenile idiopathic arthrit from children with chronic nonbacterial osteomyelitis [35].

In agreement, the low frequency of 14-3-3η in a cohort of individuals with OA supports the high specificity of 14-3-3η observed for RA. Furthermore, 14-3-3η may be used to help identify RA patients among those being followed for OA. 14-3-3η may be particularly useful in the primary care setting to screen OA patients for misclassification of RA as OA, or for concurrent inflammatory arthritis in the setting of OA [36].

This is the first study directly comparing serum and SF 14-3-3η protein in OA with RA patients. Also, it provides a window for the difference in the pathogenesis of joint damage between RA and OA. However, this research has some limitations: the small sample size

of patients and the lack of follow-up. Not including a healthy control group is another limitation for full assessment of the serum level rather than depending on a cutoff value for another study. Furthermore, the study lacks the association between 14-3-3η SF levels and other proinflammatory cytokine expression. Future prospective studies on a wider scale of patients with primary and secondary OA are warranted to examine the role of 14-3-3η on radiographic progression.

## Conclusion

In conclusion, 14-3-3η protein is a novel marker that is expressed in a high level in patients with RA compared with OA. 14-3-3η protein levels were related to the inflammatory marker, but not with the functional status or radiographic damage in patients with OA. Future larger prospective studies are recommended to examine the role of 14-3-3η protein on radiographic progression.

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### Conflicts of interest

There are no conflicts of interest.

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