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Review article

Adenosine Deaminase Activity a Biomarker for Rheumatoid Arthritis: Review

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Abstract

Rheumatoid arthritis (RA) is an autoimmune, chronic, inflammatory and symmetric disease. In order to avoid joint destruction and reduce requires knowledge of the vital components causing the disease; so it is essential to start early in diagnosis and suitable treatment. Although clinical symptoms and results of radiographic help to identify and measure the activity of RA disease, biochemical markers also act as indicators of early diagnosis of the disease activity. So it is therefore the diagnosis of the disease in an early stage must choose a strong relationship with the disease. One of the vital signs related to rheumatoid arthritis is adenosine deaminase (ADA). The destruction of adenosine by the adenosine pathway facilitates a series of infections such as rheumatoid arthritis. So there are many questions that come to our mind namely. Can the level of adenosine activity (ADA) be a biomarker of the distinction between RA patients and controls? Can adenosine deaminase be a biomarker indicator for diagnosing of rheumatoid arthritis at the stage early pre-radiographically? And, does adenosine deaminase activity give an indication of the disease activity? In this review article, we're going to show the studies that pointed to those questions.

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1. Introduction

Rheumatoid arthritis is a prolonged, systemic and inflammatory autoimmune disease [1-5]. Rheumatoid arthritis is described as persistent synovial inflammation and advanced destruction of the joint cartilage [6], disease activity is mirrored for the degree of joint destruction, which that effect on their life RA patients [7, 8]. Studies are still continuing on the knowledge of the causes of rheumatoid arthritis, and the changes that coincide with the development of the disease, so the desired goal for patients is to reach the state of remission [9-11]. RA patients need to be closely monitored for the disease in order to get them to the remission [11]. Therefore, discouraging the process of breaking joints, reducing the disease and initiating early proper management of the disease is a prerequisite [12, 13]. Adenosine deaminase (ADA) is biomarker of immune cells. Therefore, it is necessary to assess its activity not only to estimate the severity of inflammation but also to develop and monitor the therapeutic effect of rheumatoid arthritis patients [14].

1. Rheumatoid Arthritis and Synovial Joint

1.1 Normal Joint Structure

Joint is a situated where two or more bone meet [15]. The end of bone covered with cartilage[16]. Each joint is surrounded by a capsule that supports and protects it from external shocks [17]. The capsule is lined with a synovial membrane, a form of tissue that secretes the synovial fluid to soften and nourish the tissues of the joint [18-20].this lining is thin in a healthy joint [21]. A change in the structure and functions of the natural joint has been associated in causing many forms of arthritis[18]

1.2 Synovial Fluid (SF)

Synovial fluid (SF) is a biofluid that is in contact with the meniscus and synovial membrane[2, 22]. It plays an important role in mechanical metabolism matrix cartilage tissue[23, 24]. The main difference between SF and other fluids in the body is that it contains a high percentage of hyaluronic acid [2, 17, 25], that hyaluronic acid is characterized by lubrication [26]. SF is excreted in small amounts by synovium and occasionally by synovial tendon sheaths [2, 27]. until in the big joints, there are a little drops of synovial fluid existing on the joint surfaces to lip on each other [28]. Therefore, there is an onerousness of separation and

examination. That effusion continuously point out articular syndrome [24, 25, 29]. In rheumatoid arthritis (RA), the synovium is the place of inflammatory surgery that results in changes in the articular cartilage [25, 30]

1.3 Rheumatoid arthritis (RA)

Arthritis means inflammatory of joint , where arthr- indicates joint; -itis indicates inflammation [27, 31, 32]. There are many types of arthritis may affect other body parts, such as the internal organs and skin [27, 31]. The most common prevalent types of arthritis are rheumatoid arthritis and osteoarthritis (OA) [33]. Rheumatoid arthritis is a prolonged, systemic and inflammatory autoimmune disease [34-38] , in which various joints in the body are inflamed, leading to pain, swelling, stiffness, joint destruction and a potential lack of function [39-43]. It's an idiopathic autoimmune disease that attacks the body's own immune system [44-46]

1.3.1. Epidemiology and Incidence of RA

Rheumatoid arthritis spreads all over the world and affects all ethnic [23]. RA spreads among the world's population by 1-2% [14, 34, 47-50]. Annual prevalence rate of RA disease of the world's population is estimated at 0.5-1% in both developed and developing countries [49-51]. Also, prevalence of RA disease is different depending on geographical location. It is spread in North America and Northern Europe compared to parts of the developing world, such as rural West Africa [52, 53] Similarly, for Arab countries, they face a significant increase in the incidence of RA disease by about 1.5% of their population [34]. Onset of RA is rare under the age of 15 years. The prevalence of the disease rises with age up to 80, but frequently the prevalence of the disease increases among the ages of 40 and 50 years [51, 54]. RA may also happen at any other age. Women are three times more infected than men [51, 55]

1.3.2 Etiology

Although the true etiologies of RA disease are still unclear [56, 57], several factors may appear to play a role in the occurrence of the disease: physiological, genetic, immunological and hereditary [1, 7, 14, 40, 48, 58-60].

1.3.3 Effects of Rheumatoid Arthritis on a Joint

In rheumatoid arthritis, infections and synovial membrane lesions occur[59, 61]. Swelling and congestion in the synovial membrane also occur [34, 62]. Leukocytes move out of the bloodstream and strike the synovium and blood vessels in the area [45]. The synovial tissue in RA is described by prominent hyperplasia, called pannus, which contains pro-inflammatory cytokines[36, 63, 64] and extents over and under the articular cartilage[62]. In the affected joints, many substances such as tumor necrosis factor (TNF), interleukin-1 (IL-1), fibroblasts, metalloproteinases (MMPs), aggrecanases, and cathepsins are produced [22, 54, 65, 66]. components damage the extracellular matrix (ECM) of cartilage[63, 67-69]. It can also damage the surrounding cartilage, bones, tendons and ligaments (Fig. 1) [63, 70].

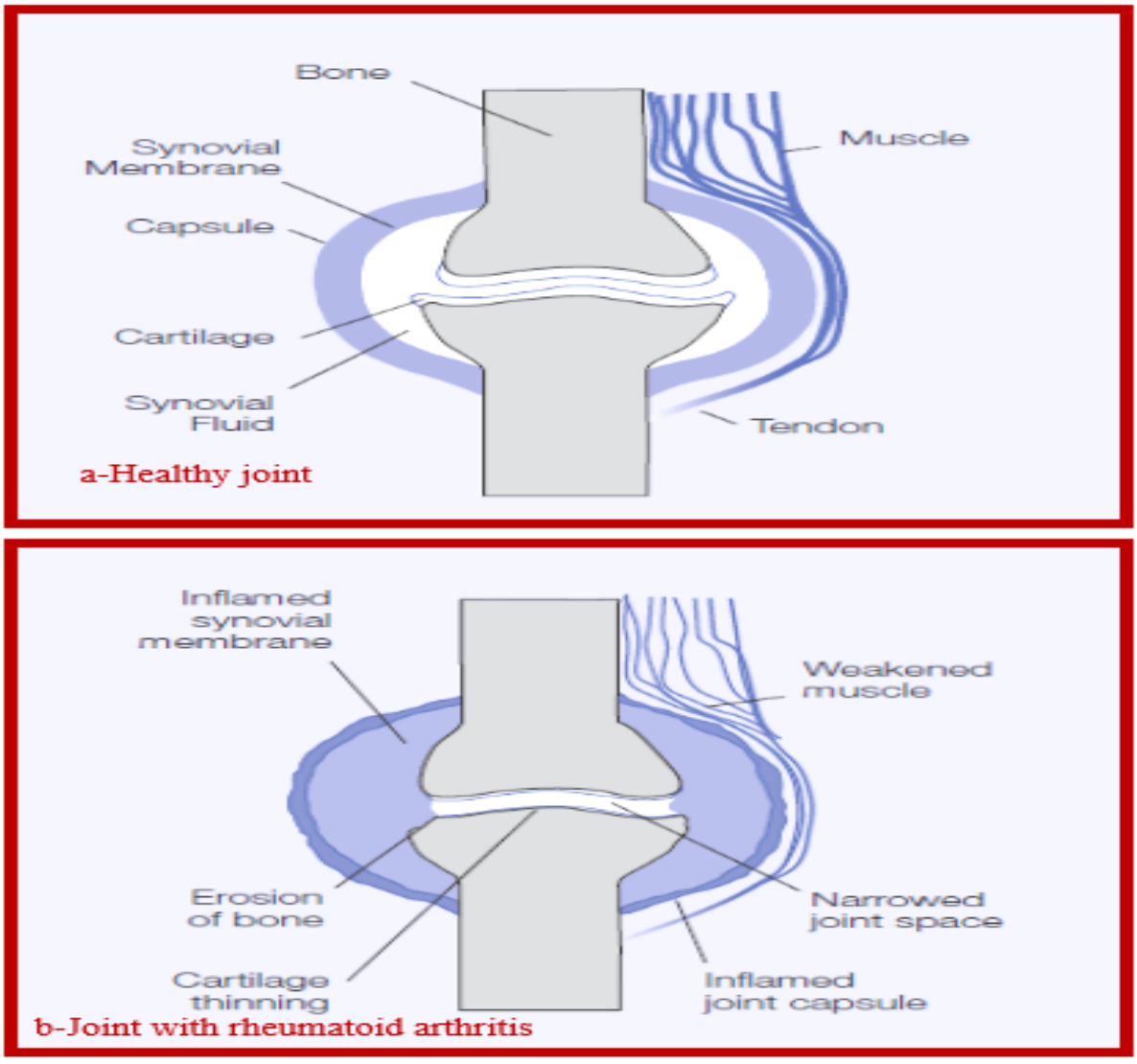

Figure 1. Joint image
a:Healthy joint ; b- Joint with rheumatoid arthritis [71]

In RA developments, patients may also grow extra-articular appearances, such as muscle atrophy and rheumatoid nodules [59]. These appearances happen frequently in patients with high titers of rheumatoid factor (RF), and associate with the severity [69, 72]. This often leads to joint deformity and damage[72, 73]. Moreover, in advanced cases of untreated rheumatoid arthritis

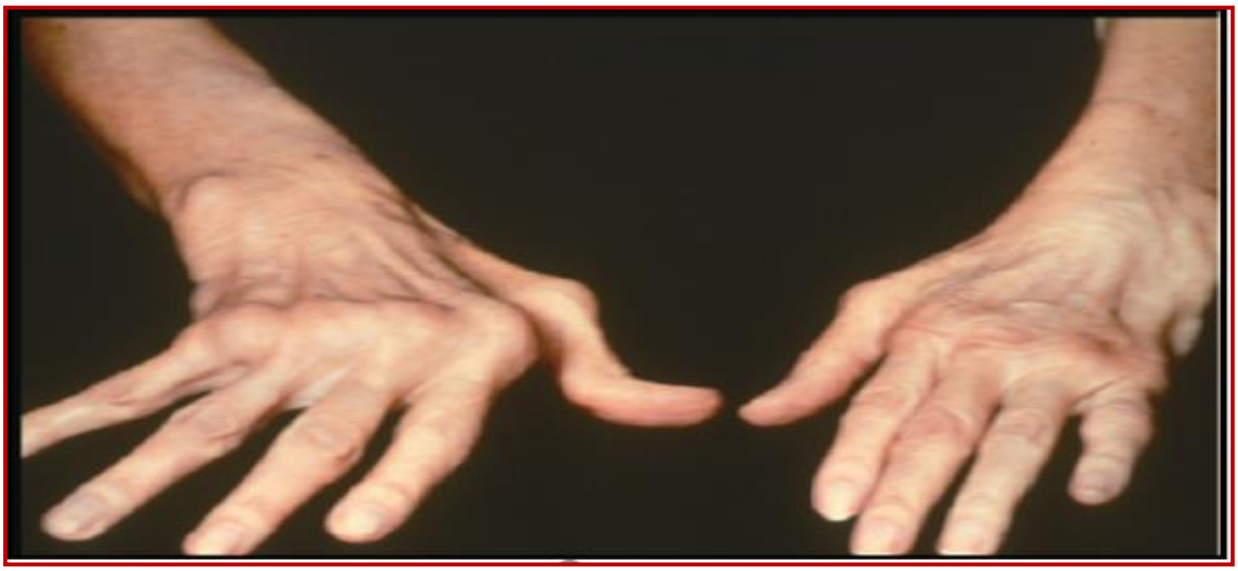

Figure 2: Hand Damaged by Rheumatoid Arthritis [74]

may lead to severe deformities, especially in the hands (Fig. 2).[19, 74, 75].

1.3.4 Clinical Features for RA

Rheumatoid arthritis is characterized by the presence of pain and swelling of the affected joint; As well as inflammation of synovium which causes the progressive breakdown of the cartilage joint, subchondral bone crack, and loss of joint function [7, 14]. Clinical features of RA vary not only from one patient to another, but also in an individual patient through the disease course [73, 76]. Early symptoms of RA are non-specific and comprise of malaise, weakness, fatigue, anorexia and diffuse musculoskeletal pain and stiffness that is not clearly localized to the articular structures [27, 77, 78].

RA Diagnosis is established on the valuation basic of clinical symptoms, radiographic examine and the outcomes of laboratory which related to criteria of American College of Rheumatology (ACR) for 1987[14, 61, 79].American College of Rheumatology and the European League against Rheumatology (EULAR) formed a new criteria for RA with a higher sensitivity in early disease, which were developed in 2010 [80]. Six from seven ACR criteria for RA are established on obvious clinical signs, one of which is founded on the positive outcome of the serum rheumatoid factor (RF). But these signs to stabilize need less than six weeks [14]. Therefore, in order for diagnosis to be early, it is necessary to diagnose and monitor other indicators more sensitive to rheumatoid arthritis in the early stage of diagnosis. One of the vital signs related to rheumatoid arthritis is adenosine deaminase (ADA) [14, 81]. Synovitis and advanced of disease lead to articular cartilage damage. Many purine turnover disorders have been associated with immune disorders. Purine metabolism may be associated with rheumatoid arthritis disease [6, 7, 10, 82]. The destruction of adenosine by the adenosine pathway facilitates a series of infections such as rheumatoid arthritis [83].

2. Adenosine Deaminase

Adenosine deaminase (ADA, E.C. 3.5.4.4) is an essential enzyme which assistance for purine turnover. ADA inducing the deamination of adenosine to inosine and release ammonia [84-95]. It is considered a biomarker for immunity disease [7, 10, 82, 96-100]. Many studies revealed the level of ADA activity reflect the activity of macrophage and monocyte in inflammatory environments, such as rheumatoid arthritis and systemic lupus system [7, 83, 99, 101, 102]. It has also an important role in severe cases as well as biological functions that include the differentiation and maturity of immune cell components [14, 103]. Whereas, adenosine deaminase (ADA) is produced from lymphocytes and participates in purine metabolism [104]. Adenosine deaminase serves as a checkpoint for regulating the level of extra cellular adenosine, thus potentially modifying inflammatory processes. Thus, although the level of adenosine deaminase may be evaluated as an suitable technique of assessing the severity of RA, it seems that adenosine deaminase may be a predictive indicator of inflammatory processes in RA [6, 58, 105, 106].

Particular attention has been given to the design of new ADA inhibitors as possibly beneficial new tools for therapeutic healing of inflammatory disorders [6]. Especially since the

level of adenosine gets a rapid rise in tissues that get metabolic disorders, it acts as a natural brake in the functions of immune cells [107, 108]. Van Ede et al. have studied the effects of pharmacological management on purine metabolism in patients suffering from RA. In particular, these researchers assessed the effects of methotrexate on ADA activity, confirming a significant decrease in ADA activity after treatment. [109].

2.1 Isoenzyme the Adenosine Deaminase

Adenosine deaminase have been recognized of two isoenzymes including: adenosine deaminase-1 (ADA-1) and adenosine deaminase-2 (ADA-2) [14, 82, 110-112]. Where, ADA-1 is present in all cells in the body, while ADA-2 is generally in monocytes and macrophage cells [82].

2.2 Adenosine Deaminase a Biomarker for Rheumatoid Arthritis Patients

Table 1 reveals several studies that estimated of total, first and seconed adenosine deaminase (tADA, ADA1 and ADA2) levels either in serum, synovial fluids or both in patients with rheumatoid arthritis. Several studies have shown that adenosine deaminase expression in the serum of RA patients is linked to the seriousness of the disease [1, 7, 8, 10, 58, 83, 99, 105, 113, 114]. Hitoglou et al.200 estimated the level of activity of the total, first and second adenosine deaminase in RA patients' serum. They found a relationship between the total and the second levels of adenosine deaminase with the severity of the disease's activity. And the progress of the disease leads to an increase in the level of effectiveness of the kidney and the second [97].

Moreover, Sari et al., 2003 showed the correlation between activity serum tADA, ADA1and ADA2 and activity disease of rheumatoid arthritis And displayed that total and second adenosine deaminase had association with activity disease of RA [113]. Sari et al.2003 concluded that ADA activity may be beneficial as appreciated indicator in identification, development; and monitoring of affect the management in patient suffering from RA[113]. Also, Zekeri et al. 2012 showed increased serum ADA activity in patients with RA when matched with osteoarthritis (OA) patients. Additionally, Zekeri et al.2012 displayed that the level of ADA activity in synovial fluid (SF) more than serum ADA for RA patients , which reflect the articular cartilage damage [99]. And concluded that, when compared with patients with OA, higher serum and synovial fluid levels of ADA activity were observed in RA patients. Also, the amount of

ADA in serum and SF in RA patients has a major difference between rheumatoid arthritis and osteoarthritis [99].

Moreover, Nalesnik et al.2012 have showed that level of activity ADA has a correlation with inflammation; and showed that the activity of serum ADA level could be a valuable biomarker for the inflammatory process of patients suffering from RA [14]. In addition, the correlation between disease activity and level of ADA activity was revealed by Zamani et al. 2012 and mentioned that level of serum ADA might be benefit to expect activity of disease in patients suffering from RA [105]. Nalesnik et al., 2011 and Zamani et al., 2012 concluded also that activity serum ADA level has been proposed to be expectation indicator or a beneficial biomarker for inflammatory process in patients caused with RA [58, 105] . Conversely, Cordero et al., 2001 showed increased level of serum ADA activity; also, he did not find out a relationship among disease activity and activity serum ADA level in RA patients [115]. Moreover, Erer et al.2009 showed higher level of serum ADA activity ; but he could not find out a correlation between disease activity and ADA level for RA patients who receiving treatment [116]. Moreover, Demir et al., 2014 found increased activity of serum ADA in patients suffering RA , also, he found no correlation between activity serum ADA and disease activity for RA patients [83]. Vinapamula et al., 2015 also showed, that level of serum ADA activity was found to be increased significantly in RA patients compared to controls [7]. Additionally, Hameed et al., 2019 found increase level of serum ADA in RA patients when compared to control [10]. Hameed et al., 2019 also found that the activity of ADA level correlated with disease activity score-28 (DAS-28) [10].

Sari et al. 2003, Zakeri et al., 2012 and Hameed et al., 2019 were showed the correlation between level of serum ADA activity and their isoenzymes with severity of RA. Also, they found that total ADA and ADA2 had association disease activity for with RA patients [10, 99, 113]. While Cordero et al., 2001, Erer et al.,2009 and Demeri et al., 2014 were concluded that did not showed a relationship between level ADA activity and activity of disease for RA patients [83, 115, 116]. Differences in outcomes may be most of these studies conducted with a size sample and did not illustrate the patient's appearance and medications in detail [10, 58, 105, 115, 116].

Table 1: Reveals several studies that estimated of total, first and second adenosine deaminase (tADA, ADA1 and ADA2) levels in serum or synovial fluids or both in patients with rheumatoid arthritis.

Author	Year	Assay of tADA, ADA1, ADA2	Type of fluid	Outcomes
Hitoglou et al., [97]	2001	tADA, ADA1, ADA2	Serum	Found a relationship between the total and the second levels of adenosine deaminase with the severity of the disease's activity. And the progress of the disease leads to an increase in the level of effectiveness of the kidney and the second.
Sari et al.,[113]	2003	tADA, ADA2	Serum	Showed the link between serum activity tADA, ADA1and ADA2 and rheumatoid arthritis activity disease and demonstrated the association of total as well as second adenosine deaminase with RA activity disease. Sari et al. confirmed which ADA activity could be advantageous as a valued indicator in the identification , development and monitoring of the management impact of RA patients.
Zekeri et al. [99]	2012	tADA,	Serum, SF	Higher serum ADA activity showed in patients with RA when compared with patients with osteoarthritis (OA). Additionally, Zekeri et al.2012 displayed that the level of ADA activity in synovial fluid (SF) higher than serum ADA for RA patients, which reflect the articular cartilage damage. And concluded that, as compared to OA patients, higher serum and synovial fluid levels of ADA activity in RA patients. Also, the level of ADA in serum and SF for RA patients have a significant difference between rheumatoid arthritis and osteoarthritis.

Nalesnik et al.[14]	2012	tADA,	serum	Moreover, Nalesnik et al.2012 have showed that level of activity ADA has a correlation with inflammation; and showed that the activity of serum ADA level could be a valuable biomarker for the inflammatory process of patients suffering from RA. Nalesnik et al., concluded also that activity serum ADA level has been proposed to be expectation indicator or a beneficial biomarker for inflammatory process in patients caused with RA.
Zamani et al. 2012 [105]	2012	tADA,	serum	Mentioned that level of serum ADA might be benefit to expect activity of disease in patients suffering from RA. And concluded also that activity serum ADA level has been proposed to be expectation indicator or a beneficial biomarker for inflammatory process in patients caused with RA.
Cordero et al., [115].	2001	tADA,	serum	Showed increased level of serum ADA activity; also, he did not find out a correlation between disease activity and activity serum ADA level in RA patients.
Erer et al.[116].	2009	tADA,	serum	Showed higher level of serum ADA activity; but he could not find out a correlation between disease activity and ADA level for RA patients who receiving treatment.
Demir et al., [83]	2014	tADA,	serum	Found increased activity of serum ADA in patients suffering RA , also, he found no correlation between activity serum ADA and disease activity for RA patients
Vinapamula et al., [7]	2015	tADA,	serum	Showed, that level of serum ADA activity was found to be increased significantly in RA patients compared to controls .

Hameed et al., [10]	2019	tADA,	serum	Additionally, found increase level of serum ADA in RA patients when compared to control. Hameed et al., 2019 also found that the activity of ADA level correlated with disease activity score-28 (DAS-28) [10].
tADA: total adenosine deaminase; ADA1: first adenosine deaminase; ADA2 second adenosine deaminase; SF: Synovial fluid				

3. Conclusions

From the above- mentioned review, we could draw the following importance conclusions:

1- Adenosine deaminase can be used as a biomarker to distinguish between rheumatoid arthritis and control.
2- It can be used also as a biomarker for diagnosis of RA at early stage pre-radiographically.
3- Adenosine deaminase can expect disease severity in rheumatoid arthritis
4- The effect of methotrexate therapy in RA patients can be monitored with adenosine deaminase.

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المستخلص

التهاب المفاصل الرثوي هو مرض مناعي وذاتي ومزمن والتهابي ومتناظر. فمن أجل تجنب تدمير المفصل والحد من ذلك يتطلب معرفة المكونات الحيوية المسببة للمرض. لذلك فمن الضروري أن يكون التشخيص والعلاج المناسب في وقت مبكر. ومع ذلك على الرغم من أن الأعراض السريرية ونتائج التصوير الإشعاعي تساعد على تحديد وقياس نشاط مرض التهاب المفاصل الرثوي، فإن العلامات الكيميائية الحيوية تعمل أيضًا كمؤشرات للتشخيص المبكر لنشاط المرض. ومن أجل التشخيص المبكر، فمن الضروري تشخيص ومراقبة المؤشرات الأخرى أكثر حساسية لالتهاب المفاصل الرثوي في مرحلة مبكرة من التشخيص. أحد العلامات الحيوية المتعلقة بالتهاب المفاصل الرثوي هو الأدينوسين دي امينيز. ان تحطم الأدينوسين من قبل مسار الأدينوسين يسهل سلسلة من الإصابات مثل التهاب المفاصل الرثوي. لذلك هناك العديد من الأسئلة التي تأتي إلى أذهاننا وهي:

هل يمكن أن يكون مستوى نشاط الأدينوسين (ADA) علامة حيوية للتمييز بين مرضى RA والضوابط؟

هل يمكن أن يكون أدينوسين دي امينيز مؤشرا حيويا لتشخيص التهاب المفاصل الرثوي في المرحلة المبكرة قبل التصوير الإشعاعي؟

وهل يعطي نشاط الأدينوسين دي امينيز مؤشراً على نشاط المرض؟

في هذه المقالة المراجعة، سنعرض الدراسات التي أشارت إلى تلك الأسئلة.