Iran J Pediatr. 2017 December; 27(6):e9888. doi: 10.5812/ijp.9888.

Published online 2017 October 16. **Research Article**

Comparison of Adenosine Deaminase Level in Serum and Synovial Fluid in Patients with Juvenile Idiopathic Arthritis and Its Relation to Inflammatory Acute Phase Reactants

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Received 2016 December 02; **Revised** 2017 July 06; **Accepted** 2017 August 07.

Abstract

Background: In JIA, cell-mediated immune response results in secretion of different inflammatory products from activated lymphocytes, macrophages, fibroblasts and leukocytes in synovial joints. Adenosine deaminase (ADA) regulates this immune system activity by metabolizing adenosine through purine metabolic pathway.
Objectives: The aim of this study was to compare the level of serum ADA with synovial fluid ADA in JIA patients and to see whether it can be utilized as a marker for the activity of the disease
Methods: JIA was diagnosed based on International League of Associations for Rheumatology diagnosis criteria. ADA was measured using special kits.
Results: 80% of the patients had oligoarticular and 20% polarticulare JIA. There was a significant relation between erythrocyte sedimentation rate (ESR) and high level of synovial fluid ADA. Synovial ADA level was significantly higher than serum ADA in polyarticular JIA. C-reactive protein (CRP), leukocytes and platelets count were increased in high levels of synovial fluid ADA. No correlation was observed between level of serum and synovial fluid ADA.
Conclusions: Synovial fluid ADA seems a more precise index than serum ADA to assess the inflammatory condition. In addition, acute-phase response reactants such as ESR, CRP, and platelets count could be suitable predicting parameters for arthritis.

Keywords: Juvenile Idiopathic Arthritis, Adenosine Deaminase, Synovial Fluid, Acute-Phase Reactant, ADA

1. Background

One of the common causes of chronic inflammatory disorders is arthritis which affects cartilage and joints (1-4). Synovial inflammation is often progressive and leads to joint destruction (5, 6). Juvenile idiopathic arthritis (JIA) is the common form of arthritis among children and adolescents from the age of 7 to 12. Characteristics for JIA is the appearance of immunological abnormalities such as the presence of circulating immune complexes, the production of a variety of autoantibodies, and dysregulation of T-cell/B-cell interactions along with the involvement of multiple systems or organs (7, 8).

Clinical data (such as number of tender or swelling joints), global pain reported by the patients, and serological markers have been widely used to extract different indices in order to diagnose the disease activity. Inflammatory biomarkers and acute-phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are related to progression of RA and are useful for evaluation of disease activity and its response to treatment (9-11).

Cell-mediated immune response, manifests as secretion of different inflammatory products from activated lymphocytes, macrophages, fibroblasts and leukocytes in synovial joints. Endogenous adenosine remarkably suppresses this process and actually adenosine pathway mediates the inflammatory cascade (12). The level of extracellular adenosine is important in determining its ability

to regulate various biological processes (13, 14). Adenosine deaminase (ADA) is one of the main enzymes of purine metabolic pathway, and is responsible to metabolize adenosine. ADA represents an exclusive checkpoint in the extracellular adenosine regulation and, consequently, in the control of immune system activity through its modulation of adenosine pathways (15-20).

Studies have shown that level of serum ADA is higher in RA patients compared with the healthy controls (19, 21, 22). Also, serum ADA is widely used to differentiate between various infectious and malignant conditions in body fluids (23-25). Moreover, ADA has been suggested as an alternative parameter representing disease activity in systemic lupus erythematous, Juvenile Idiopathic arthritis, and Behcet's Disease (18, 20, 26). Synovial fluid ADA can also differentiate between RA and non-inflammatory arthritis (27). Thus, determination of serum and synovial fluid adenosine level can be a suitable way to assess disease activity.

Currently, there is not an exact clinical finding or laboratory test for diagnosis of JIA. Thus, the detection and control of disease recurrence is difficult. The aim of this study was, comparing the level of serum ADA with synovial fluid ADA in JIA patients, to find a correlation with oligoarticular and polyarticular subtypes of the disease and its blood acute-phase responses.

2. Methods

This cross-sectional study was conducted on 55 children who were diagnosed with juvenile idiopathic arthritis (JIA) based on International League of Associations for Rheumatology (ILAR) diagnosis criteria, referred to division of rheumatology of children's medical center, pediatrics center of excellence (Tehran, Iran) during February 2013 - May 2014.

2.1. Inclusion and Exclusion Criteria

Synovial fluid aspiration and synovial fluid ADA measure were performed routinely. Children with joint diseases other than JIA such as septic arthritis, brucellosis, and other rheumatoid diseases like as systemic lupus erythematosus (SLE) were excluded from the study.

2.2. Performance

Information of patients were extracted from their files and recorded in questionnaires. Clinical and paraclinical data, including number of involved joints, systemic symptoms, and results of blood and synovial fluid tests in addition to patients' demographical data such as age and gender were recorded. Blood laboratory finings like Coomb's test, Wright test, anti-cyclic citrullinated peptide (anti-CCP), anti-nuclear antibodies (ANA), rheumatoid factor (RF), CRP, ESR, complete blood count (CBC), ADA, 2-mercaptoethanol (2ME) were recorded. If there was more than one CBC vakue, the one with highest measure was chosen. In this study, correlation between synovial fluid ADA and blood ADA, and its relation to acute-phase reaction, duration of the disease and number of involved joints were assessed. Amounts of both blood and synovial fluid ADA were measured using special kits, and the normal range of serum ADA was considered 0-15 IU/L.

2.3. Ethics

Personal identity of patients was confidentially recorded in questionnaires and only analysis of results was reported. Moreover, the researchers regarded all contents of the Declaration of Helsinki (DoH) throughout the study.

2.4. Data Analysis

Quantitative and qualitative data were analyzed and reported using SPSS software (version 18) as average$\pm$standard deviation, number and percent. For all patients, average number of platelet, ESR, and CRP of blood serum, and glucose, protein, and LDH of synovial fluid have been reported. Statistical analyses were performed using t-test, Mann-Whitney U test, ANOVA, and chi-square test. Correlation study was done by Pearson correlation test. P value < 0.05 was considered significant.

3. Results

Of 55 patients (24 females and 24 31 males), 44 (80%) cases had oligoarticular JIA. Some of the serum and synovial fluid laboratory findings are presented in Table 1. It can be seen that there is no significant difference between number of white blood cells (WBC), and polymorphonuclear leukocytes of serum with synovial fluid.

As shown in Table 2, most of the patients had oligoarticular than poly-articular JIA subtype (44 vs 11). However, there was no significant difference of JIA subtype distribution between males and females. Also, the age of patients of the two subtypes did not show any significant difference. Similarly, the average number of affected joints, serum ADA levels in average, and synovial fluid ADA levels in average do not significantly differ in relation to patient's gender.

Level of ADA in serum and synovial fluid, JIA subtype, disease duration, and blood acute phase reactants (WBC, CRP, platelets, and ESR) were recorded separately for both genders (Table 3). Then, amount of ADA in serum and synovial fluid was compared regarding each criterion to find a

Table 1. Laboratory Findings of Blood Serum and Synovial Fluid in Studied Patients[a]

Variable	Mean (SD)	Range
Serum content		
Average number of white blood cells (WBC), mm^{-3}	10379 ± 4535	4,000 - 34,000
Polymorphonuclear leukocytes (PMN), %	53.2 ± 17.2	15.4 - 91.4
Average number of platelets, mm^{-3}	400910 ± 126840	196,000 - 677,000
Erythrocyte sedimentation rate (ESR)	34.0 ± 11.9	7 - 101
C-reactive protein (CRP), mg/mL	35.5 ± 5.69	5 - 260
Synovial fluid content		
Average number of WBC, mm^{-3}	10604.5 ± 13129.6	60 - 64,000
PMN, %	62.6 ± 29.6	8 - 98
Glucose, mg/dL	79.7 ± 22.2	9 - 210
Protein, mg/dL	4501.7 ± 1683.9	1030 - 15,500
LDH, U/L	981.3 ± 750.8	232.7 - 3,599

[a]Values are expressed as mean ± standard deviation (range of alteration).

Table 2. Distribution of Patients' Characteristics in Relation to Gender[a]

Variable	Value	P Value
Gender		0.6
Female	24 (43.6)	
Male	31 (56.4)	
Average age, y	8.42 ± 4.67 (1.5 - 15.8)	0.4
Female	7.7	
Male	8.7	
JIA type[b]		0.6
Oligoarticular	44 (80)	0.6
Female	20	
Male	24	
Polyarticular	11 (20)	0.7
Female	4	
Male	7	
Average age according to JIA type, y[c]		0.2
Oligo-articular	8.2 ± 4.7	0.3
Female	7.9	
Male	8.7	
Poly-articular	9.0 ± 2.7	0.04
Female	7.9	
Male	10.1	
Average level of serum ADA, UI/L[d]	16.2 ± 5.5	0.02
Average level of synovial fluid ADA, UI/L[d]	26.9 ± 11.5	
Average level of serum ADA, UI/L[e]	16.2 ± 5.5	0.5
Female	13.9 ± 2.8	
Male	15.2 ± 6.8	
Average l evel of synovial fluid ADA, UI/L[e]	26.9 ± 13.5	0.2
Female	24.9 ± 14.8	
Male	28.4 ± 12.6	

Abbreviations: ADA, adenosine deaminase; JIA, juvenile idiopathic arthritis.
[a]Values are expressed as No. (%) and mean ± standard deviation (range of alteration).
[b]Chi2 was 0.002.
[c]Independent t-test was -1.361.
[d]Independent t-test was 0.652.
[e]Independent t-test was 1.346.

correlation between them. Results showed that there was no significant correlation between these criteria and level of ADA or for serum and synovial fluid. It should be noted that the difference of synovial fluid ADA in relation to low and high levels of CRP was not significant (P value = 0.1), although it might be significant in larger populations.

Overall, synovial ADA was significantly higher than serum ADA (P = 0.03). Although synovial ADA was higher in both subtypes of JIA, this difference was statistically only significant in polyarticular subtype (P = 004). In patients with evidence of laboratory inflammation such as higher ESR, CRP and peripheral leukocytosis and thrombocytosis, synovial ADA was significantly higher than in serum ADA level.

Also there was no significant difference between acute phase responses, including WBC, platelet, and CRP at low and high ADA level of synovial fluid (Table 4). On the other hand, difference of ESR at low and high level synovial fluid ADA was statistically significant. This result demonstrates ESR as a remarkable indicator for the high level of ADA and presence of high inflammation.

Correlation of serum ADA with synovial fluid ADA was assessed to find whether these variables have any impact on each other. There was no correlation between serum ADA and synovial fluid ADA (P value = 0.2) indicating that alteration in ADA level of serum does not affect the ADA level of synovial fluid, and vice versa.

4. Discussion

In spite of investigation of many possible causes, including infectious, genetic, immunologic etc., the etiology of rheumatic diseases such as JIA is a mystery (28). Adenosine is a purine nucleoside and has anti-inflammatory functions by decreasing proinflammatory cytokines, in-

Table 3. Level of Blood Serum ADA and Synovial Fluid ADA in Relation to Blood Acute-Phase Reactants, JIA Subtypes, and Gender[a]

	Average Serum ADA	Average Synovial Fluid ADA	P Value
Total	15.2 ± 5.5	27.9 ± 11.5	0.03
JIA subtype			
Oligoarticular	13.8 ± 3.2	24.5 ± 12.7	0.2
Polyarticular	18.3 ± 7.7	37.0 ± 9.4	0.04
P Value	0.3	0.2	
Negative rheumatoid factor	14.8 ± 5.6	30.5 ± 15.7	0.1
WBC, mm^{-3}			
Normal, < 12,000	14.7 ± 6.1	31.06 ± 12.5	0.09
High, > 12,000	12.2 ± 1.9	30.87 ± 12.4	0.04
P Value	0.5	0.9	
CRP, mg/mL			
Low, < 10	13.8 ± 2.4	26.4 ± 16.2	0.2
High, > 10	15.9 ± 7.2	35.6 ± 10.0	0.03
P Value	0.3	0.1	
Platelets, mm^{-3}			
Normal, < 400,000	14.5 ± 2.9	24.3 ± 14.5	0.3
High, > 400,000	15.2 ± 7.5	33.5 ± 9.5	0.03
P Value	0.7	0.09	
ESR, mm/h			
Low, < 20	13.2 ± 2.5	24.0 ± 1.1	0.1
Moderate, 20 < ESR < 40	18.1 ± 6.4	27.5 ± 1.2	0.03
High, > 40	13.1 ± 3.2	38.1 ± 1.5	0.001
P Value	0.1	0.2	

Abbreviations: ADA, adenosine deaminase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; WBC, white blood cells.
[a]Values are expressed as mean ± standard deviation.

Table 4. Blood Acute-Phase Reactants in Relation to Low and High Levels of ADA in Synovial Fluid[a]

	Synovial Fluid ADA < 20	Synovial Fluid ADA > 20	P Value
Average of WBC, mm3	10104.5 ± 4573.94	10830.3 ± 5962.53	0.7
Average platelet count, mm3	363181 ± 130927	447666 ± 110599	0.5
Average ESR, mm/h	22.72 ± 15.58	48.20 ± 33.73	0.004
Average CRP, mg/L	21.99 ± 39.02	53.05 ± 61.54	0.1

Abbreviations: ADA, adenosine deaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells.
[a]Values are expressed as mean ± standard deviation.

creasing anti-inflammatory cytokines, cytokine modulation of macrophages and monocytes and regulation of endothelial cell inflammatory functions (29-31). It has been suggested that ADA concentration may help in identification of immune system activity and differentiation of inflammatory from non-inflammatory conditions (32).

In this study, the average level of serum ADA in female and male groups was normal (i.e. < 15 IU/L), and no significant difference was observed between them. This result was compatible with the previous studies (32, 33). The average of synovial fluid ADA was 30.73 ± 15.55 UI/L which was higher than the differentiation cut-off of inflammatory and non-inflammatory arthritis (16). This result indicates the direct relation of synovial fluid ADA with arthritis in comparison with serum ADA, even though there was no significant difference between female and male groups. Same relation was observed between synovial fluid ADA and oligo-articular and poly-articular JIA subtypes which demonstrates higher diagnostic precision of synovial fluid ADA.

There was no significant relation between level of serum ADA and blood acute-phase reactants such as WBC, platelet, CRP, and ESR at high and low levels. In our previous study, we found inverse correlation between serum ADA level and ESR during acute phase of JIA and between serum ADA level and WBC counts after disease control (25). Salesi et al reported significant correlation between serum ADA and ESR (15), but the result of our recent study was compatible with that of Sari et al. (19). Vinapamula et al found significant positive correlation between serum ADA and CRP in RA patients. They reported cut-off value of 25.3 IU/L for serum ADA level in RA with 82.6% sensitivity and 65.2% specificity (34). It seems that cut off point for serum and synovial level of ADA is an important factor that influences various results in different studies. On the contrary, level of synovial fluid ADA results in higher levels of acute-phase responses (except for WBC); however, there was no significant difference between synovial fluid ADA at higher and lower levels of WBC, platelets, ESR, and CRP. This result depicts the close relation of synovial fluid ADA with inflammatory arthritis than serum ADA does.

Unlike the results of Yuksel et al. (32), in our study, there was no correlation between serum ADA and synovial

fluid ADA which means that increases in serum and synovial ADA do not affect each other. Also, there was no relation between duration of disease and the level of synovial fluid ADA.

Comparison of blood acute-phase reactions between two groups of synovial fluid ADA higher and lower than 20 showed no significant difference for WBC, CRP and platelets; although, the amount of CRP and number of platelets increased in higher level of ADA. On the other hand, significant difference was observed in average ESR in two groups of synovial fluid ADA. This result shows direct relation of ESR with synovial fluid ADA in arthritis activity. Entirely, it seems that ESR, platelet and CRP are predicting indices of high levels of synovial fluid ADA, and consequently, inflammatory arthritis, and their simultaneous measurement would represent the active inflammation.

There were some limitations in this study which should be removed in future studies. First there were only 38 cases which is not a suitable number for statistical analysis. Larger numbers of patients could alter both negative and positive rheumatoid factors. Second, unavailable measurement of subjective pain and joint inflammation was an obstacle to determine the intensity of symptoms in each patient and at different times of hospitalization. Thus, there is a need to record information more precisely.

In conclusion, our results demonstrated that the level of synovial fluid ADA is a more precise index than level of serum ADA to assess the activity of arthritis. Also, synovial fluid ADA is in relation with blood acute phase responses including platelets, CRP, and ESR which could be used to diagnose inflammatory from non-inflammatory arthritis.

Acknowledgments

This study was a part of a dissertation of Dr Kh. Rahmani and was approved by vice-chancellor for research of school of medicine, Tehran University of Medical Sciences. The authors would like to thank Dr. F. Tahghighi for her contribution in the data gathering of this study.

References

1. Davatchi F. Rheumatology in Iran. *Int J Rheum Dis.* 2009;**12**:283–7.
2. Davatchi F, Jamshidi AR, Banihashemi AT, Gholami J, Forouzanfar MH, Akhlaghi M, et al. WHO-ILAR COPCORD Study (Stage 1, Urban Study) in Iran. *J Rheumatol.* 2008;**35**(7):1384. [PubMed: 18464299].
3. Davatchi F, Jamshidi AR, Tehrani Banihashemi A, Gholami J, Hossein Forouzanfar M, Akhlaghi M, et al. Effect of ethnic origin (Caucasians versus Turks) on the prevalence of rheumatic diseases: a WHO-ILAR COPCORD urban study in Iran. *Clin Rheumatol.* 2009;**28**(11):1275–82. doi: 10.1007/s10067-009-1235-7. [PubMed: 19633969].
4. Davatchi F, Tehrani Banihashemi A, Gholami J, Faezi ST, Forouzanfar MH, Salesi M, et al. The prevalence of musculoskeletal complaints in a rural area in Iran: a WHO-ILAR COPCORD study (stage 1, rural study) in Iran. *Clin Rheumatol.* 2009;**28**(11):1267–74. doi: 10.1007/s10067-009-1234-8. [PubMed: 19629618].
5. Brasington RD. In: Rheumatology. Hochberg MC, Silman AJ, Smolen JS, editors. Philadelphia: Mosby-Elsevier; 2011. pp. 829–38.Clinical features of rheumatoid arthritis.
6. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med.* 2011;**365**(23):2205–19. doi: 10.1056/NEJMra1004965. [PubMed: 22150039].
7. Appelboom T, Mandelbaum I, Vertongen F. Purine enzyme levels in rheumatoid arthritis. *J Rheumatol.* 1985;**12**(6):1075–8. [PubMed: 3005561].
8. Samsonov MY, Tilz GP, Egorova O, Reibnegger G, Balabanova RM, Nassonov EL, et al. Serum soluble markers of immune activation and disease activity in systemic lupus erythematosus. *Lupus.* 1995;**4**(1):29–32. doi: 10.1177/096120339500400107. [PubMed: 7767335].
9. Weinblatt ME, Keystone EC, Cohen MD, Freundlich B, Li J, Chon Y, et al. Factors associated with radiographic progression in patients with rheumatoid arthritis who were treated with methotrexate. *J Rheumatol.* 2011;**38**(2):242–6. doi: 10.3899/jrheum.091446. [PubMed: 21078715].
10. Markatseli TE, Voulgari PV, Alamanos Y, Drosos AA. Prognostic factors of radiological damage in rheumatoid arthritis: a 10-year retrospective study. *J Rheumatol.* 2011;**38**(1):44–52. doi: 10.3899/jrheum.100514. [PubMed: 20952476].
11. Cylwik B, Chrostek L, Gindzienska-Sieskiewicz E, Sierakowski S, Szmitkowski M. Relationship between serum acute-phase proteins and high disease activity in patients with rheumatoid arthritis. *Adv Med Sci.* 2010;**55**(1):80–5. doi: 10.2478/v10039-010-0006-7. [PubMed: 20371432].
12. Iwaki-Egawa S, Yamamoto T, Watanabe Y. Human plasma adenosine deaminase 2 is secreted by activated monocytes. *Biol Chem.* 2006;**387**(3):319–21. doi: 10.1515/BC.2006.042. [PubMed: 16542154].
13. Antonioli L, Colucci R, La Motta C, Tuccori M, Awwad O, Da Settimo F, et al. Adenosine deaminase in the modulation of immune system and its potential as a novel target for treatment of inflammatory disorders. *Curr Drug Targets.* 2012;**13**(6):842–62. [PubMed: 22250650].
14. Nakamachi Y, Koshiba M, Nakazawa T, Hatachi S, Saura R, Kurosaka M, et al. Specific increase in enzymatic activity of adenosine deaminase 1 in rheumatoid synovial fibroblasts. *Arthritis Rheum.* 2003;**48**(3):668–74. doi: 10.1002/art.10956. [PubMed: 12632419].
15. Salesi M, Ghazvini RA, Farajzadegan Z, Karimifar M, Karimzadeh H, Masoumi M, et al. Serum adenosine deaminase in patients with rheumatoid arthritis treated with methotrexate. *J Res Pharm Pract.* 2012;**1**(2):72–6. doi: 10.4103/2279-042X.108374. [PubMed: 24991593].
16. Zakeri Z, Izadi S, Niazi A, Bari Z, Zendeboodi S, Shakiba M, et al. Comparison of adenosine deaminase levels in serum and synovial fluid between patients with rheumatoid arthritis and osteoarthritis. *Int J Clin Exp Med.* 2012;**5**(2):195–200. [PubMed: 22567181].
17. Zamani B, Jamali R, Jamali A. Serum adenosine deaminase may predict disease activity in rheumatoid arthritis. *Rheumatol Int.* 2012;**32**(7):1967–75. doi: 10.1007/s00296-011-1912-0. [PubMed: 21461854].
18. Calis M, Ates F, Yazici C, Kose K, Kirnap M, Demir M, et al. Adenosine deaminase enzyme levels, their relation with disease activity, and the effect of colchicine on adenosine deaminase levels in patients with Behcet's disease. *Rheumatol Int.* 2005;**25**(6):452–6. doi: 10.1007/s00296-005-0612-z. [PubMed: 15868151].
19. Sari RA, Taysi S, Yilmaz O, Bakan N. Correlation of serum levels of adenosine deaminase activity and its isoenzymes with disease activity in rheumatoid arthritis. *Clin Exp Rheumatol.* 2003;**21**(1):87–90. [PubMed: 12673895].
20. Hitoglou S, Hatzistilianou M, Gougoustamou D, Athanassiadou F, Kotsis A, Catriu D. Adenosine deaminase activity and its isoenzyme pattern in patients with juvenile rheumatoid arthritis and systemic lupus erythematosus. *Clin Rheumatol.* 2001;**20**(6):411–6. [PubMed: 11771524].

21. Pallinti V, Ganesan N, Anbazhagan M, Rajasekhar G. Serum biochemical markers in rheumatoid arthritis. *Indian J Biochem Biophys.* 2009;**46**(4):342–4. [PubMed: 19788068].
22. Erer B, Yilmaz G, Yilmaz FM, Koklu S. Assessment of adenosine deaminase levels in rheumatoid arthritis patients receiving anti-TNF-alpha therapy. *Rheumatol Int.* 2009;**29**(6):651–4. doi: 10.1007/s00296-008-0750-1. [PubMed: 18953538].
23. Krenke R, Korczynski P. Use of pleural fluid levels of adenosine deaminase and interferon gamma in the diagnosis of tuberculous pleuritis. *Curr Opin Pulm Med.* 2010;**16**(4):367–75. doi: 10.1097/MCP.0b013e32833a7154. [PubMed: 20473171].
24. Moghtaderi A, Niazi A, Alavi-Naini R, Yaghoobi S, Narouie B. Comparative analysis of cerebrospinal fluid adenosine deaminase in tuberculous and non-tuberculous meningitis. *Clin Neurol Neurosurg.* 2010;**112**(6):459–62. doi: 10.1016/j.clineuro.2009.12.006. [PubMed: 20399005].
25. Alborzi A, Hosseini-nasab A, Zeyaeian M. A case of hypogammaglobulinemia with enteroviral meningoencephalitis, associated with increased adenosine deaminase in cerebrospinal fluid. *Iran J Allergy Asthma Immunol.* 2009;**8**:117–9.
26. Ziaee V, Amiran A, Moradinejad MH, HaghiAshtiani MT. Evaluation of Serum Adenosine Deaminase Changes Before and After Treatment in Patients with Systemic Lupus Erythematosus, Henoch-Schonlein Purpura and Juvenile Idiopathic Arthritis. *Ann Paediatr Rheumatol.* 2013;**2**(1):21. doi: 10.5455/apr.021820131558.
27. Zamani B, Jamali R, Ehteram H. Synovial fluid adenosine deaminase and high-sensitivity C-reactive protein activity in differentiating monoarthritis. *Rheumatol Int.* 2012;**32**(1):183–8. doi: 10.1007/s00296-010-1602-3. [PubMed: 20721560].
28. Currey HLF. In: Copeman's Textbook of the rheumatic diseases. Copeman WSC, Scott J, editors. Edinburgh: Churchill Livingstone; 1978. pp. 261–72.Aetiology and pathogenesis of rheumatoid arthritis.
29. Guieu R, Dussol B, Halimi G, Bechis G, Sampieri F, Berland Y, et al. Adenosine and the nervous system: pharmacological data and therapeutic perspectives. *Gen Pharmacol.* 1998;**31**(4):553–61. [PubMed: 9792214].
30. Ralevic V, Burnstock G. Receptors for purines and pyrimidines. *Pharmacol Rev.* 1998;**50**(3):413–92. [PubMed: 9755289].
31. Shryock JC, Belardinelli L. Adenosine and adenosine receptors in the cardiovascular system: biochemistry, physiology, and pharmacology. *Am J Cardiol.* 1997;**79**(12A):2–10. [PubMed: 9223356].
32. Yuksel H, Akoglu TF. Serum and synovial fluid adenosine deaminase activity in patients with rheumatoid arthritis, osteoarthritis, and reactive arthritis. *Ann Rheum Dis.* 1988;**47**(6):492–5. [PubMed: 3382270].
33. Doudkani-Fard M, Ziaee V, Moradinejad MH, Sedaghat M, Haghi-Ashtiani MT, Ahmadinejad Z. Sensitivity and specificity of adenosine deaminase in diagnosis of juvenile idiopathic arthritis. *Med J Islam Repub Iran.* 2014;**28**:113. [PubMed: 25678992].
34. Vinapamula KS, Pemmaraju SV, Bhattaram SK, Bitla AR, Manohar SM. Serum Adenosine Deaminase as Inflammatory Marker in Rheumatoid Arthritis. *J Clin Diagn Res.* 2015;**9**(9):BC08–10. doi: 10.7860/JCDR/2015/14296.6483. [PubMed: 26500897].