A Cross-Sectional Hospital Based Study on Correlation between Serum Uric Acid Levels and Disease Activity in Recently Diagnosed Rheumatoid Arthritis in Chennai, Tamilnadu

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ABSTRACT

BACKGROUND

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disorder. Uric acid is a by-product of purine metabolism, associated with diseases such as gouty arthritis, hypertension and cardiovascular disease (CVD). The association between serum uric acid concentrations and inflammation in patients with RA has been controversial. Some case reports suggest coexistence of gout and RA. Uric acid crystals can induce robust inflammation causing joint destruction and fibrosis. The purpose of this study was to estimate the serum uric acid levels in subjects with recently diagnosed rheumatoid arthritis and to correlate with disease activity.

METHODS

This cross-sectional study was done on 55 recently diagnosed RA subjects [American college of Rheumatology (ACR) criteria 2010] attending the rheumatology out-patient department (OPD) of a tertiary care institute in Chennai, Tamil Nadu. After clinical examination, evaluation of disease activity score (DAS), serum uric acid and rheumatoid factor (RF) were done. Data was analysed using Statistical Package for Social Sciences (SPSS trial version 28). Descriptive and inferential analysis was done. Correlation between serum uric acid levels and DAS was the main outcome.

RESULTS

The mean age was 41.51 ± 11.7 years. 87.3 % were females. Majority (58.2 %) were aged between 31 to 50 years. The mean duration of symptoms was 4.78 months. The mean serum uric acid level was 4.99 ± 1.2 mg/dl with 95 % C.I. of 4.66 to 5.31. The mean DAS was 5.34 ± 0.96. 56 % had high disease activity while only 44 % had moderate disease activity. 44 % were RF positive. There was no significant difference in serum uric acid levels across groups based on RF positivity and DAS severity respectively. There was no statistically significant correlation serum uric acid levels and DAS (-0.024, P value = 0.861).

CONCLUSIONS

Mean serum uric acid levels were elevated in recently diagnosed rheumatoid arthritis. Serum uric acid levels have no association with DAS and RF positivity in rheumatoid arthritis. Further studies are needed to investigate the role of specific treatment of elevated uric acid levels in rheumatoid arthritis independent of rheumatoid arthritis treatment.

KEYWORDS

Rheumatoid Arthritis, Uric Acid, Rheumatoid Factor, Disease Activity Score (DAS), Correlation, Recently Diagnosed Rheumatoid Arthritis

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BACKGROUND

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder of unknown aetiology which involves multiple systems primarily affecting the joints.[1-3] It has a global adult prevalence of 0.5 % to 1 % approximately with higher prevalence in Europe and North America compared to Asia.[4-6] The prevalence of RA has been taught to be 1 % for years.[7] But WHO-ILAR COPCORD (World Health Organization-International League of Associations for Rheumatology. Community Oriented Program for Control of Rheumatic Diseases) surveys and other studies conducted worldwide do not support this contention.[4, 8-10] Though the estimated prevalence of RA at 0.34 % in India is very low compared to the 1 % taught for years worldwide, its burden is extremely high in India and needs to be addressed seriously at the national level.[4,8] It is characterized by persistent inflammation of joints along with cartilage. It causes bone damage leading to significant restriction of activity, decrease in the quality of life besides the systemic complications.[11] If left uncontrolled, it may lead to deterioration of joints, significant restriction of activity, severe disability, decrease in the quality of life, premature mortality and increased co-morbidities like cardiovascular disease, cancer (specifically lymphoma and lympho-proliferative diseases, lung cancer and melanoma), infections, depression and gastrointestinal disease. High disease activity involves many joints and high inflammatory markers, be measured using the disease activity score (DAS 28) in RA.[12,13] Uric acid is an universal by-product of purine metabolism.[14,15] Uric acid is one of the major antioxidants found in the human body. It has the potential to predict the development of conditions and has been associated with oxidative stress such as obesity, hypertension, and cardiovascular disease.[15,16] But the association is not consistent across studies and there has been conflicting evidence. Several case reports and studies have observed that there is coexistence of RA and gout and it has also been observed that there is correlation of increased uric acid levels at a high degree of RA disease activity.[17-20] Hence, there is a complex association between serum uric acid levels and rheumatoid arthritis disease activity. The benefit of early recognition and treatment has led to an increased interest in the early phases of disease. The discovery of new risk factors and auto antibodies has led to new theories about the putative mechanisms involved in disease development. Finally, the outcome measures have also evolved, with more emphasis on sustained drug-free remission and patient-reported outcomes. The present study is one of its kind in Tamilnadu, which is more of explorative in nature, carried out to describe the correlation between serum uric acid levels and disease activity in recently diagnosed rheumatoid arthritis.

Objectives

The objective of the study was to estimate the serum uric acid levels in subjects with recently diagnosed rheumatoid arthritis and to correlate serum uric acid levels with disease activity in recently diagnosed rheumatoid arthritis.

METHODS

A hospital based observational cross-sectional study on 55 recently diagnosed rheumatoid arthritis in the Institute of Biochemistry in a Tertiary Care Teaching Hospital (Madras Medical College and Rajiv Gandhi Government General Hospital) from January 2014 to September 2014. The subjects were recently diagnosed rheumatoid arthritis patients screened by the rheumatologists in the rheumatology OPD according to American college of rheumatology (ACR) 2010 criteria. Diagnostic criteria for rheumatoid arthritis includes clinical & serological variables. The total points need to be more than or equal to 6 to have a diagnosis of rheumatoid arthritis.[21] According to the involved number of small or/and large, points are assigned. 0 point for 1 large joint, 1 point for 2 – 10 large joints, 2 points for involvement of 1 – 3 small joints (with or without involvement of large joints), 3 points for involvement of 4 – 10 small joints (with or without involvement of large joints), 5 points for involvement of more than 10 joints (with involvement of at least 1 small joint).The small joints are metacarpophalangeal joints, proximal interphalangeal joints, the interphalangeal joint of the thumb, second through fifth metatarsophalangeal joint and wrist. Large joints include shoulders, elbows, hip joints, knees, and ankles.

The minimum sample size for calculating mean serum uric acid levels is estimated as 55 assuming a standard deviation of 1, absolute precision of 0.3 with addition of 20 % for non-response. The minimum sample size for calculating correlation co-efficient is estimated as 55 assuming a correlation co-efficient of 0.5, type I error as 5 % and type II error as 10 % with addition of 20 % for non-response.

The study was conducted following ethical committee approval from Institutional Ethics Committee, Madras Medical College. Volunteers were enrolled only after obtaining informed consent by consecutive sampling. The following subjects were excluded from the study

1. Rheumatoid arthritis patients already on treatment-steroids, NSAIDS (Non-steroidal anti-inflammatory drugs), DMARDS (Disease modifying anti-rheumatic drugs),
2. Pregnant and lactating mothers, infertile individuals, women on oral contraceptive pills.
3. PCOS (Poly cystic ovarian syndrome), hypothyroidism, renal failure, diabetes mellitus and hypertension.
4. Other autoimmune diseases or any chronic illness.
5. Individuals with signs and symptoms of hyperprolactinemia, pituitary microadenoma, macroadenoma.
6. Patients on H2blockers, dopamine agonist, antipsychotics, isoniazid, antidepressants, anticonvulsants, calcium channel blockers (CCB), chemotherapy, hormone replacement therapy, methyl dopa, cannabis abuse.
7. People with recent chest wall trauma or irritation/pain in chest region. After enrolment, the following parameters were assessed - Clinical examination: number of swollen and tender joints, DAS (28), serum

uric acid, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), RF.[13,22]

The patients attending rheumatology OPD with symptoms of early morning stiffness of more than 1-hour, symmetrical joint involvement – pain, tenderness, swelling in the joints above 20 years of age, clinically diagnosed as rheumatoid arthritis were considered. They were seated, height, weight and blood pressure measured. The swollen and tender joints were counted. Haemoglobin, ESR, rheumatoid factor, CRP and anti-citrullinated protein antibody (ACPA) of these patients were determined in the serum obtained from centrifugation of peripheral venous blood collected from these patients. Subjects with elevated TSH > 5 µIU/mL, creatinine, urea were excluded. DAS calculation was done using the following formula[13, 22]

$$DAS = [0.56 * \sqrt{T28} + 0.28 * \sqrt{S28} + 0.7* \text{ in (ESR)}] * 1.08 + 0.16$$

Where, T is no of tender joints and S is no of swollen joints. Grades of disease activity are < 3.2 for low activity, 3.2 – 5.1 for moderate activity and > 5.1 for high activity.[23, 24]

Statistical Analysis

Statistical analysis was performed using SPSS trial version 28 and the following tests were carried out. Descriptive analysis was carried out by expressing mean and standard deviation for quantitative variables, frequency and proportion for categorical variables with 95 % confidence intervals. Inferential analysis involved cross-tabulation, correlation between serum uric acid levels and DAS. Tests of significance at alpha error of 5 % significance using unpaired students t-test were done to compare quantitative variables. Pearson's correlation co-efficient was done to measure the linear relation relationship between DAS28 (3) and serum uric acid. One way ANOVA (analysis of variance) to compare more than 2 groups.

Ethics

Only participants consenting to the study participated in the study. The confidentiality of the data and autonomy of the subjects were maintained throughout the study. The study involved only a minimal risk of sample collection for biochemical analysis. The present study reports a section of results from the parent study, which was approved by the Institutional Ethics Committee of Madras Medical College and Rajiv Gandhi Government General Hospital (ECR/270/Inst. / TN/2013-No. 09122013)

RESULTS

The mean age of the study population was 41.51 ± 11.7 years. 87.3% of the study population were females. Majority (58.2 %) were aged between 31 to 50 years. 56 % had high disease activity while only 44 % had moderate disease activity. 44 % were RF positive while 56 % were RF negative.

Sl. No.	Characteristic		Mean ± S.D. Median (Range)	95% Confidence Interval
1	Mean age in years (± S.D.)		41.51 ± 11.7	38.35 to 44.67
2	Median age in years (Range)		40 (21 to 62)	
3	Gender	Male	7 (12.73%)	5.27 % to 24.48 %
		Female	48 (87.27 %)	75.52 % to 94.73 %
4	Age group	21 to 30 years	10 (18.18 %)	7.99 % to 28.38 %
		31 to 40 years	18 (32.73 %)	20.68 % to 46.71 %
		41 to 50 years	14 (25.45%)	14.67 % to 39 %
		51 to 60 years	10 (18.18%)	9.08 % to 30.91 %
		➢ 60 years	3 (5.5 %)	
5	Duration of symptoms in months		4.78 ± 2.27	4.17 to 5.39
6	Mean serum uric acid (mg/dl)		4.99 ± 1.2	4.66 to 5.31
	Median serum uric acid (mg/dl)		4.8 (3 to 7.2)	
7	Mean disease activity score		5.34 ± 0.96	5.08 to 5.6
	Median disease activity score		5.3 (3.49 to 7.7)	
8	Disease activity score	Low	0	0
		Moderate	24 (43.64 %)	30.3 % to 57.68 %
		High	31 (56.36 %)	43.26 % to 69.47 %
9	Rheumatoid factor	Positive	24 (43.64 %)	30.3 % to 57.68 %
		Negative	31 (56.36 %)	43.26 % to 69.47 %

Table 1. Baseline Characteristics of the study population (n = 55)

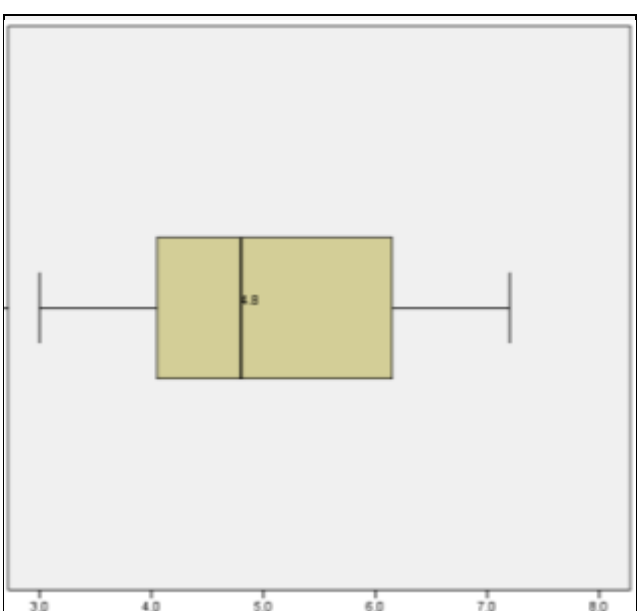

Figure 1. Box and Whisker Plot of Serum Uric Acid Levels in the Study Population

The mean serum uric acid level was 4.99 ± 1.2 mg/dl with 95 % C.I. of 4.66 to 5.31. The median serum uric acid level was 4.8 mg/dl with range of 3 to 7.2 mg/dl.

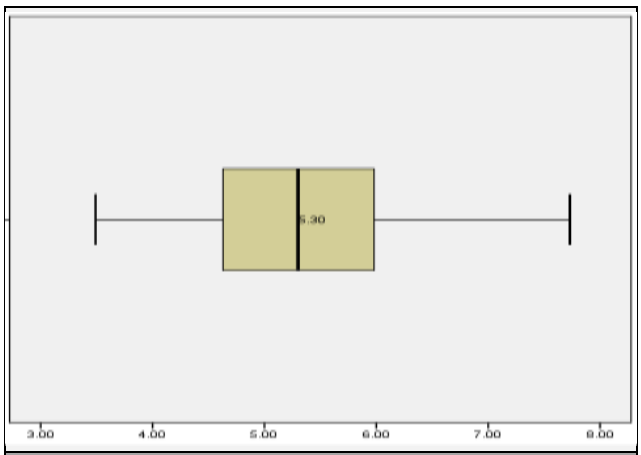

Figure 2. Box and Whisker Plot of Disease Activity Score in the Study Population

The mean DAS was 5.34 ± 0.96 with 95 % C.I. of 5.08 to 5.6. The median DAS was 5.3 with range of 3.49 to 7.73.

Grouping Variable	Mean Serum Uric Acid Levels (Mean ± S.D.)		95% C.I. of the Difference	P Value
Disease activity score	High (n = 31)	Moderate (n = 24)	-0.83 to +0.49	0.614
	5.06 ± 1.25	4.89 ± 1.15		
Rheumatoid factor	Positive (n = 24)	Negative (n = 31)		
	4.88 ± 1.36	5.07 ± 1.07	-0.84 to +0.48	0.583

Table 2. Comparison of Mean Serum Uric Acid Level across Groups Characterised by DAS and RF

S.D. = Standard deviation, C.I. = Confidence Interval

There was no significant difference in serum uric acid levels across groups classified based on RF positivity and DAS severity respectively.

There was a very weak negative correlation between serum uric acid levels and DAS (Pearson correlation co-efficient = -0.024, P value = 0.861) in the study population, which was statistically not significant.

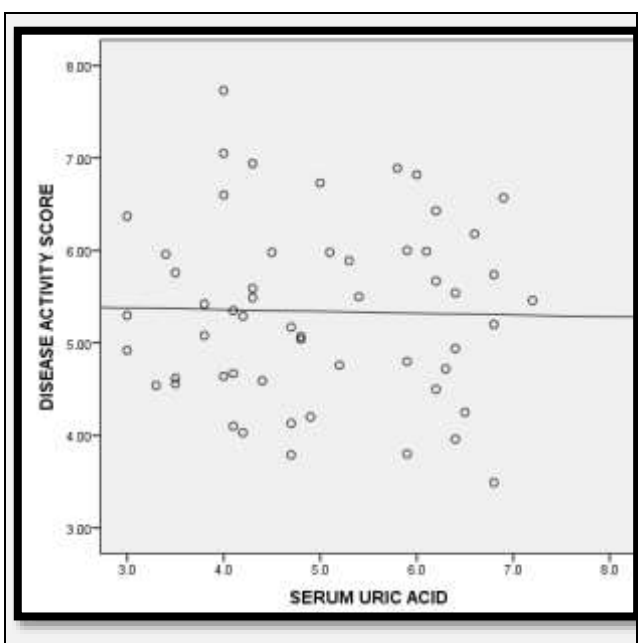

Figure 3. Correlation between Disease Activity Score and Serum Uric Acid Levels

DISCUSSION

Rheumatoid arthritis is a chronic inflammatory autoimmune disease affecting joints, their synovium, cartilage and bursa causing functional disability. This disease present worldwide occurs by an interplay of immunological, inflammatory, genetic and environmental genetic factors. Autoimmunity plays a pivotal role in pathogenesis of RA. Predominance of CD4+ T- cells in circulation and presence of IL2 in synovial fluid and blood indicates that rheumatoid arthritis is an immunologically mediated event. The inappropriate response of immune system towards self-components is autoimmunity. Normal healthy individuals possess self-reactive cells in circulation and it is suppressed by clonal suppression; defect in clonal suppression leads to activation of these self-reactive clones.

Uric acid plays a role in provoking inflammation by activating fibroblast like synoviocyte (FLS). FLS are mesenchymal cells in synovial joints. FLS releases a substance that binds with the receptor of nuclear factor-κB. Activation of this pathway recruit's macrophages from circulation and tissues converting them in to Osteoclast. Uric acid activates intracellular signal transduction pathways like c-Jun-N-terminal Kinase, mitogen activated protein kinase pathway by increasing the release of IL-6, CXCL8, MMP-1. Formation of osteoclast and release of tissue destroying chemokines causes joint destruction. IL-6 may stimulate the production of autoantibodies in rheumatoid arthritis.[25] Uric acid crystals have a role of innate host defense mechanisms in robust inflammation.[26] Uric acid induce maturation of dendritic cells and augments priming of $CD8^+$ cells to cross presented antigens.[27] Uric acid can trigger NALP3 pathway that activates caspase 1-dependent IL-1β production causing inflammation and fibrosis. There was no statistically significant correlation (r = -0.024) between serum uric acid levels and DAS in the present study. The present study included a total of 55 subjects with recently diagnosed RA with mean duration of symptoms of 4.78 months. Only 18 % (n = 10) of cases had presented within 3 months of onset of symptoms. Majority of patients 65 % (n = 36) presented 3 to 6 months of onset of symptoms. ESR was elevated in 49 (89.1 %) patients and was within normal limits for 6 patients. CRP was positive for 70.9 % of patients. The mean serum uric acid level was 4.99 ± 1.2 mg/dl while the mean DAS was 5.34 ± 0.96. The mean serum uric acid level was elevated at least 3 times the maximum upper limit. 56 % had high disease activity while only 44 % had moderate disease activity. These patients were not under any other treatment. 87.27 % were females in the study population which matches with the literature that autoimmune diseases are common in women.[28] The onset of rheumatoid arthritis among the cases in this study was between 30 to 40 years of age which again matches with the literature where it is mentioned that 80 % of patients develop the disease between 35 and 50 years of age.[29] Women in premenopausal status is more than postmenopausal status. The incidence is more common in women older than 60 years of age.[29] In this study, the predominant age group is 31 to 40 years of age. Since only recently diagnosed RA patients and not under any treatment were included, the

major contribution is by patients in 31 to 40 years of age. Only 18 % (n = 10) of cases had presented within 3 months of onset of symptoms. Majority of patients 65 % (n = 36) presented 3 to 6 months of onset of symptoms. In the present study, only 44 % of patients with RA were positive for RF in the present study. Although rheumatoid factor is not specific for rheumatoid arthritis, RF positivity is a cardinal feature of RA. It is mentioned that seroconversion in RF negative patients may occur during the first year of disease activity, hence these seronegative RA patients in the present study might turn seropositive for RF later.

Presence of rheumatoid factor is a cardinal feature of RA. The antibody that binds with Fc fragment of heavy chain of IgG is the rheumatoid factor. Presence of RF is an evidence for autoimmunity in rheumatoid arthritis. Presence of rheumatoid factor precedes disease onset by many years. Seroconversion occurs during the 1st year of disease activity. These antibodies activate the classic complement pathway. Large quantities of IgG RF produced by synovial tissues form complexes with one another and get deposited over the synovial tissues, facilitating complement fixation and release of chemokines. The proof of involvement of RF in RA is that RF level increases with clinical relapse and decreases with remission of disease activity. Some patients initially though seronegative to RF, subsequently convert to seropositive, typically during the first year of disease activity. RF directed against IgG and IgM are abundant in patients with RA.

There is a controversial association in rheumatoid arthritis between serum uric acid concentration and disease activity or inflammation. It has been reported that persistent hyperuricemia may decrease or protect against rheumatoid inflammation.[30] High level of serum uric acid in subjects with RA was associated with metabolic conditions such as obesity, hypertension, coronary artery disease, myocardial infarction and could have aggravated the inflammatory process in RA by increasing the degree of disease activity in RA.[15,16] In the present study, there was a very weak negative correlation between serum uric acid levels and DAS (Pearson correlation co-efficient = -0.024). Similar to the present study, Choe JY et al.[31] also observed there was no effect of uric acid on systemic inflammation in RA. They concluded that leflunomide reduced serum uric acid concentrations but there was no change in disease activity status. But contrary to the present findings, Agudelo CA et al.[30] observed that there is reduced expression of rheumatoid inflammation in subects with persistent hyperuricaemia. Turner RA et al.[25] in their in vitro studies had also observed that high levels of uric acid inhibit the RF production. They also observed that uric acid has immunosuppressive properties. This difference could be due to the stage of rheumatoid arthritis. This could be due to that in early stages of RA, serum uric acid may not have any significant effect on disease activity but with disease progression, there could be a disease activity lowering effect, which needs further exploration.

CONCLUSIONS

Mean serum uric acid levels were elevated in recently diagnosed rheumatoid arthritis in the present study. Serum uric acid levels had no correlation with DAS in recently diagnosed rheumatoid arthritis. Further studies are needed to investigate the role of uric acid levels in rheumatoid arthritis.

Limitations of the Study

The present study was limited by the fact that it was a cross sectional study. Causal association could not be made from our study. A prospective study with longer duration of follow up would be ideal. The study population was predominantly females. The association between serum uric acid and DAS could be different in males, which needs to be explored. Juvenile rheumatoid arthritis patients were also not included in the present study.

Further Scope of the Study

There is a scope for investigating the role of specific treatment of elevated uric acid levels in rheumatoid arthritis independent of rheumatoid arthritis treatment.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Sparks JA. Rheumatoid Arthritis. Ann Intern Med 2019;170(1):ITC1-ITC16.
[2] Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320(13):1360-1372.
[3] Chauhan K, Jandu JS, Goyal A, et al. Rheumatoid Arthritis. In: StatPearls. Treasure Island (FL): StatPearls Publishing Jan, 2021.
[4] Handa R, Rao UR, Lewis JF, et al. Literature review of rheumatoid arthritis in India. Int J Rheum Dis 2016;19(5):440-451.
[5] Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376(9746):1094-1108.
[6] Carmona L, Cross M, Williams B, et al. Rheumatoid arthritis. Best Pract Res Clin Rheumatol 2010;24(6):733-745.
[7] Chopra A, Abdel-Nasser A. Epidemiology of rheumatic musculoskeletal disorders in the developing world. Best Pract Res Clin Rheumatol 2008;22(4):583-604.
[8] Chopra A, Ghorpade R, Sarmukkadam S, et al. 5 Million patients and not 0.34% is worrisome: burden of rheumatoid arthritis in India based on a Bone and Joint Decade India Community Oriented Program for Control of Rheumatic Disease: No. 58. Arthritis & Rheumatism 2012.

[9] Minaur N, Sawyers S, Parker J, et al. Rheumatic disease in an Australian Aboriginal community in North Queensland, Australia. A WHO-ILAR COPCORD survey. J Rheumatol 2004;31(5):965-972.
[10] Darmawan J. World Health Organization-International League of Associations for Rheumatology Community Oriented Program for Control of Rheumatic Disease. Recommendations from the Community Oriented Program for Control of Rheumatic Disease for data collection for the measurement and monitoring of health in developing countries. Clin Rheumatol 2007;26(6):853-857.
[11] Sariyildiza MA, Batmaza I, Bozkurta M, et al. Sleep quality in rheumatoid arthritis: relationship between the disease severity, depression, functional status and the quality of life. J Clin Med Res 2014;6(1):44-52.
[12] Orr CK, Najm A, Young F, et al. The utility and limitations of CRP, ESR and DAS28-CRP in appraising disease activity in rheumatoid arthritis. Front Med (Lausanne) 2018;5:185.
[13] van Riel PL, Renskers L. The Disease Activity Score (DAS) and the Disease Activity Score using 28 joint counts (DAS28) in the management of rheumatoid arthritis. Clin Exp Rheumatol 2016;34(5 Suppl 101):S40-S44.
[14] Pasalic D, Marinkovic N, Feher-Turkovic L. Uric acid as one of the important factors in multifactorial disorders-facts and controversies. Biochem Med (Zagreb) 2012;22(1):63-75.
[15] Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 2008;27(6):608-619.
[16] Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359(17):1811-1821. Erratum in: N Engl J Med 2010;362(23):2235.
[17] Zhao G, Wang X, Fu P. Recognition of gout in rheumatoid arthritis: a case report. Medicine (Baltimore) 2018;97(50):e13540.
[18] Khosla P, Gogia A, Agarwal PK, et al. Concomitant gout and rheumatoid arthritis--a case report. Indian J Med Sci 2004;58(8):349-352.
[19] Yanti AE, Faridin HP, Bakri S, et al. Correlation between the degree of disease activity in rheumatoid arthritis with serum Uric acid in patients at wahidin sudirohusodo. International Journal of Current Research 2018;10(7):71861-71864.
[20] Ghosh B, Baidya D, Halder P, et al. Correlation of serum uric acid with disease activity and c-reactive protein in patients suffering from rheumatoid arthritis. Open Journal of Rheumatology and Autoimmune Diseases 2016;6(3) 79-84.
[21] Bykerk VP, Massarotti EM. The new ACR/EULAR classification criteria for RA: How are the new criteria performing in the clinic? Rheumatology (Oxford) 2012;(51 Suppl 6):vi10-15.
[22] van Riel PL. The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). Clin Exp Rheumatol 2014;32(5 Suppl 85):S65-S74.
[23] Singh H, Kumar H, Handa R, et al. Use of clinical disease activity index score for assessment of disease activity in rheumatoid arthritis patients: an Indian experience. Arthritis 2011;2011:146398.
[24] Van der Heijde DM, van't Hof M, van Riel PL, et al. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20(3):579-581.
[25] Turner RA, Pisko EJ, Agudelo CA, et al. Uric acid effects on in vitro models of rheumatoid inflammatory and autoimmune processes. Ann Rheum Dis 1983;42(3):338-342.
[26] Chen DP, Wong CK, Tam LS, et al. Activation of human fibroblast-like synoviocytes by uric acid crystals in rheumatoid arthritis. Cellular and Molecular Immunology 2011;8(6):469-478.
[27] Shi Y, Mucsi AD, Ng G. Monosodium urate crystals in inflammation and immunity. Immunol Rev 2010;233(1):203-217.
[28] Angum F, Khan T, Kaler J, et al. The prevalence of autoimmune disorders in women: a narrative review. Cureus 2020;12(5):e8094.
[29] Firestein GS, Budd RC, Gabriel SE, et al. Kelley's Textbook of Rheumatology. 9th edn. Elsevier Health Sciences Aug 31, 2012.
[30] Agudelo CA, Turner RA, Panetti M, et al. Does hyperuricemia protect from rheumatoid inflammation? A clinical study. Arthritis Rheum 1984;27(4):443-448.
[31] Choe JY, Kim SK. Association between serum Uric acid and inflammation in rheumatoid arthritis: perspective on lowering serum Uric acid of leflunomide. Clin Chim Acta 2015;438:29-34.