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Original Research Article

Assessment of serum uric acid level among patients with rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily effects elderly population and commonly involves pain in the joints (the wrist and hands). Gout is a form of arthritis caused by excess uric acid in the blood stream, which can affect several joints. The co-occurrence of RA and gout in the same patient is rarely reported. The aim of this study was to assess the level of serum uric acid among patients with RA, and to observe any associations of serum uric acid levels with RA.
Methods: In a descriptive cross-sectional study, a total of 70 blood samples were collected from patients. Anti-cyclic citrullinated peptide (anti-CCP) antibodies measured by ELISA method, serum C-reactive protein (CRP), Rheumatoid factor (RF) measured by latex agglutination test and serum uric acid levels measured with semi-autoanalyzer were carried out. Data was analyzed using a statistical package for social science for windows version 15.0. A $p<0.05$ was taken as level of significance.
Results: Out of a total of 70 subjects, 15 (21.4%) were positive for RF, anti-CCP antibodies positivity was present in 10 (14.3%) of the cases and serum high sensitive CRP was present in 36 (51.43%) of the cases. Of 70 cases. The 50 had hyperuricemia (23 male vs 27 female). Distribution of subjects having a high serum uric acid level on the basis of RF, anti-CCP Ab, and CRP status were statistically different.
Conclusions: The present study summarizes the level of uric acid in patients with RA (either seropositive or seronegative arthritis). The data concluded that serum uric acid did not show association with RA as revealed by the lack of association with specific markers.

Keywords: Anti-CCP Ab, Gout, RA, Uric acid

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory condition of the synovial tissue and mainly affects small joints, which potentially leads to joint destruction. The morbidity and mortality due to RA occur as result of local and systemic inflammatory processes that destruct bone, cartilage and soft tissue.[1] RA is considered to be an autoimmune disease, although, the exact pathological basis is not fully understood yet.[2] The worldwide prevalence of RA is found to be 0.4% and 0.7% in urban and rural populations, respectively.[3] The majority of RA infected patients are in the age group between 40 to 60 years old with a female preponderance.[4] Early diagnosis and treatment of RA is a challenge for most physicians. A study conducted in U.S. showed that only 66% of RA patients indicate seropositivity for RF and 69% for an anti-CCP antibody.[5] Anti-CCP antibodies are diagnostic markers which are more reliable than IgM RF and may also indicate prognoses. A survey between a positive anti-CCP antibody test and RA has proven to be a highly specific diagnostic tool for RA patients, anti-CCP antibodies are more frequently identified in those with arthritis than in those without arthritis. A recent study found a significant correlation between anti-CCP antibodies and

joint symptoms in patients with familial Mediterranean fever.[6] Anti-CCP is more sensitive than RF and may appear much earlier in the course of RA. A positive RF or anti-CCP is present in conjunction with pain and swelling of the joints, morning stiffness and involvement of many joints.[7] Seronegative cases are still present with an almost similar type of clinical features.[8]

Gout is a form of arthritis caused by excess uric acid in the blood stream in addition to RA, some patients present with a typical pain in the big toe 'called gout'. Gout is defined as the deposition of uric acid crystals in the synovial fluid at the big toe joint space and injured synovial membrane.[9] Uric acid is the metabolic end product of purine breakdown.[10] Gout mainly affects middle-aged and elderly men and postmenopausal women, and it is six times more common in males than females. Gout usually shows a sudden onset of symptoms and subsides within one or two weeks. If neglected or poorly treated, one or several joints can become permanently inflamed, thus the clinical picture of gout can mimic RA, and the diseases can be confused.[10] Asymptomatic hyperuricemia is the period prior to the first gout attack during which no symptoms can be seen, but serum uric acid levels are high and crystals are depositing in the joint. The classical symptoms of gout usually subside after a few days and normally go away in less than 10 days. An estimated 60% of people who have a gout attack will have a second one within a year and overall, 84% may have another attack within three years. Interval gout is the time between two subsequent attacks. Although sometimes there is no pain, it doesn't mean gout has gone and low-level (unnoticed) inflammation may be damaging joints. This is the time to begin managing gout via lifestyle changes and medication to prevent future attacks or chronic gout. Chronic gout develops in patients whose serum uric acid levels remain high over a several years. Attacks become more frequent and the pain may not go away as it used to be in acute form. Joint damage may occur, which can lead to loss of mobility. With proper management and treatment, this stage is preventable.[11] Many conditions can cause joint pain, inflammation, and swelling. No single test or examination can be used to confirm a diagnosis of gout as such medical history and patient information are important. Serum uric acid test is usually performed 4 to 6 weeks after an attack of gout.[12] The role of serum uric acid in the pathogenesis of RA is still debated however, there is evidence which suggests that hyperuricemia is prerequisite for the deposition of monosodium urate crystals in tissues.[13] A recent study exploring the relationship between gout and RA, showed the co-existence of gout and RA in the same patient. The findings of this study contradict previous reports that claimed gout does not typically occur in individuals with RA.[14] It is essential that research into the frequency of the co-existence of gout and RA, which would clarify whether the coexistence of both diseases changes the presentation, the prognosis, or the response to treatment to be carried out.[15] Such studies-in addition to efforts aimed at raising awareness among clinicians and technicians about the proper diagnosis, management, and prevention of gout, will likely provide significant benefits for patients who have, or are likely to develop, this painful yet treatable condition.

METHODS

A hospital-based cross-sectional study was conducted, RA was diagnosed based on patient history, physical exam, and radiographs. Blood samples were also collected from patients who were attended the Bangladesh Institute of health sciences and general hospital (BIHSH) in Dhaka, Bangladesh.

Serological detection of RF and CRP was done by latex slide agglutination tests (Cypress diagnostics, Belgium). Anti-CCP antibody was done by the 4th generation ELISA kit (Uro-diagnostic, Sweden) and finally, uric acid levels were estimated with semi-autoanalyzer (DIRUI DR-7000D, China) by using a biochemical reagent from Randox Laboratories Ltd, UK. All laboratory analysis was done at the immunology laboratory, Bangladesh university of health sciences. Results were expressed as the mean ± SD and number (percent) as appropriate. Statistical tools like Unpaired Student's t-test and Chi-squared tests were performed to calculate the statistical difference. Odds ratio (OR) and relative risk (RR) were calculated in appropriate situations. Statistical analyses were performed using a Statistical Package for Social Science (SPSS version 15). P<0.05 was considered as the level of significance.

RESULTS

A total of 70 participants attending at Bangladesh institute of health sciences and general hospital in Dhaka Bangladesh were recruited for the present study. Of the 70 subjects, 30 (42.9%) were men and 40 (57.1%) were women. Gender distribution did not show any statistically significant difference. The average age of study subjects was 46.2±13.9. In male and female, the values were 48.6±15.8 and 44.3±12.1, respectively but did not show a statistically significant difference (p=0.204) (Figure 1).

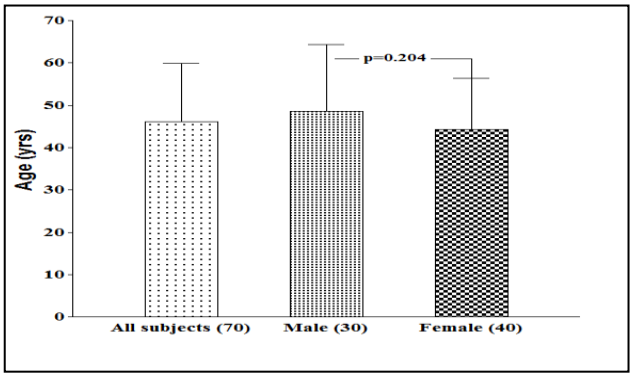

Figure 1: Age of the study subjects (total, male and female).

CRP, RF and anti-CCP antibody status of the study subjects

Of the total 70 subjects, 15 (21.43%) and 36 (51.43%) were positive for RF and CRP respectively and 10 (14.3%) carried anti-CCP antibody. Out of the 15 RF positive subjects, 9 (60%) were also positive with CRP and 6 (40%) showed a negative result. For 55 RF negative subjects, 27 (49%) were positive with CRP (Table 1). The distribution did not show a statistically significant difference (p=0.454).

Table 1: RF and CRP status of the study subjects.

RF status	CRP status	
	Positive, n (%)	**Negative, n (%)**
Positive (15)	9 (60)	6 (40)
Negative (55)	27 (49)	28 (51)
	$\chi2$=0.561/0.454	

CRP positive if the value of CRP ≥6 mg/L, otherwise is negative, RF positive if the value of RF≥8 IU/ml; otherwise, is negative

Anti-CCP and RF status of the study subjects

Anti-CCP with RF positive cases was 8 out of 10 patients (80%). Of the 60 Anti-CCP negative cases, 7 (11.7%) were positive for RF (Table 2). The distribution showed a statistically significant association (p<0.001).

Table 2: Anti-CCP and RF status of the study subjects.

Anti- CCP Ab status	RF status	
	Positive, n (%)	**Negative, n (%)**
Positive (10)	8 (80)	2 (20)
Negative (60)	7 (11.7)	53 (88.3)
	$\chi2$= 23.772/<0.001	

Serum uric acid status of the subjects

The mean uric acid of the study subjects was 7.3 mg/dl. The mean uric acid for women (7.5 mg/dl) is slightly higher than those for men (7.1 mg/dl), but it is not statistically significant (p=0.653) (Figure 2).

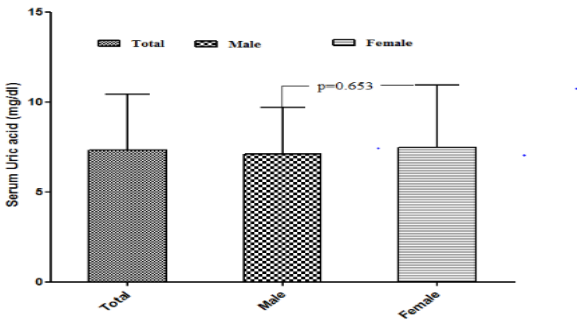

Figure 2: Serum uric acid level of study subjects.

Uric acid status in male and female subjects

Of the total 30 males, 7 (23.3%) cases had normal uric acid, the remaining 23 (76.7%) had shown high levels. For 40 females, 27 (67.5%) had a high uric acid level and the remaining 13 (32.5%) were normal **(**Table 3). The distribution didn't show statistically significant association (p=0.401).

Table 3: Uric acid status and gender of study subjects.

Gender	Uric acid level	
	Normal, n (%)	**High, n (%)**
Male (30)	7 (23.3)	23 (76.7)
Female (40)	13 (32.5)	27 (67.5)
	$\chi2$=0.706/0.401	

High uric acid level; >7 mg/dl for male and >5.7 mg/dl for female.

Association of serum uric acid with anti-CCP antibody

Anti-CCP Ab and uric acid status of subject (Table 4), of the total 10 anti-CCP Ab positive cases 6 (60%) had high uric acid and 4 (40%) normal. For 60 subjects with anti-CCP Ab negativity 44 (73.3%) had normal serum uric acid and 16 (26.7%) high. The distribution didn't show statistically significant association (p=0.388).

Table 4: Anti-CCP and uric acid status of the study subjects.

Anti-CCP Ab	Uric acid level	
	High, n (%)	**Normal, n (%)**
Positive (10)	6 (60)	4 (40)
Negative (60)	44 (73.3)	16 (26.7)
	$\chi2$=0.747/0.388	

Anti-CCP Ab positive, anti-CCP Ab ≥25 U/ml; anti-CCP Ab negative, anti-CCP Ab<25 U/ml, uric acid normal, serum uric acid level ≤7 mg/dl for male and ≤5.7 mg/dl for female, uric acid high, serum uric level >7 mg/dl for male and >5.7 mg/dl for female.

Relationship of RF with serum uric acid

RF and uric acid status of the subject is shown in table 5. Of the total 15 RF positive cases, 11 (73.3%) had high uric acid and 4 (26.7%) normal. Of 55 subjects with RF negativity 39 (70.9%) have a normal uric acid level and 16 (29.1%) high. The distribution did not show a statistically significant association (p=0.854).

Table 5: RF and uric acid status of the study subjects.

RF status	Uric acid status	
	High, n (%)	**Normal, n (%)**
Positive (15)	11 (73.3)	4 (26.7)
Negative (55)	39 (70.9)	16 (29.1)
	$\chi2$=0.034/0.854	

RF positive, RF≥8 IU/ml; RF negative, RF<8 IU/ml. Uric acid normal, serum uric acid level ≤7 mg/dl for male and ≤5.7 mg/dl for female. Uric acid high, serum uric level >7 mg/dl for male and >5.7 mg/dl for female.

DISCUSSION

RA is an autoimmune disease, where the body's immune system attacks the joints wrongfully. Risk factors for RA include being a female, over 40 years old and obese, having a family history of RA, and smoking that usually exposed to environmental pollutants.[16] Gout has very similar clinical features to RA and is caused by the deposition of excessively high levels of uric acid that crystallize in joints and surrounding tissue. Risk factors for gout include eating a diet rich in purines, being overweight or obese, having family history of gout and being male over the age of 40.[17] Diagnosis of gout can be made by detecting monosodium urate crystals in synovial fluid, synovial/node biopsy, or using positive dual-energy CT-gout protocol if available.[18] These two conditions can be expressed with varying severity and may cause significant physical and functional disability.[19] In general, hyperuricemia (gout) has become more prevalent in developed and developing countries such as the United States, the United Kingdom, New Zealand, and China. In the United States gout affects 1- 2% of the population and approximately 6% of men over the age of 80. In the United Kingdom gout affects 7% of men aged over 75 years.[20] However, the mean age of the study subjects was 46.2±13.9 and female (57.1%) predominate more than male in our study.

RF and anti-CCP antibody are commonly used by the physicians to diagnose a case of RA. For adult RA, diagnostic usefulness of anti-CCP antibodies is important because of its high specificity (95%) and sensitivity (67%). It is present in only a quarter to half of the patients before or at diagnosis, so a negative result does not rule out RA. However**,** anti-CCP only assists with the diagnosis of RA.[7] In the present study, only 10 (14.3%) cases out of 70 were diagnosed as RA considering the CCP antibody seropositivity. Coexistence of RA and gout is extremely rare, it might be explained by hyperuricemia having a protective immunosuppressive effect, protecting against or decreasing the expression of rheumatoid inflammation.[21] Another hypothesis suggests that monosodium urate crystals coating the RF, with a combination of genetic, biochemical and immunological factors, might block Fc receptors adsorbed on crystal surfaces, thus accounting for the apparent dissociation between these two diseases.[21]

It can be difficult to clinically differentiate RA from hyperuricemia (gout) especially when it involves the hands. Only RF, anti-CCP antibodies, uric acid level, and radiographic evidence are important to discriminate between these two clinical conditions. In the present study, 6 (60%) out of 10 anti-CCP positive cases had shown a high uric acid level. On the other hand, 44(73%) subjects out of 60 anti-CCP negative cases had a high uric acid level. The distribution did not show a statistically significant association (p=0.388). Only 33 cases of RA coexisting with gout have been reported. Another study reported eight cases of coexisting RA and gout between 1994 and 2005 at Chang Gung memorial hospital Taiwan.[22] All these findings are not in line with our study.

Anti-CCP antibodies are used as a clinical biomarker for the diagnosis of RA, having a 55-80% sensitivity and specificity of 90-98% for RA. RF has a sensitivity of 69% with a specificity of 85%. 11 (73.3%) out of 15 RF positive cases had a high uric acid level. Similar finding of elevated uric acid level with RA was reported by Kozin at el.[19] RA and gout may coexist in the same patient as reported in some studies.[19] However, our findings do not support the coexistence of elevated uric acid and RA. Knowledge regarding clinical awareness, pathogenesis, and appropriate concomitant diagnostic parameters is crucial for the timely intervention of these disorders, especially in patients with polyarticular diseases.

CONCLUSIONS

The data concluded that serum uric acid did not show association with RA as revealed by the lack of association with specific markers. However, higher proportion of both male and female subjects with arthritis presented hyperuricemia, and any risk associated with arthralgia due to hyperuricemia could not be elucidated in this study.

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