Original Research Article

Effect of thyroid dysfunction on disease activity of patients with rheumatoid arthritis

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Received: 12 December 2018
Accepted: 03 January 2019

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory multisystem disease of unknown cause that may affect many tissues and organs, but principally attacks synovial joints, primarily affecting the peripheral joints in a symmetrical pattern. The pathology of the disease process often leads to destruction of articular cartilage. It is the commonest inflammatory arthropathy worldwide with a gender predilection towards women. Prevalence of RA in the adult general population is approximately 1%. An association between RA and thyroid dysfunction with or without autoimmune origin has been reported in 6% to 34% of patients with RA. On the contrary, when presence of thyroid antibodies is considered, despite normal thyroid function, the prevalence can rise up to about 38%. These rates are significantly greater when compared with the general population.

Methods: RA patients who were diagnosed according to the new 2010 EULAR/ACR criteria and thyroid function tests were done and patients with thyroid dysfunction were identified and then patients were divided into two groups based on presence of thyroid dysfunction with rheumatoid arthritis and disease activity was illustrated in both groups based on different scales.

Results: In all, 250 patients 215 (86.8%) were females and 33 (13.2%) were males. ESR was elevated in 85 (34%) patients while as it was normal in 165(66%) patients. CRP was positive in 127 (52.7%) negative in 123 (47.3%) patients. Although subclinical hypothyroidism was the most frequent abnormality observed in 38.3% patients, only 30% had concomitant anti-TPO raised and 71.4% patients of overt hypothyroidism had raised anti-TPO antibody. Disease activity parameters were significantly higher in patients of RA with hypothyroidism as compared to other group. Although most of parameters of disease activity showed a higher frequency in the group having patients with thyroid disorder but the swollen joint count was comparable in both the groups and was not statistically significant.

Conclusions: Presence of thyroid disorders in RA patients is suggestive of a more aggressive disease. To diagnose concurrent thyroid disorders at an earlier stage, routine measurement of serum thyroid- stimulating hormone is recommended in all RA patients at the time of diagnosis and with yearly interval thereafter.

Keywords: Autoimmunity, Hypothyroidism, Peripheral joints, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory multisystem disease of unknown cause that may affect many tissues and organs, but
principally attacks synovial joints, primarily affecting the
peripheral joints in a symmetrical pattern.1 The pathology
of the disease process often leads to destruction of
articular cartilage.2 It is the commonest inflammatory
arthropathy worldwide with a gender predilection
towards women. Prevalence of RA in the adult general
population is approximately 1%.3,4 The worldwide
prevalence of autoimmune thyroid disease (AITD) in RA
varies considerably, ranging from 0.5% in Morocco to
27% in Slovakia.3,4 An association between RA and
thyroid dysfunction with or without autoimmune origin
has been reported in 6% to 34% of patients with RA.5 On
the contrary, when presence of thyroid antibodies is
considered, despite normal thyroid function, the
prevalence can rise up to about 38%.4 These rates are
significantly greater when compared with the general
population (about 2-3 times).5,7 Routine screening of the
population for thyroid dysfunction is not recommended;
however, assessment of high-risk group, for example,
patients with abnormal findings on physical examination,
symptoms suggestive of hyperthyroidism or hypothyroidism,
women with a positive family history of
thyroid disease, previous thyroid dysfunction, and also a
history of other autoimmune disease, for example, type 1
diabetes or Addison disease, has been encouraged.8
Previous studies were in favour of the hypothesis that an
association between thyroid dysfunction and RA exists,
probably due to autoimmunity; however, the results of
these studies were not consistent.9 Furthermore, most of
these studies focused on the clinical characteristic of
thyroid dysfunction, and just a few of them discussed the
impact of thyroid dysfunction on disease activity and
treatment response of RA.

The primary objective of this study was to reveal the
prevalence of thyroid disorders among RA patients and to
find whether thyroid disorders are more prevalent among
the RA patients. The secondary objectives of the study
were to illustrate the effect of thyroid dysfunction on
disease activity of rheumatoid arthritis and response of
patients to treatment of thyroid dysfunction.

Aim and objective of research work was to study the
effect of thyroid dysfunction on disease activity in
rheumatoid arthritis.

METHODS

The present study was conducted in, Government
Medical College Srinagar and Associated Hospitals,
Jammu and Kashmir, India in patients attending
rheumatology/medicine opd clinic. The study was of
prospective nature, and analytical cross sectional study.
Ethical clearance was taken from the institution. We had
included 250 patients in our study based on an anticipated
prevalence of thyroid dysfunction among rheumatoid
arthritis and an absolute error of 5% with 30% prevalence
and 95% confidence level.

Inclusion criteria

The study included patients of rheumatoid arthritis who
fulfilled European League Against Rheumatism
(EULAR)/American College of Rheumatology (ACR)-
2010 criteria for rheumatoid arthritis and were screened
for: triiodothyronine (T3), thyroxine (T4), free T4 (free
thyroxine) thyroid stimulating hormone (TSH), antithyroid
peroxidase antibodies (anti-TPO) antibodies.

Exclusion criteria

Patients with history of:

- Surgical removal of thyroid gland,
- Any malignancy on radiotherapy and damage to
  thyroid,
- Patients on drugs causing hypothyroidism,
- Pregnancy,
- Patients on oral contraceptives,
- Sepsis and serious underlying diseases.

Procedure

Patients attending Outpatient Department of Medicine at
SMHS Hospital were evaluated for a history of thyroid
disease, use of thyroid drugs or supplementation. Blood
samples were obtained for the measurement of thyroxine,
triiodothyronine, and thyroid stimulating hormone.
Samples of blood were also obtained for the detection of
rheumatoid factor and anti-TPO antibody. Taking all
aseptic and antiseptic precautions about 3-5 ml of venous
blood from median cubital vein was collected in clot
activating vacutainer. The blood was collected after 10 to
12hours of fasting. After clot formation, the samples were
centrifuged at 4000 rpm to separate serum from the cells.

Serum aliquots were stored at 4°C to be run in batches.
The samples were allowed to thaw prior to assay and
mixed thoroughly. Hemolysed and lipemic samples were
rejected.

Thyroid function test (TFT) T3, T4, FT3, FT4, TSH and
anti-TPO were estimated by Chemiluminescent
Microparticle Immunoassay (CMIA) method using
ABBOTT ARCHITECT i1000 SR analyzer. It is a two-
step immunoassay using chemiluminescent microparticle.10
Immunoassay (CMIA) technology with flexible assay
protocols, referred to as chemiflex. Patients with a serum
level TSH of 0.35mIU/L-4.2mIU/L was considered as
normal. Levels more than or equal to 4.2mIU/L with normal
T4 and FT4 levels was considered as subclinical
hypothyroidism and patients having raised
TSH and low T4, FT4 levels were considered overt
hypothyroid. T3 value of 0.6-1.6ng/ml, T4 value of 4.5-
11.7ng/dl and FT4 levels of 0.8-1.7 were considered as
normal. Anti-TPO estimation was also done
Chemiluminescent Microparticle Immunoassay (CMIA)
method using ABBOTT ARCHITECT i1000 SR
analyzer, for quantitative determination of IgG class of
thyroid antibodies in human serum and plasma on the ARCHITEST iSYSTEM. A value of >5.6ng/ml was taken as positive. Global assessments of disease activity were recorded independently by physician, using the standard 100mm horizontal visual analogue scale (VAS) in which 0 no activity and 100 maximal activity. DAS-28 was calculated in each patient. The following DAS-28 values relate to clinical status:
- Remission: DAS-28 -2.6;
- Low disease activity: DAS-28 - 2.6-3.1;
- Moderate disease activity: DAS-28 - 3.2-5.1;

**Statistical analysis**

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorial variables were summarized as percentages. Frequency distribution tables, bar and pie charts were used for data presentation. Chi-square test or Fisher’s exact test, whichever appropriate, was used to determine association between various categorical variables. P-value less than 0.05 was considered statistically significant. All P-values were two tailed.

Patients were divided into two groups: RA with hypothyroidism (Group A) and RA without hypothyroidism (Group B). The Mann-Whitney U and 2 tests were used to calculate the significance of the median of continuous variables between the two groups, and frequency of discrete variables for non-parametric data, respectively.

**RESULTS**

The mean age of patients was 49.2±12.1. Most common age group was 37-52 years with 40% patients belonging to this group and next 30% belonging to 53-64 years age group. Out of a total of 250 patients, 215 (86.8%) were females and 33 (13.2%) were males. ESR was elevated in 85 (34%) patients while as it was normal in 165 (66%) patients. CRP was positive in 127 (52.7%) patients while as it was negative in 123 (47.3%) patients. RF was more than 3 times elevated in 154 (61.8%) patients, <3 times raised in 85 (34%) patients and negative in only 11 (4.2%) patients. Anti CCP was more than 3 times elevated in 195 (78.1%) patients, <3 times raised in 16 (6.3%) patients and negative in 39 (16.5%) patients. Anti-TPO antibodies were negative in 195 (78.4%) patients with rheumatoid arthritis and was positive in 54 (22.5%) patients. Although subclinical hypothyroidism was the most frequent abnormality observed in 38.3% patients, only 30% had concomitant anti-TPO raised and 71.4% patients of overt hypothyroidism had raised anti-TPO antibody. Spectrum is illustrated in Table 1.

The patients were divided into two groups based on thyroid dysfunction present or not present and the disease severity was checked in both the groups and results compared as described in Table 2.

Disease activity parameters such as the visual analogue scale for pain, patients’ global health assessment score, tender joint count, DAS-28 and ESR were significantly higher in patients of Group A as compared to Group B (Table 2).

**Table 1: Spectrum of thyroid dysfunction in rheumatoid arthritis (n=250).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patient %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical hypothyroidism</td>
<td>96 (38.3)</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Euthyroid with elevated anti-TPO levels</td>
<td>13 (4.8)</td>
</tr>
</tbody>
</table>

**Table 2: Disease activity.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (RA with thyroid dysfunction n=103)</th>
<th>Group B (RA without thyroid dysfunction n=147)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analogue scale</td>
<td>78±12.2</td>
<td>58.6±15</td>
<td>0.002</td>
</tr>
<tr>
<td>Patient global assessment score</td>
<td>67.8±3.4</td>
<td>55.4±18</td>
<td>0.0012</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>23.6±4.2</td>
<td>17.3±5.5</td>
<td>0.002</td>
</tr>
<tr>
<td>swollen joint count</td>
<td>8.3±4.4</td>
<td>5.2±3.4</td>
<td>0.067</td>
</tr>
<tr>
<td>DAS-28-ESR</td>
<td>6.7±0.9</td>
<td>5.5±1.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Low disease activity.</td>
<td>1(1%)</td>
<td>50(34%)</td>
<td>0.977</td>
</tr>
<tr>
<td>Moderate disease activity.</td>
<td>5(5%)</td>
<td>41(28.1%)</td>
<td>0.090</td>
</tr>
<tr>
<td>High disease activity.</td>
<td>97(95%)</td>
<td>69(37%)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Although most of parameters of disease activity showed a higher frequency in the group having patients with thyroid disorder but the swollen joint count was comparable in both the groups and was not statistically significant. No patient in our study was in remission. low disease activity according to DAS28 scores was more
frequent in group B. Moderate disease activity was found in 5 patients whereas high disease activity was found in 97 patients. Group A had a higher number of high disease activity patients as compared to group B; however, the difference in frequency was statistically significant (P=0.0002). ESR levels were found significantly increased in high disease activity patients than that of moderate disease activity patients with p value of 0.004. we did a multinomial logistic regression analysis to see the independently associated variables with Group A and Group B as dependent variables. All the variables found significantly associated in univariate analysis were used as independent variables and stepwise model was used for the analysis. VAS was observed significantly independently associated with hypothyroidism in RA when compared from patients with RA only. We performed Linear regression to see the independent factors associated with TSH level in a stepwise manner and we observed that ESR and tender joint count were independently significantly positively correlated with TSH levels in RA patients as shown in Table 3.

Table 3: Linear regression analysis with TSH levels as dependent variable in ESR and tender joint count.

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>Standardized coefficient beta</th>
<th>95%cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>0.004</td>
<td>0.369</td>
<td>0.169-0.711</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>0.002</td>
<td>0.362</td>
<td>0.094-0.459</td>
</tr>
</tbody>
</table>

DISCUSSION

Rheumatoid arthritis has been an important research area due to the nature of disease and due to autoimmunity which is the cause of association with other autoimmune diseases as autoimmune disorders run parallel. A similar association between RA and hypothyroidism has been demonstrated since the 1960s. One of the first studies reported thyroiditis in up to 12% of patients with RA. Most common thyroid dysfunction observed was subclinical hypothyroidism seen in 38.3% of the patients when compared to general population in the same geographical area. Kashmir our results were two times higher (Hamid Bashir and others 21.56%, Rama Jailkhani and others 33%).

The results of our study were similar to the study done by Tekaya R and others in Tunisia who found that thyroid abnormalities were detected in 40% of the patients. We measured the disease activity using DAS-ESR score and VAS and we found significant correlation between serum levels of TSH and disease activity parameters (ESR and DAS-28), as did the study by Elattar et al. The comparison between two groups created in patients based on presence or absence of thyroid dysfunction showed disease activity parameters such as the visual analogue scale for pain, patients’ global health assessment score, tender joint count, DAS-28 and ESR were significantly higher in patients of thyroid dysfunction group as compared to patients of normal thyroid functions. Swollen joint count was also higher in first group but this difference was not statistically significant the results where correlating with study done by Prakash Joshi et al.

CONCLUSION

The conclusion which we derived from this study was not only thyroid dysfunction is more frequent in rheumatoid arthritis but it has a very significant impact on the disease activity and patients who are a diagnosed case of rheumatoid arthritis should be screened for thyroid dysfunction if minimal symptoms of same are suspected. The recommendations are further extended to patients having high disease activity should routinely screened for thyroid dysfunction. Both the disorders should be managed spontaneously and hit early and hit hard should be the minimum possible goal.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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8. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004 Jan 14;291(2):228-38.