Original Article:

Prevalence of thyroid disorders and metabolic syndrome in adult patients with rheumatoid arthritis

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ABSTRACT

Background: The clinical association between rheumatoid arthritis (RA) and hypothyroidism is important as both these conditions are associated with metabolic syndrome (MetS) which in turn makes the patients more prone for cardiovascular disease.

Material and methods: In this cross-sectional study, the prevalence of thyroid disorders and MetS were studied in 54 consecutive adult patients with RA (mean age 46.0±10.4 years; 48 females) and 54 age - and gender-matched healthy control subjects.

Results: The prevalence of thyroid disorders was higher in patients with RA than in control subjects; however, this difference was not statistically significant [19/54 (35.2%) Vs 12/54 (22.2%); p=0.201]. Nine patients with RA already known to have hypothyroidism were receiving levothyroxine treatment. Among the remaining RA patients (n=45), a significantly higher prevalence of autoimmune thyroid disease (AITD) (10/45 Vs 4/54; χ^2=4.437, p=0.045) and subclinical hypothyroidism with anti-thyroid peroxidase (anti-TPO) antibody positivity (4/45 Vs 0/54; χ^2=5.002, p=0.040) were observed compared with healthy control subjects. The prevalence of MetS was higher in patients with RA than in control subjects; however, this difference was not statistically significant [31/54 (57.4%) Vs 25/54 (46.3%); p=0.336].

Conclusions: A significantly higher prevalence of AITD and subclinical hypothyroidism with anti-TPO antibody positivity in patients with RA suggests that these patients would benefit from screening for AITD. The co-existence of hypothyroidism and RA reiterates the need for monitoring and early identification of cardiovascular risk factors in patients with RA.

Key words: *Arthritis, Rheumatoid, Hypothyroidism, Metabolic syndrome, India*

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INTRODUCTION

Rheumatoid arthritis (RA) is considered an autoimmune disease[1] and the overall systemic and articular inflammation leads to the destructive progression of the disease. The disease predominantly affects the synovial joints. The intriguing clinical association between RA and thyroid disorders has been a subject of investigation for a long period. Thyroid disorders in RA patients are thought to be most often of autoimmune nature because they were accompanied by elevated thyroid autoantibody titres. Many patients diagnosed initially to have RA develop thyroid disorders at a later point in time.[2,3] The converse is also frequently observed, i.e., musculoskeletal disorders, including RA are known to develop in patients with various thyroid disorders.[2] Patients with thyroid disorders may present with musculoskeletal manifestations, such as, arthralgias, myalgias, joint swelling and muscle

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weakness and these symptoms of thyroid disease can be confused with those of RA.

The extent of inflammation has been linked to an increased risk of cardiovascular events in patients with RA; a higher morbidity and mortality due to cardiovascular disease (CVD) has been reported in patients with RA when compared to general population.[4,5] The clinical association between RA and hypothyroidism assumes more significance as both these conditions are associated with metabolic syndrome (MetS) which in turn makes the patient more prone for CVD.[6,7] This is particularly relevant in Indian patients, because, as an ethnic group, Asian Indians are predisposed to a high risk of MetS, and premature atherosclerosis and patients with RA are more prone for accelerated atherosclerosis.

Investigations into the relationship between RA and the thyroid disorders have yielded conflicting results. While some studies[3,8-11] reported a higher prevalence of thyroid disorders in patients with RA, others[12,13] did not document any such association. Little published data are available regarding the burden of thyroid disorders and MetS in patients with RA from India, especially, from south India. The present study, was therefore, undertaken to study the burden of thyroid disorders and the prevalence of MetS in patients with RA.

MATERIAL AND METHODS

Patients with RA presenting to the Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati during the period between March 2011 and August 2012 were included in this cross-sectional prospective study. Patients satisfying the following criteria were included in the study: adult patients (aged 18 years or more) with RA who consented to participate in the study. Patients with RA aged under 18 years; with other rheumatic diseases; pregnant women; and patients unwilling to participate in the study were excluded. An equal number of age and gender matched apparently healthy subjects from among relatives of patients and hospital staff were also included in the study.

The study was cleared by the Institutional Research Approval and Ethical Committees. After obtaining a written informed consent, all the patients were subjected to a thorough clinical evaluation which included, detailed history and a thorough physical examination. All the details were recorded in a structured proforma. The diagnosis of RA was made based on American Rheumatism Association (ARA) criteria.[14] Severity of RA was assessed by using the disease activity score based on 28 joints with erythrocyte sedimentation rate (ESR) (DAS28).[15] Specific enquiry was made to know if any of the patients were already known to have thyroid disorders. In the patients already known to have thyroid disorders, details regarding the time of onset, basis for diagnosis and treatment if any being taken for the same were noted.

The MetS was defined as per the National Cholesterol Education Programme-Adult Treatment Panel III (NCEP-ATP III) criteria (2001),[16] with elevated fasting glucose defined as ≥100 mg/dL,[17] and cut-off for waist circumference defined as appropriate for south Asians;[18] and as per the International Diabetes Federation (IDF) criteria.[19] Waist circumference was measured at the midpoint between the lower margin of the lowest palpable rib and the top of the iliac crest, at the end of a normal expiration.[20] Hip measurement was taken as the greatest circumference at the level of greater trochanters (the widest portion of the buttocks).[20] Waist-to-hip ratio (WHR) was calculated by dividing the waist circumference (cm) by the hip circumference (cm). For these measurements, the patients were asked to stand erect in a relaxed position with both feet together and wearing one layer of clothing. Measurements were made using a non-

stretchable fibre measure tape, with the tape held parallel to the floor.

Hypertension was defined as per the Joint National Committee (JNC) VII classification.[21] Type 2 diabetes mellitus was diagnosed by the American Diabetes Association 2011 criteria.[22] Obesity was classified as proposed by International Obesity Task Force Guidelines for Asians.[18] The prevalence of dyslipidaemia was defined as per the NCEP-ATP III criteria.[16]

Peripheral venous blood samples were obtained after an overnight 8-12 hours of fasting for serum biochemistry evaluation. In all the patients, the following laboratory investigations were carried out: complete haemogram, fasting and post-prandial venous plasma glucose, serum creatinine, total cholesterol, triglycerides (TG), high density lipoprotein (HDL) cholesterol, rheumatoid factor (RF), C-reactive protein (CRP), anti-cyclic citrullinated peptide (anti-CCP) antibody, anti-nuclear antibody (ANA), serum total thyroxin (T_4), serum total triiodothyronine (T_3), serum thyroid stimulating hormone (TSH), serum anti-thyroid peroxidase (TPO) antibody, and plain radiographs of the hands including the wrists. The low density lipoprotein (LDL) cholesterol level was calculated using the Friedwald's formula.[23]

RF and CRP were estimated in the fresh serum samples by qualitative latex agglutination method using a commercially available RA Latex Test and CRP Latex Test kits, respectively (Plasmatec Laboratory Products, Bridport, United Kingdom) as per the manufacturer's instructions. Anti-CCP antibody was estimated by qualitative enzyme linked immunosorbent assay (ELISA) technique using Anti-CCP ELISA (IgG) kit (Euroimmun AG Laboratory, Lubeck, Deutschland) as per the manufacturer's instructions. ANA was estimated by qualitative ELISA technique using AUTOSTAT™II ANA Screen kit (Hycor Biomedical Ltd., Penicuik, United Kingdom) as per the manufacturer's instructions.

Serum total T_3 and total T_4 were measured by radioimmunoassay (RIA) method by using MAG 3B and MAG 4B kits, respectively [Board of Radiation and Isotope Technology (BRIT), Mumbai, India] as per the manufacturer's instructions. TSH was measured by immunoradiometric assay (IRMA) method by using IRMAK-9 kit (BRIT, Mumbai, India) as per the manufacturer's instructions. Anti-TPO antibody was measured by RIA method using Anti-h TPO (I-125) RIA kit (Izotop, Institute of Isotopes Co. Ltd, Budapest, Hungary) as per the manufacturer's instructions. The normal physiological range, in serum (as listed in the manufacturer's brochure) were: total T_3 = 0.7-2.1 ng/mL; total T_4 = 55-135 ng/mL; TSH = 0.17-4.05 μIU/mL. Anti-TPO antibody was considered positive if its serum level was more than 100 IU/mL (as per the manufacturer's instructions) and patient was labelled as having autoimmune thyroid disease (AITD).[24] The subject was considered to be euthyroid if, levels of serum total T_3, T_4 and TSH were found to be in the normal physiological range.[24] Overt hypothyroidism was characterized by elevated TSH and low T_4 levels, overt hyperthyroidism was characterized by low TSH and elevated T_4 levels.[24] Subclinical hypothyroidism was characterized by normal T_4 and elevated TSH levels while subclinical hyperthyroidism was characterized by normal T_4 and low TSH levels.[24]

Statistical analysis

Data were recorded on a predesigned proforma and managed using Microsoft Excel 2007 (Microsoft Corp, Redmond, WA). All the entries were double checked for any possible error. Descriptive statistics for the categorical variables were performed by computing the frequencies (percentages) in each category. For the quantitative variables, approximate normality of the distribution was assessed. Variables following normal distribution were summarized by mean and standard deviation

(SD); the remaining variables were summarized as median [interquartile range (IQR)]. The association between two categorical variables was evaluated by Chi-square (χ^2) test or Fisher's exact test as appropriate. Student's 't'-test or Mann-Whitney U test, as appropriate, were used to compare continuous variables between the groups. All tests were two-tailed; a p-value <0.05 was considered as significant. Statistical analysis was carried out using IBM SPSS, Version 20, (IBM SPSS Statistics, Somers NY, USA); Systat 12, Version 12.00.08 (Systat Software, Inc, Chicago IL, USA); and MedCalc Version 11.3.0 for Windows 2000/XP/Vista/7 (MedCalc Software bvba, Belgium).

RESULTS

During the study period, 75 consecutive patients with RA were screened for inclusion in the study. Of these, 54 patients satisfying the inclusion criteria were studied; 21 were excluded from the study due to presence of overlap syndrome (n=12), and unwillingness to participate in study (n=9). The baseline demographic characteristics of patients with RA, and age- and gender-matched healthy control subjects are shown in Table 1. Majority of patients with RA were in their fifth decade of life; females (n=48) outnumbered males (n=6). None of the subjects studied (n=108) were smokers. There was no statistically significant difference in the mean body mass index (BMI) (kg/m^2) (26.36±5.58 Vs 26.04±3.58; p=0.725); prevalence of obesity (BMI ≥ 25) (χ^2=0.354; p=0.692); normal BMI (BMI=18.5-22.9), underweight (BMI <18.5) and overweight (BMI ≥ 23) (χ^2=1.377; p=0.523) between the study group and healthy control subjects.

The median (IQR) symptom duration among patients with RA was 62.5 (IQR 28-158) weeks. The mean DAS28 at presentation in patients with RA was 5.6±1.0. Majority of patients with RA (n=39; 72.2%) had severe disease (DAS28 >5.1); followed by moderate severity (n=14; 26%). Only one patient was in remission. Seventeen of the 54 patients with RA (31.5%) were treatment naive and were receiving symptomatic treatment with non-steroidal antiinflammatory drugs (NSAIDS); the remaining 37 (68.5%) patients were receiving a combination of disease modifying antirheumatic drugs (DMARDs). Seventeen of the 54 (31.5%) patients with RA had other co-morbid conditions for which they were receiving treatment. These included hypertension (n=13; 24.1%); and type 2 diabetes mellitus (n=7; 13%). None of the patients with RA were receiving treatment with statins/lipid lowering agents.

The median (IQR) ESR (mm at the end of the first hour) was significantly higher in patients with RA compared with healthy control subjects [33.0 (IQR 17.5-60.0) Vs 23.0 (IQR 10.0-45.2); p=0.035]. High CRP levels were observed in 26 (48.1%) patients with RA. RF and anti-CCP antibody positivity was evident in 26 (48.1%) and 24 (44.4%) patients with RA, respectively.

Table 1: Baseline demographic characteristics of patients with RA and healthy control subjects

Variable	Patients with RA (n=54)	Healthy control subjects (n=54)	p-value
Age (years)	46.0±10.4	45.4±10.3	0.739
Male:Female	6:48	6:48	1.000
Waist-hip ratio	0.86±0.05	0.86±0.06	0.430
BMI (kg/m^2)	26.36±5.58	26.04±3.58	0.725

RA = rheumatoid arthritis; BMI = body mass index

Dyslipidaemia defined as per the NCEP-ATP III criteria[16] was evident in 70.4% patients with RA. The profile of dyslipidaemia in patients with RA and healthy control subjects is shown in Table 2. Low serum HDL levels were the most common abnormality among both groups. The proportion of patients with a high serum cholesterol, high serum TG, high serum LDL and low serum HDL were comparable between the two groups.

At the time of initial presentation, 9 (16.7%) patients were already receiving treatment for hypothyroidism. Comparison of serum thyroid profile among patients with RA and healthy control subjects is shown in Table 3. There was no statistically significant difference in the median serum total T_4 and serum TSH and mean serum total T_3 levels between the two groups. The prevalence of thyroid disorders in patients with RA and healthy control subjects

Table 2: Profile of dyslipidaemia in patients with RA and healthy control subjects

Variable	Cut-off value (mg/dL) as per NCEP-ATP III guidelines[16]	Patients with RA(n=54) No. (%)	Healthy control subjects (n=54) No. (%)	χ^2	p-value
High serum total cholesterol	≥240	1 (1.8)	5 (9.2)	2.824	0.205
High serum triglycerides	≥200	5 (9.2)	9 (16.7)	1.313	0.391
High serum LDL*	≥160	3 (5.7)	5 (9.4)	0.541	0.716
Low serum HDL	<40	37 (68.5)	40 (74.1)	0.407	0.671

* 53 patients with RA and 53 healthy control subjects were considered for analysis as one patient with RA and one healthy control subject were having serum TG levels of more than 400 mg/dL and therefore, LDL levels in these subjects could not be calculated applying Friedwald's formula.[23]

RA = rheumatoid arthritis; LDL = low density lipoproteins; HDL = high density lipoproteins; NCEP-ATP III = National Cholesterol Education Programme Adult treatment Panel III

Table 3: Comparison of thyroid profile among patients with RA and healthy control subjects

Variable	Patients with RA(n=54)	Healthy control subjects (n=54)	p-value
Serum total T_3 (ng/mL)*	1.1 (0.9-1.3)	1.1 (0.9-1.2)	0.821
Serum total T_4 (ng/mL)†	86.0±24.0	84.0±23.8	0.670
Serum TSH (microIU/mL)*	2.5 (1.8-3.8)	2.5 (1.8-3.6)	0.851

* expressed as median (IQR)

† expressed as mean±SD

RA = rheumatoid arthritis; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid stimulating hormone; IQR = interquartile range; SD = standard deviation

Table 4: Comparison of prevalence of thyroid disorders in patients with RA and healthy control subjects

Variable	Patients with RA (n=54) No. (%)	Healthy control subjects (n=54) No. (%)	χ^2	p-value
Overall thyroid disorders	19 (35.2)	12 (22.2)	2.217	0.201
Overt hypothyroidism	9 (16.7)	4 (7.4)	2.186	0.236
Subclinical hypothyroidism	9 (16.7)	8 (14.8)	0.070	1.000
Subclinical hyperthyroidism	1 (1.8)	0	1.009	1.000
Autoimmune thyroid disease	12 (22.2)	4 (7.4)	4.696	0.055

RA = rheumatoid arthritis

is shown in Table 4. More patients with RA had associated AITD compared with healthy control subjects; however, this difference did not reach statistical significance. No statistically significant difference was observed in the prevalence of other thyroid disorders between the two groups. However, there was statistically significant higher prevalence of AITD in patients with RA than in healthy control subjects (10/45 Vs 4/54; χ^2=4.437, p=0.045), after excluding the patients with RA (n=9), who were known to have hypothyroidism and were receiving treatment with levothyroxine. Also, there was statistically significant higher prevalence of subclinical hypothyroidism with anti-TPO antibody positivity in patients with RA than in healthy control subjects (4/45 Vs 0/54; χ^2=5.002, p=0.040), after excluding the patients with RA (n=9), who were known to have hypothyroidism.

Comparison of MetS and its components among patients with RA and healthy control subjects is shown in Table 5. There was no statistically significant difference in the prevalence of MetS and its components between the two groups.

DISCUSSION

RA is a systemic disease with many extra-articular manifestations. Furthermore, several well-recognized associations between RA and other medical conditions are being increasingly recognized. Some of these include, thyroid disorders and MetS. Evaluation of patients with RA for thyroid disorders, especially hypothyroidism; and MetS is clinically important. This is because, not only are patients with RA significantly more prone to develop atherosclerotic CVD, but also due to the fact that this risk is likely to be further amplified if associated hypothyroidism and MetS are also co-existent.

Majority of the patients with RA in the present study conducted at Tirupati were in their fifth decade of life; women were more frequently affected than men. These findings are similar to the observations reported in other published epidemiological studies.[25,26] In the present study, none of the patients with RA and none of the healthy control subjects were smokers. Tobacco smoking enhances the risk of development of MetS[27] and is associated with thyroid dysfunction.[28]

Table 5: Comparison of prevalence of metabolic syndrome and its components among patients with rheumatoid arthritis and healthy control subjects

Variable	NCEP-ATP III criteria[16,17]			IDF criteria[19]		
	Patients with RA (n=54)	Healthy control subjects (n=54)	p-value	Patients with RA (n=54)	Healthy control subjects (n=54)	p-value
Metabolic syndrome	31	25	0.336	29	23	0.336
High waist circumference*	41	42	1.000	41	42	1.000
Elevated serum triglyceride	14	15	1.000	14	15	1.000
Low serum HDL cholesterol	52	53	1.000	52	53	1.000
High blood pressure	14	7	0.144	14	7	0.144
High fasting plasma glucose†	15	12	0.657	15	12	0.657

* waist circumference appropriate for south Asians was considered i.e., male: ≥90 cm, female: ≥80 cm.[18,19]

† high fasting plasma glucose was defined as ≥100 mg/dL.[17]

NCEP-ATP III = National Cholesterol Education Programme Adult Treatment Panel III; IDF = International Diabetes Federation;

RA = rheumatoid arthritis; HDL = high-density lipoprotein

The prevalence of dyslipidaemia among patients with RA in the present study (70.4%) was higher than the figure (33%) reported in another study from India.[29] Other studies[29,30] have shown a higher prevalence of asymptomatic atherosclerosis in patients with RA as compared to healthy control subjects based on measurement of carotid intima media thickness (CIMT), even when prevalence of dyslipidaemias were similar in both study and control subjects.

Relationship between RA and the thyroid disorders has been investigated with conflicting results. While some studies[3,8-11] reported a higher prevalence of thyroid disorders in patients with RA, others[12,13] did not document any such association. In the present study, though the prevalence of thyroid disorders was higher in patients with RA than in healthy control subjects, but this difference did not reach statistical significance (Table 4). In the present study, the prevalence of AITD was higher in patients with RA than in healthy control subjects, but this difference also, did not reach statistical significance. However, on analyzing the data after excluding patients already known to have hypothyroidism at initial presentation and were receiving levothyroxine treatment for the same, a statistically significant higher prevalence of AITD (p=0.045) was observed in patients with RA (n=45) than in healthy control subjects (n=54). This could be explained by the fact that treatment for hypothyroidism with levothyroxine (n=9) is known to decrease the levels of anti-TPO antibodies in the serum.[31]

Thyroid disorders in RA patients are thought to be most often of autoimmune nature because they are accompanied by elevated thyroid autoantibody titres. Observation from the present study have been similar to other published studies[11,32] suggesting that patients with RA should be assessed and monitored for AITD so that the early detection and institution of appropriate treatment could be done. The need for screening for thyroid disorders in patients with RA has been debated with evidence from one study[33] supporting the need for screening and another study contradicting this view.[12] This needs to be further clarified in community-based studies with a larger sample size.

In present study, though the prevalence of MetS was found higher in patients with RA compared with healthy control subjects (Table 5) by both NCEP-ATP III[16,17] and IDF[19] criteria this difference did not attain statistically significance. This can be explained by the following reasons: RA patients in the present study were younger compared to the observations from other studies[6,34] which showed statistically significant higher prevalence of MetS in patients with RA. It has been observed that the prevalence of the MetS increases strongly with age.[35,36] Secondly, most (n=37, 68.5%) patients with RA were receiving treatment with DMARDs in the present study. It has been demonstrated that use of methotrexate[37] and hydroxychloroquine[38] decreases the prevalence of components of MetS in patients with RA and thus reduces the risk of development of CVD. Furthermore, as the patients in the present study were not treatment naïve, other general health measures advocated by physicians and rheumatologists, such as, regular exercise, in addition to aggressive control of inflammation, could have contributed to the reduction in the prevalence of components of MetS.

The limitations of the present study include that the present study is a hospital-based study. Observations from the present study may not reflect the scenario in the community. The sample size in the present study is small (n=54). At the time of assessment, majority of the patients with RA (68.5%) were on treatment for RA with DMARDs and corticosteroids. These drugs are known to affect the

components of MetS and their effect on thyroid gland function has not been studied in detail. Larger population based studies in the community in treatment naive patients with RA at the time of initial diagnosis are required to understand the relationship between thyroid disorders and RA in more detail.

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