Frequency of thyroid dysfunction among rheumatoid arthritis patients at the Kenyatta National Hospital, Nairobi, Kenya

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Abstract

Background: Rheumatoid Arthritis (RA) affects 0.5-1% of the adult population. A higher prevalence of thyroid dysfunction is observed in patients with RA compared to the general population.

Objectives: To establish the frequency of thyroid dysfunction among ambulatory RA patients and to describe the association between thyroid dysfunction and the patients' socio-demographic characteristics, clinical characteristics, level of disease activity, and their functional status.

Design: This was a cross-sectional descriptive study.

Methods: Adult patients on follow up for RA at the outpatient clinic were sampled. Sociodemographic data was recorded. The Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ) scores were computed from examination findings and questionnaires respectively. A venous blood sample was analyzed for Thyroid-Stimulating Hormone (TSH), free triidothyronine (fT3), and free tetraiodothyronine (fT4). This data was analyzed to determine frequencies and associations.

Results: Seventy-six patients were recruited into the study. Sixty-one participants were female. The mean TSH level was 5.8Miu/L. The frequency of thyroid dysfunction was 47.4%. Overt hypothyroidism was the most common form of thyroid dysfunction at 39.5% while 6.6% had Sick Euthyroid. Majority of the participants, 75%, had low disease activity, mean CDAI was 11.6. Forty-one (53.9%) participants had no disability, mean HAQ was 0.5. Correlations between thyroid dysfunction and advancing age, duration of disease, level of disease activity, and functional disability did not attain statistical significance.

Conclusion: Thyroid dysfunction is common among patients with RA with no significant association found between thyroid dysfunction socio-demographic characteristics, clinical characteristics, level of disease activity, and functional status.

Key words: Thyroid dysfunction, Rheumatoid arthritis, Disease activity, Functional disability

Introduction

Rheumatoid Arthritis (RA) is a symmetric polyarthritis with a variety of systemic manifestations. In the general population thyroid dysfunction affects 1-10% of adults, with variations in geographical areas, age and sex[1]. The causes of thyroid dysfunction include; iodine deficiency, infections and autoimmune associated thyroid disease[2]. Thyroid dysfunction is more prevalent in patients with autoimmune diseases such as RA. This is attributed to overlap of autoimmune conditions that are initiated by loss of tolerance to self-antigens[3].

The burden of thyroid dysfunction among RA patients has been found to vary between 6-47% in various studies. The entire spectrum of thyroid dysfunction has been described, however, hypothyroidism occurs more frequently. Patients with thyroid dysfunction have higher RA disease activity scores and poorer functional status measured using the health assessment questionnaire[4,5].

The clinical manifestations of RA overlap significantly with the musculoskeletal manifestations of thyroid dysfunction. This overlap may mask the diagnosis of thyroid

dysfunction; patients with a diagnosis of RA who develop concurrent thyroid dysfunction may remain symptomatic despite optimal RA management, they will also have worse physical functional status[6].

Both RA and thyroid dysfunction are known risk factors for cardiovascular disease, their co-occurrence confers additional risk above that attributed to the conventional cardiovascular disease risk factors[5,6]. Identifying RA patients with thyroid dysfunction will support instituting more stringent risk factor modification in addition to the benefit of treating both conditions optimally.

This study sought to determine the frequency of thyroid dysfunction among RA patients. Additionally, we sought to describe the association between presence of thyroid dysfunction and patient's demographic characteristics, duration of RA disease, clinical disease activity scores and functional status.

Materials and methods

This was a cross sectional study conducted at the Kenyatta National Hospital outpatient rheumatology clinic. The study population comprised of male and female patients aged above 18 years who had a confirmed diagnosis of RA having met the 2010 ACR/EULAR classification criteria.

Following approval by the ethics committee of the University of Nairobi and the Kenyatta National Hospital, 76 patients were recruited to the study using consecutive sampling technique. Recruited patients provided written informed consent and had their demographic data and medical history including current management and duration of disease recorded. A general and musckuloskeletal examination was conducted and used to compute the Clinical Disease Activity Index (CDAI). The health assessment questionnaire was also administered to determine patients' functional status. ELISA was used to determine TSH, FT4 and FT3 levels.

SPSS version 21.0 Chicago Illinois was used for data entry and analysis. The frequency of thyroid dysfunction was calculated as a percentage. The various types of thyroid function abnormalities were presented as percentages. Odds ratio was used to test the association between the presence of thyroid function abnormalities and patient demographic characteristics, disease activity scores, and functional status. P-values and 95% Confidence Intervals (CIs) were calculated where applicable. P-value <0.05 was considered statistically significant.

Results

Seventy-six patients were recruited out of the 86 patients screened during the study period. The mean age was of 41 years (range 18-78 years). Fifteen participants were male (19.7%) and 61(80.5%) participants were female. The male to female ratio was 1:4. Majority of participants (84.2%) had attained post-primary education and 73.7% were married.

Fifty five point three percent of the patients had the diagnosis of RA for 5 years or less. Thirty six point eight percent of patients had RA for 6 to 10 years while 7.9% had had RA for more than 10 years.

All the study subjects were on DMARDS while 44.7% were on steroids. None of the study participants were on biological agents.

The mean CDAI score was 11.6 (IQR 4-10). Low disease activity was the most prevalent at 75%. Only 2.6% were in remission. Almost twelve percent (11.8%) of the study population had high disease activity.

HAQ score mean was 0.5 (IQR 0.0-0.8). Eighty six point three percent of patients had mild to no disability while 8 (10.5%) participants were found to have high disease activity. The demographic and

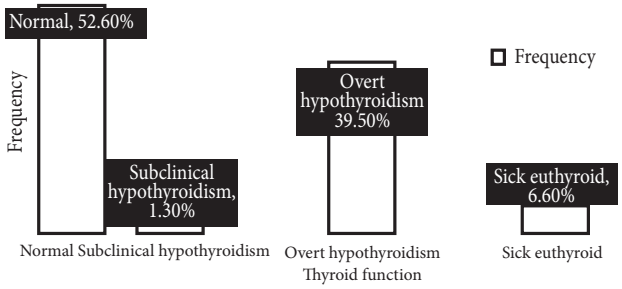
clinical characteristics of the study participants are depicted in Table 1.

Table 1: Participants sociodemographic and clinical characteristics

	Frequency N (%)
Age (years)	
≤30	7(9.2)
31-40	15(19.7)
41-50	22(28.9)
51-60	17(22.4)
>60	15(19.7)
Gender	
Male	15(19.7)
Female	61(80.3)
Education	
None	3(3.9)
Primary	9(11.8)
Secondary	44(57.9)
Tertiary	20(26.3)
Marital status	
Married	56(73.7)
Single	15(19.7)
Widowed	5(6.6)
Duration of disease	
<6	42(55.3)
6-10	28(36.8)
>10	6(7.9)
RA medication	
DMARDS	35(46.1)
DMARDS+steroids	34(44.7)
DMARDS+other	7(9.2)
Biological agents	0
CDAI	
Remission	2(3)
Low activity	57(75)
Moderate activity	8(10)
High activity	9(12)
HAQ score	
No disability	41(54)
Mild disability	25(33)
Moderate disability	2(3)
Severe disability	8(10)

The median TSH levels were 5.8 (IQR 4.1-7.5), higher than the laboratory reference range provided. The frequency of thyroid dysfunction was 47.4%. The majority of the patients 39.5% had overt hypothyroidism with only 1% having subclinical hypothyroidism. The distribution of thyroid function is depicted in Figure 1.

Figure 1: Distribution of thyroid function



Univariate analysis was done to interrogate the presence of correlations between thyroid dysfunction and various patient and disease characteristics: Age, sex, duration of disease, CDAI, and HAQ scores.

Participants that were less than 30 years old had three times the likelihood of having thyroid dysfunction compared to those above 60 years. This observation was however not significant, P-value 0.297.

Male participants had a higher likelihood of having thyroid dysfunction compared to females OR 1.3; this observation was not significant, P-value 0.6. Participants with a duration of disease >6 years were more likely to have thyroid dysfunction compared to those who had RA for less than 6 years OR 1.2 (P-value 0.6). The participants with low disease activity were less likely to have thyroid dysfunction compared to those with high disease activity OR 0.72, this observation was not significant P-value=0.72. Participants with severe disability had a marginally higher likelihood of having thyroid dysfunction compared to those with no disability; OR 1.2.

Table 2: Factors associated with thyroid dysfunction, univariate analysis

	Thyroid hormone abnormal				
	Yes	No	Total	OR (95% CI)	P-value
Age (years)					
≤30	4 (11.1)	3 (7.5)	7 (9.2)	2.67 (0.42-16.83)	0.297
31-40	6 (16.7)	9 (22.5)	15 (19.7)	1.33 (0.30-5.91)	0.705
41-50	11 (30.6)	11 (27.5)	22 (28.9)	2.00 (0.51-7.80)	0.318
51-60	10 (27.8)	7 (17.5)	17 (22.4)	2.86 (0.67-12.11)	0.154
>60	5 (13.9)	10 (25.0)	15 (19.7)		
Gender					
Male	8 (22.2)	7 (17.5)	15 (19.7)	1.35 (0.43 -4.18)	0.606
Female	28 (77.8)	33 (82.5)	61 (80.3)		
Duration of disease (years)					
<6	19 (52.8)	23 (57.5)	42 (55.3)		
6-10	14 (38.9)	14 (35)	28 (36.8)	1.21 (0.46 -3.16)	0.696
>10	3 (8.3)	3 (7.5)	6 (7.9)	1.21 (0.22 -6.7)	0.827
Drugs					
DMARDS	14 (38.9)	21 (52.5)	35 (46.1)	0.27 (0.05 -1.57)	0.144
DMARDS + steroids	17 (47.2)	17 (42.5)	34 (44.7)	0.40 (0.07 -2.35)	0.311
DMARDS + other	5 (13.9)	2 (5)	7 (9.2)		
CDAI					
0.0-2.8 (Remission)	0 (0.0)	2 (5.0)	2 (2.6)	-	
2.9-10.0 (Low activity)	27 (75.0)	30 (75.0)	57 (75.0)	0.72 (0.18-2.96)	0.720
10.1-22.0 (Moderate activity)	4 (11.1)	4 (10.0)	8 (10.5)	0.80 (0.12-5.40)	0.800
22.1-76.0 (High activity)	5 (13.9)	4 (10.0)	9 (11.8)		
HAQ					
0 (No disability)	18 (50.0)	23 (57.5)	41 (53.9)		
<0.3 (Mild)	13 (36.1)	12 (30.0)	25 (32.9)	1.38 (0.51-3.76)	0.523
0.3-1.8 (Moderate)	1 (2.8)	1 (2.5)	2 (2.6)	1.28 (0.07-21.86)	0.866
>1.8 (Severe)	4 (11.1)	4 (10.0)	8 (10.5)	1.28 (0.28-5.82)	0.751

Discussion

The association between RA and thyroid dysfunction has been envisaged for a long time and several studies have been done to quantify the co-occurrence. This is the first study in Kenya describing the frequency of thyroid dysfunction among RA patients.

This study investigated 76 RA patients who were attending the outpatient Rheumatology clinic at the KNH. The frequency of thyroid dysfunction was 47.4%. The predominant pattern of thyroid dysfunction was overt hypothyroidism at 39.5%, while one (1.3%) participant had subclinical hypothyroidism.

A wide range of thyroid abnormalities has been observed in various studies around the world. Our prevalence was higher than most studies reviewed. The differences in prevalence across various populations has been attributed to: Differences in assay techniques, presence of other goitrogens that alter thyroid function and the influence of medications such as steroids. Persistent inflammation characterized by high disease activity also causes thyroid dysfunction[7-9].

Nadeem *et al*[5] in India found that 42% of the patients studied had thyroid dysfunction. Unlike our observation, 37.9% of participants in Nadeem's study had subclinical hypothyroidism and only 3.6% had overt hypothyroidism.

In another study in India by Joshi *et al*[10] looking at the prevalence of hypothyroidism in RA demonstrated a prevalence of 38.4% which is similar to the prevalence of overt hypothyroidism in our study.

A study done in China by Li *et al*[11] in 2019 observed a prevalence of 32.3% thyroid dysfunction of which there was a predominance of overt hypothyroidism at 26.2%. In a Danish population of newly diagnosed RA patients, one study demonstrated a high rate of overt hypothyroidism among the proportion of participants who had thyroid dysfunction. The prevalence of overt hypothyroidism was 30.4%, 26% of the population had subclinical hyperthyroidism or hypothyroidism[12]. These studies had lower prevalence demonstrated than our study but were similar in that the majority of cases had overt hypothyroidism. SCH has been shown advance to overt hypothyroidism at an estimated rate of 1-4% per year[13].

The lack of standard reference ranges for interpretation of thyroid function results provides a possible explanation for the variations in prevalence reported. Different studies used different assay and laboratory specific reference ranges. ELISA and chemiluminescence are second and third generation thyroid hormone assays respectively. At the lower ranges of TSH for the detection of hyperthyroidism, chemiluminescence has been shown to have higher precision than ELISA. At the upper ranges of euthyroidism, these two immunoassays have comparable precision. In one study comparing the sensitivity of ELISA and chemiluminescence in the estimation of TSH, in patients with hypothyroidism, ELISA had a sensitivity of 96% compared to 100% for chemiluminescence. The sensitivity of ELISA makes it suitable for the detection of thyroid hormone abnormalities at baseline. In our study, we employed the ELISA technique which is appropriate for initial assessment of thyroid disorders[7,14].

Joshi and colleagues[10] in India while utilizing the ELISA method of thyroid hormone assay observed a high prevalence of 38% hypothyroidism. This is similar to the prevalence of overt hypothyroidism we demonstrated at 39.5%.

Mousa and colleagues[15] in a study on thyroid dysfunction in RA patients in Egypt utilized the ELISA method of thyroid hormone assay and observed a low prevalence of 8.3%. In another study in Jordan, thyroid dysfunction in a population of RA patients was determined by utilizing the ELISA method and a prevalence of 14.3% was observed[16]. These findings were low compared to the prevalence we observed despite utilizing the same assay technique.

Among the studies that utilized the chemiluminescence method of thyroid hormone assay, they also observed a wide variation in the prevalence of thyroid dysfunction. Nadeem and colleagues[5] demonstrated a high prevalence of thyroid dysfunction at 47% which was comparable to what we observed. In Italy a study by Atzeni and colleagues[17] utilizing this assay technique for thyroid hormones, observed a low prevalence of thyroid dysfunction at 7.1%. These varied results demonstrated even with similar assay techniques utilized suggest caution should be used in drawing comparisons.

While the local rate co-occurrence of thyroid dysfunction in the RA patient population and at the community level in Kenya is not known, comparisons can be made to prevalence in select population groups. Ngugi[18] in a study on patients with type 2 diabetes at the KNH, determined the presence of thyroid dysfunction by utilizing ELISA

assay thyroid hormones. This study described a prevalence of 60% which was higher than what we observed in our study. These findings may indicate that thyroid dysfunction is prevalent in the general population and hence more pronounced in these patient groups with other factors contributing to dysfunction. The high prevalence observed in both studies is expected because, in addition to being in the same geographical location and having exposure to common possible goitrogens, some of the pathogenetic mechanisms underlying the development of thyroid dysfunction in these patient populations such as chronic inflammation are similar[8]. Forty four point seven percent of our study participants were found to be on steroids at various doses. Glucocorticoids suppress thyroid hormone production leading to low FT4 and high TSH[9]. This may explain the high prevalence of thyroid dysfunction which we observed to be predominantly hypothyroidism.

Thyroid dysfunction, especially hypothyroidism has been found to occur in chronic inflammation. Cytokines elaborated during inflammation such as IL1 and IL6 suppress the hypothalamic-pituitary and thyroid axis. TSH action on the thyroid gland and peripheral conversion of T3 to T4 is inhibited directly by IL1 and to a lesser degree IL6. These cytokines are targets for biological agents in RA disease control which results in improvement in thyroid function[19]. Thyroid dysfunction as a disease of chronic inflammation was also evident in conditions that involve chronic sustained inflammation. Inflammation can impair thyroid tissue and cause thyroiditis directly and it can also promote hyperplasia of thyroid cells causing thyroid nodules. Thyroid nodules coexists with the elevated TSH[20].

Iron, selenium, and iodine deficiency are also known goitrogens that are prevalent in our region and may explain the high prevalence observed.

Thyroid hormone synthesis is influenced by iron deficiency which has been shown to reduce the activity of the heme-dependent thyroid hormones especially thyroid peroxidase. This has been noted to blunt the effects of iodine supplementation in areas of low iodine[21]. The prevalence of iron deficiency in the national nutritional survey of 2011 in Kenya which included 2851 participants was 18.4%. In this survey, the prevalence of iodine deficiency ranged from 19.1% among adult males to 30% among non-pregnant women. Salt is the main mode of supplementing iodine in Kenya it was hence significant to note that 48% of salt samples tested during this survey had lower than the recommended levels of iodine[22]. In an Indian study that included 50 newly diagnosed hypothyroid patients and 50 appropriate controls, Dahiya *et al*[23] observed that levels of ferritin and serum iron were low in those who were hypothyroid relative to the controls, P-value less than 0.005.

High concentrations of selenium are found in the thyroid gland where seleno-proteins are incorporated into iodinases in thyroid hormone synthesis. Selenium levels are dependent on diet and geographical areas. One study identified the risk of the inadequacy of dietary selenium at 22% across Africa[24]. In Istanbul a 9-month selenium supplementation study in patients with AITD on therapy with thyroxine was conducted, after the follow up period it was observed that there was the suppression of levels of TPOab by 26.2% to 30% P-value=<0.001[25]. This indicates an association between selenium deficiency and thyroid function.

Our study did not demonstrate a significant relationship between advancing age and having RA for a longer duration with occurrence of thyroid dysfunction. Presence of high disease activity and increasing functional limitation did not correlate significantly with occurrence of thyroid dysfunction.

Previous studies have however made some associations. In one case-control study in Canada that recruited 119 RA patients and 108 appropriate controls, age and thyroid disease were not significantly correlated. There was a significant correlation between thyroid dysfunction and duration of disease, P value=0.03[4]. Similarly, in India, a prospective study of 52 RA patients found no statistically significant relationship between advancing age and occurrence of thyroid function, P-value=0.99 but there was a correlation with duration of disease, P-value=0.33[10]. This study in India demonstrated an association between TSH levels and severity of RA, P-value=0.003. In contrast, another prospective study involving 385 RA patients in India did not find a correlation between thyroid dysfunction and severity of RA. For those who had SCH the P-value was 0.075 and among those with overt hypothyroidism P-value was 0.28[5].

A case-control study in Egypt involving 200 participants found that high TSH levels were associated with higher Modified Health Assessment

Questionnaire scores, P-value= 0.01. Similarly, high TSH was associated with high disease severity estimated using MDAS, P value=0.02[17].

The varied results on associations between thyroid dysfunction and patient demographics, disease severity, and functional disability, delineate the need for more investigation to further explore these associations.

Study limitations

(i) This study provides data on a one-time estimate of thyroid function whereas changes in thyroid hormone levels occur from time to time. However, this study provides a baseline assessment that will inform decisions on the need for screening of RA patients for thyroid dysfunction and further follow up schedule for those with established thyroid dysfunction.

(ii) There is no population data on the prevalence of thyroid dysfunction from which comparisons with the prevalence in our population could be drawn**.**

Conclusion

Thyroid dysfunction is prevalent among RA patients. No significant associations were found between thyroid dysfunction and advancing age, having RA for a longer duration, increasing severity of disease, and functional disability.

Recommendations

All patients with rheumatoid arthritis should be screened for thyroid dysfunction.

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