

## DISCUSSION

Autoimmune thyroid disease (AITD) is a term used to bring together a group of pathologies that has thyroid dysfunction and an autoimmune response against this endocrine organ as its hallmark<sup>(241,242)</sup>. However, being a group of autoimmune diseases (ADs) clustered together, the clinical presentation varies among these diseases; it can be divided into those that cause hypothyroidism, hyperthyroidism, or both.<sup>(243)</sup>

AITD includes various clinical forms of autoimmune thyroiditis such as Graves' disease (GD), Hashimoto's thyroiditis, being the two commonest types and other less common types such as: atrophic autoimmune hypothyroidism, postpartum thyroiditis (PPT) and thyroid associated orbitopathy (TAO), 2 other rare types of AITDs include silent thyroiditis and iatrogenic thyroiditis.<sup>(2)</sup>

Rheumatoid arthritis (RA) is an autoimmune disease with chronic inflammation characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality.<sup>(85-89,94,95)</sup>

Given the presence of autoantibodies, such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide [anti-CCP]), which can precede the clinical manifestation of RA by many years; RA is considered an autoimmune disease.<sup>(90-93)</sup>

The relationship between RA and the thyroid gland has been studied extensively, with several studies demonstrating the autoimmune nature of thyroid dysfunctions in RA, however the exact pathogenic mechanism is still unclear.<sup>(244,245)</sup>

The aim of our work was to study the presence of thyroid dysfunction (hyperthyroidism or hypothyroidism) in seropositive versus seronegative rheumatoid arthritis patients. Also to study the presence of autoimmune thyroid markers namely anti-TPO, anti-TG and particularly TRAbs in seropositive versus seronegative RA patients and their relation to overt thyroid dysfunction and rheumatoid arthritis auto antibodies namely anti-CCP & RF.

The study was carried out on 70 patients with rheumatoid arthritis who were attending rheumatology outpatient clinic and inpatient in Alexandria Main University Hospital.

They were divided according to the results of their serological tests (RF and anti-CCP) into 2 groups:

**Group I:**Included 35 patients with seropositive rheumatoid arthritis(positive to one or both seromarkers), **GroupII:** Included 35 patients with seronegative rheumatoid arthritis(negative to both seromarkers) and a third group (**Group III**):Including 20 healthy age matched individuals who are not suffering of any rheumatologic disorder were included as a control group.

Our study showed that the age of group I (seropositive RA) ranged from 23 to 73 years with a mean of 46.23±11.90. While the age of group II (seronegative) ranged from 20 to 70 years with a mean of 44.97±13.01 and the age of group III ranged from 23 to 69

years with a mean of  $46.20 \pm 15.88$  with no significant difference between patients with RA and controls in agreement with the designed protocol of our study.

It was found that about 89 % of our patients in group I (seropositive RA) were females versus 11% males, while it was found that around 94 % were females versus 6% males in group II (seronegative RA).

Our results were consistent with other studies which showed female predominance in the course of RA as those done by Kvien TK et al in 2006<sup>(246)</sup> and Inmaculada del Rinco'n et al in 2002.<sup>(247)</sup>

The mean duration of illness (RA duration) was found to be significantly different according to the sero-status of the patient as it was found in our study to be significantly higher in group I (seropositive RA) than group II (seronegative RA).

Disease activity score (DAS 28) as an indicator of disease activity in RA was assessed in our study and it was found that around 63 % of group I (seropositive) had severe disease activity versus around 46% in group II (seronegative). While 31% had moderate activity in group I versus 46% in group II and 6% had mild activity in group I versus 9% in group II.

Clinical features of thyroid dysfunction either hypothyroidism or hyperthyroidism were thoroughly assessed in our study. 63% of patients in group I (seropositive) versus 66% in group II (seronegative) were clinically euthyroid. While 23 % in group I versus 26% in group II had suggestive symptoms of hypothyroidism and features of hyperthyroidism were consistent in 14 % of patients in group I versus 9% of patients in group II.

In our study, in group I (seropositive RA) 100% of those with mild activity were clinically euthyroid. The majority of patients having moderate DAS score were clinically euthyroid (64%) versus 27% hyperthyroid and 9% hypothyroid, while in those patients with severe DAS score 59% were clinically euthyroid, 31% were hypothyroid and 9% were hyperthyroid. On the other hand in group II (seronegative) those having mild DAS score, clinical picture of thyroid dysfunction was equally divided (33%) between euthyroidism, hypothyroidism and hyperthyroidism. In moderately active patients 69% were clinically euthyroid, 25% were hypothyroid and 6% were clinically hyperthyroid while in severely active seronegative RA patients 69% were clinically euthyroid, 25% were hypothyroid and 6% were clinically hyperthyroid. According to our results no statistical significant correlation was found between disease activity assessed by DAS score and clinical picture of thyroid dysfunction in our RA patients whether seropositive or seronegative.

Similar results were declared by Jorge CR et al in 2012 who conducted his study on 800 colombian RA patients and found that there was no relation between disease activity assessed by DAS score and the clinical presentation of AITD<sup>(248)</sup>. This was also supported by Charles et al who found the same results<sup>(249)</sup>. However, Cojocar-Gofita et al found that women with RA and clinical hypothyroidism had a higher DAS28 score compared to RA women without clinical hypothyroidism.<sup>(250)</sup>

Laboratory inflammatory markers namely ESR and C-reactive protein (CRP) reflecting disease activity in patients with RA were shown to be significantly higher in

## Discussion

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patients with RA as compared to control group. In group I ESR and CRP ranged from 13 to 143 with a mean of  $46.11 \pm 30.79$  and 4 to 126 mg/L with a mean of  $23.86 \pm 26.31$  respectively. While in group II ESR and CRP ranged from 15 to 100 with a mean of  $45.11 \pm 30.21$  and 1.02 to 176 mg/L with a mean of  $26.46 \pm 41.6$  respectively. In group III ESR and CRP ranged from 7 to 36 with a mean of  $21.15 \pm 9.67$  and 3 to 11 mg/L with a mean of  $5.19 \pm 2.08$  respectively with no significant difference in terms of ESR and CRP according to the serostatus of our patients.

Our study is consistent with the study mentioned by Yildirim K et al in 2004<sup>(251)</sup>, Wolfe and Michaud et al where ESR was found to be higher in RA patients versus controls.<sup>(252)</sup>

RF has been widely used as a screening test for patients with arthritis. Moreover it constitutes one of the classification criteria proposed by the American College of Rheumatology (ACR).<sup>(253,254)</sup> Relative to rheumatoid factor, more recently anti-CCP has been described for RA. About 35–40% of the RF-negative patients are anti-CCP antibody-positive.<sup>(255)</sup>

Anti-CCP antibodies are now well suited as a frontline diagnostic test for RA and especially early RA. It should be mentioned that patients can be classified according to their RF and anti-CCP antibodies (ACPA) assay into seropositive (positive to one or both of them) and seronegative (negative to both) and hence anti-CCP antibodies in RF negative patients can be helpful in confirming the diagnosis of RA.

In our study it was found that RF in group I ranged from 8 to 724 IU/ml with a mean of  $112.49 \pm 181.77$  and in group II it ranged from 2.7 to 14.6 IU/ml with a mean of  $8.29 \pm 3.49$  while in group III it ranged from 3 to 16 IU/ml with a mean of  $6.24 \pm 3.3$ . As regards anti-CCP it was found that in group I it ranged from 13.5 to 531 U/ml with a mean of  $128.47 \pm 149.74$  and in group II it ranged from 0.7 to 22 U/ml with a mean of  $9.27 \pm 6.08$  while in group III it ranged from 0.6 to 18 U/ml with a mean of  $7.12 \pm 4.99$ .

A significant statistical difference was observed among the studied groups regarding RF where it was higher in group I than group II and III, and it was higher in group II than group III. While as regards to Anti-CCP a significant statistical difference was observed between the studied groups where it was higher in group I compared to group II and III.

In group I 86% of patients were positive for RF versus no one in group II and only 5% in group III with a significant statistical difference among the studied groups ( $p < 0.001$ ). While as regards Anti-CCP 86% of patients in group I were positive and no one in group II or the control group had positive anti-CCP with statistical significant difference ( $p < 0.001$ ).

Recent study by Bienes F et al in 2014 compared the diagnostic value of anti-CCP and RF in patients with RA and revealed that combination of anti-CCP and RF tests rather anti-CCP or RF alone get the best results in the diagnosis of RA.<sup>(256)</sup>

On interpreting thyroid function tests of patients and controls in our study it was found that about 29 % of patients in group I (seropositive RA) showed hypothyroidism while 3 % were hyperthyroid and the majority of patients in this group were euthyroid. Similarly 29 % were hypothyroid in group II (seronegative RA), 9 % were hyperthyroid

and around 63 % were euthyroid . In group III (control) 15 % were hypothyroid and 85 % were euthyroid.

It is clearly demonstrated in our study that there is higher incidence of thyroid dysfunction (mainly hypothyroidism) in patients with RA whether seropositive or seronegative as compared to controls, and this is consistent with many studies as the one elicited by Sherif et al in 2004 where it was reported the higher incidence of thyroid dysfunction in patients with rheumatoid arthritis and also in their families versus normal individuals. <sup>(257)</sup>

Another study by Shiroki JB et al conducted on 91 RA patients evaluated for the presence of thyroid dysfunction and he found that 30% of patients had evidence of thyroid disorders compared to 11 % of controls and he concluded that thyroid dysfunction namely hypothyroidism is three fold higher in patients with RA versus controls <sup>(245)</sup>. However a study done by Silman et al in 2008 demonstrated no significant difference in the incidence of AITDs in RA patients as compared to controls and he concluded that there is no need to screen routinely for the presence of thyroid dysfunction in patients with RA, this finding is most probably due to the fact that the study was conducted on young aged patients. <sup>(258)</sup>

In our study hypothyroidism was more prevalent than hyperthyroidism in patients with RA (both group I and group II) where 29% of both groups were hypothyroid versus 3% in group I and 9 % in group II who were hyperthyroid.

A strong evidence of higher incidence of hypothyroidism as compared to hyperthyroidism in patients with RA was found in many reviews and studies where in China 2003, Porkodi R et al studied the prevalence of thyroid dysfunction on 800 patient with RA and his study showed 73 % incidence of hypothyroidism versus 5 % of his studied patients were hyperthyroid, this high incidence is mostly attributed to patient selection where those with thyromegaly or evidence of thyroid dysfunction were included in the study. <sup>(259)</sup>

It was found that there is no statistical significant difference among the studied groups as regards mean serum TSH, T3 and T4. However, Singh et al in 2002 found a significant statistical higher mean serum T4 in patients with RA as compared to controls and he correlated this increased incidence to the duration of illness of RA. <sup>(260)</sup>

Moreover in the study conducted by Welby et al in 2001, mean serum TSH was within normal range in all the studied RA patients while there was significant decrease in serum T3 and T4 in patients versus controls, and most probably this finding was attributed to the fact that they studied the incidence of thyroid dysfunction in patients with recent onset RA. <sup>(261)</sup>

It was observed in our study that there was no correlation between disease activity assessed by DAS score and mean serum TSH level, however Enas AE et al in 2014 studied the relationship between thyroid functions in patients with RA and its relation to RA activity assessed by DAS score and she found that there is a positive correlation between DAS score and mean serum TSH. <sup>(262)</sup>

Autoimmune destruction of the thyroid gland by an immune response both humoral and cell mediated results in thyroid gland damage and hence the appearance of thyroid

autoantibodies namely thyroglobulin and thyroid peroxidase antibodies which are considered to be markers of autoimmunity in autoimmune thyroid diseases.

Our results demonstrated that in patients with rheumatoid arthritis ( group I and group II) there were higher mean levels of autoimmune thyroid markers namely anti-TPO and anti-TG antibodies as compared to controls suggesting increased incidence of autoimmune thyroid diseases (AITDs). Moreover, in our study there was a statistical significant difference in the mean level of anti-TPO and anti-TG antibodies according to the serostatus of RA patients (higher levels in seropositive versus seronegative patients).

Consistent with our results Raterman H et al 2009 who concluded his results from the CARRE' study conducted on 353 patients with RA and he and his group found a higher levels of TPO antibodies in patients with RA when compared to controls. Furthermore he found in his study that TSH is relatively high in TPO positive RA patients than TPO negative ones.<sup>(263)</sup>, however in our study no significant difference was found in mean serum TSH in anti-TPO positive versus anti-TPO negative patients. Similar results were reported in Norway and Canada.<sup>(245,264)</sup>

In our study it was found that in group I 100 % were positive for anti-TPO and anti-TG while in group II 100 % were positive for anti-TPO, as regards anti-TG 82.9% were positive, 8.6% were equivocal and 8.6% were negative, and in group III 95% were negative for anti-TPO and 5% were equivocal, as regards anti-TG, 85% were negative, 10% equivocal and 5% positive. Similar results were found by Porkodi R et al where anti-TPO antibodies were positive in 88% and anti-TG in 56 % of RA patients.<sup>(259)</sup>

Innocencio et al, have reported positivity for anti-TG and anti-TPO of 32% and 4%, respectively<sup>(265)</sup>. This was also emphasized by B.askan et al who found positive anti-TPO and anti-TG in 2.6% and 5.1% respectively in 92 RA patients in Turkey.<sup>(266)</sup>

In 2013 Koszarny A et al, measured the level of antithyrotropin receptor antibodies (TRAbs), where he found that TSH receptor antibodies were not detected in any of the RA patients<sup>(267)</sup>. We detected the level of TSH receptor antibodies in a small proportion of our RA patients (4 patients positive and 6 patients equivocal) where we found that in group I (seropositive RA) the majority were negative to TRAbs ( 91.4%) , 2.9% were equivocal and 5.7% were positive while in group II (seronegative RA) 80 % were negative ,14.3% were equivocal and 5.7% were positive to TRAbs.

In the same study there was found a significant positive correlation between DAS score and the level of thyroid antibodies (anti-TPO and anti-TG) where the more severe form of disease activity is associated with higher antibodies level. However in our study no statistical significant correlation was found between disease activity and thyroid autoantibodies level.

Andonopoulos AD et al studied thyroid functions and immune profile in patients with rheumatoid arthritis where he measured thyroid functions, antibodies to thyroid peroxidase (anti-TPO) and TRAbs. He found a high level of anti-TPO in patients with RA whereas no one had high TRAbs level. Moreover he concluded that there was no detectable association between thyroid abnormalities and any serological RA findings in his study.<sup>(268)</sup>

On contrary to our study in 2001. Koga Y et al, studied thyroid autoimmune disorders in patients with juvenile idiopathic arthritis where he measured the levels of anti-TPO, anti-TG and thyroid receptor antibodies both blocking and stimulatory ones and he concluded from his study high levels of both TSH receptor stimulatory and blocking antibodies in patients with RA with higher incidence of positivity to TSH receptor stimulatory than the blocking ones.<sup>(269)</sup>

It was shown in our study a higher mean levels of anti-TPO, anti-TG and TRAbs in patients with RA regardless their Serostatus when compared to controls. Moreover a higher levels of anti-TPO, anti-TG and TRAbs were detected in patients with seropositive RA (group I) versus seronegative RA patients (group II) suggesting a higher incidence of autoimmune process in seropositive versus seronegative patients.

Regardless the clinical picture suggestive of thyroid dysfunction i.e. patients having suggestive manifestations of hyperthyroidism or hypothyroidism or no suggestive manifestations of thyroid dysfunction (euthyroid), the sera of patients with RA in our study were 100% positive for anti-TPO antibodies while as regards to anti-TG, it was observed that in group I (seropositive) 100% were positive whatever their clinical presentation and in group II (seronegative) 83% of the clinically euthyroid patients were positive and 84% of those with clinically overt thyroid dysfunction (hyperthyroidism or hypothyroidism) were positive and as regards TRAbs 9% of the clinically euthyroid seropositive patients were positive for TRAbs and only 16% of those seronegative patients clinically presented with thyroid dysfunction were positive for TRAbs.

It was concluded from our study that RA duration didn't influence the titer of thyroid autoantibodies and in agreement with our results, Yavasoglu I et al, in 2008 illustrated no significant correlation between duration of illness of RA and thyroid autoantibodies titer.<sup>(270)</sup>

In a trial to link the two autoimmune diseases together, we observed a significant positive correlation between anti-TPO, TRAbs and RF titer, while we failed to observe any statistical significant positive correlation between anti-TG levels and RF.

In agreement with our results, Raterman HG et al in 2008 concluded from his study conducted on 353 patients with RA that a higher percentage of anti-TPO positive patients was among those with high RF titer with a significant positive correlation between the two autoantibodies.<sup>(271)</sup>

On contrary, in the study held by Yavasoglu I et al, it was suggested that antithyroid autoantibodies are independent from Rheumatoid factor (RF) titer.<sup>(270)</sup>

Moreover the prognostic autoantibody in RA namely anti-CCP was also found to be significantly correlated with anti-TPO and TRAbs level in patients with RA. This finding goes with the previously discussed common autoimmune process involving both diseases, however no statistical significant correlation was found between anti-TG and anti-CCP antibodies. In 2011 Charles P.J. et al didn't find a relationship between the presence of thyroid autoantibodies and anti-CCP positivity.<sup>(249,263)</sup>

Evidence of thyroiditis by thyroid ultrasonography in our study, was illustrated in 34% of patients in group I (seropositive) versus 51% in group II (seronegative). While

## *Discussion*

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none of the individuals in the control group showed any suggestive signs of thyroiditis on ultrasonography. No statistical significant difference was found in our study in ultrasound findings between seropositive versus seronegative groups, however a significant difference was observed between patients and controls.

In a study done by Przygodzka M et al in 2009, suggestive signs of thyroiditis in thyroid ultrasonography in patients whom he studied with RA were in the form of heterogeneity of thyroid tissue illustrated in 5% of patients as well as diffuse hypo echogenicity was observed in 2 % of patients. <sup>(272)</sup>

In 2010 Yeon-Ah L et al screened 110 RA patients for thyroid disorders by thyroid ultrasonography and suggested an interesting finding in his study where he detected a high incidence of papillary thyroid cancer in patients with RA and most of the thyroid cancer patients had a solid and hypo echoic pattern in thyroid ultrasonography. <sup>(273)</sup>

## CONCLUSIONS

1. Thyroid dysfunction is common in RA patients, with hypothyroidism being the most common disorder prevalent in 29% of patients regardless their serostatus, this association was independent from disease activity assessed by DAS 28.
2. No Relation Between Disease Activity Assessed By DAS Score and the Clinical Presentation Of AITD.
3. AITD are common in RA with higher Levels Of autoimmune Thyroid Markers namely Anti- TPO, TG Abs As Well as TRAbs in Patients With Rheumatoid Arthritis Regardless their Serostatus when compared to normal individuals suggesting increased incidence of autoimmune thyroid diseases (AITD) in patients with RA.
4. Increased Incidence Of Thyroid Autoimmunity In Seropositive RA Versus Seronegative RA as Evidenced By Higher Levels Of Thyroid Autoimmune Markers In The Former.
5. TRAbs Were Detectable In A Small Subset Of Patients With RA.
6. A Strong Link between AITD And RA suggested From a strong correlation of autoimmune markers of both diseases.
7. Suggestive Signs Of thyroiditis shown in neck ultrasonography in patients with RA versus normal individuals, which did not differ according to their serostatus.

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## SUMMARY

Autoimmune diseases (ADs) are conditions under which an individual develops antibodies against their own cells, tissues and/or organ systems. An AD can be either organ-specific or non-organ specific (systemic) in its clinical presentation, of which autoimmune thyroid diseases (AITD) are considered organ-specific, being represented by Graves' disease and Hashimoto's thyroiditis (HT) being the two commonest types and mainly characterized by the presence of autoantibodies namely anti thyroid peroxidase and anti-thyroglobulin antibodies.

Rheumatoid arthritis is a chronic inflammatory autoimmune diseases in which immunologically mediated inflammation of synovial joints result in marked disruption of both joint structure and function where RF and anti-CCP autoantibodies can be detected in patients' sera and according to their presence RA can be divided into seropositive and seronegative varieties (seropositive is positive to one or both of them) and seronegative (negative to both).

Based on similar immunological mechanism, autoimmune disease tend to cluster together where they share common clinical and genetic background and hence the relationship between AITDs and RA was previously studied and however the exact mechanism was still unclear, it was found that autoimmune thyroiditis is more frequent than in the normal population in the course of rheumatoid arthritis.

The aim of our work was to study the presence of thyroid dysfunction (hyperthyroidism or hypothyroidism) in seropositive versus seronegative rheumatoid arthritis patients, and also to study the presence of autoimmune thyroid markers namely anti-TPO, anti-TG and particularly TRABs in seropositive versus seronegative RA patients and their relation to overt thyroid dysfunction and rheumatoid arthritis auto antibodies namely anti-CCP & RF.

The study was carried out on 70 patients with rheumatoid arthritis who were attending rheumatology outpatient clinic and inpatient in Alexandria Main University Hospital.

They were divided according to the results of their serological tests (RF and anti-CCP) into 2 groups:

**Group I:**Included 35 patients with seropositive rheumatoid arthritis(positive to one or both seromarkers), **GroupII:** Included 35 patients with seronegative rheumatoid arthritis(negative to both seromarkers) and a third group (**Group III**):Including 20 healthy age matched individuals who are not suffering of any rheumatologic disorder were included as a control group.

All patients in this study were subjected to thorough history taking, clinical examination with DAS 28, laboratory investigations (CBC, serum urea, serum creatinine, SGOT, SGPT, ESR, CRP, RF, anti-CCP, TSH, T3, T4, anti-TPO, anti-TG and TRABs) and ultrasonography of thyroid gland.

It was found that ESR, CRP, RF and anti-CCP were significantly higher in RA patients versus control particularly in seropositive versus seronegative .Higher incidence of

## *Summary*

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thyroid dysfunction mainly hypothyroidism was clearly evidenced in our study in RA patients versus controls, also it was shown that thyroid auto antibodies (anti-TPO and anti-TG antibodies) were significantly higher in RA patients versus controls and specifically in seropositive versus seronegative suggesting a higher incidence of autoimmune process in seropositive versus seronegative patients, however TRABs were detected in a small proportion of RA patients.

It was observed in our study that RA duration didn't influence the titer of thyroid autoantibodies but we observed a significant positive correlation between anti-TPO, TRABs and RF titer, moreover anti-CCP was also found to be significantly correlated with anti-TPO and TRABs level in patients with RA and lastly evidence of thyroiditis by ultrasonography was significantly higher in RA patients versus controls.