

Prevalence of Hypothyroidism in Rheumatoid Arthritis and its Correlation with Disease Activity

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Submitted: 21 Dec 2022; Accepted: 27 Dec 2022; Published: 25 Jan 2023

Citation: Jeha, M., Jeha, S. (2023). Prevalence of Hypothyroidism in Rheumatoid Arthritis and its Correlation with Disease Activity. *Biomed Sci Clin Res*, 2(1), 49-60.

Abstract

Background: Several recent studies have shown an increased incidence of hypothyroidism in many chronic inflammatory diseases, especially rheumatoid arthritis, and others studies have shown a relationship between hypothyroidism in patients with rheumatoid disease and the degree of disease activity.

Aim of the Study: To know the extent of hypothyroidism in a sample of patients with rheumatoid arthritis in Al-Assad and Al-Mowasat University Hospital in Damascus, to link this to the effectiveness of rheumatoid disease, and to compare with a group of healthy controls.

Materials and Methods: A cross-sectional/case-control study was conducted on 134 patients diagnosed with rheumatoid arthritis, and a healthy cohort of 134 people from the University Hospitals in Damascus.

The presence of hypothyroidism was compared between the two groups of patients and controls. Hypothyroidism in patients was also compared with the disease activity index, after dividing them according to the effectiveness index (DAS28-ESR) into three groups: mild, moderate, and severe disease activity. The data was analyzed using the statistical analysis program (SPSS) version and the variable was considered statistically significant when the P-Value is less than (0.05) [1].

Results: The average age of both patients and controls was (50.6±3.9) and (44.3±2.01) years, respectively. The proportion of females in the sample of patients was (%84.3) and the percentage of females in the control sample (%80.6), the number of patients with hypothyroidism was 43 patients (%32), and the number of infected controls was 10 people (%7.5) P-Value < 0.000. The type of hypothyroidism in patients was classified into clinical hypothyroidism (%67.44) and subclinical hypothyroidism (%32.56). %24.6 of patients and %6 of controls had positive TPO antibodies (P-Value < 0.000). The study has shown a positive correlation between hypothyroidism and disease activity indicator (DAS28-ESR).

Conclusion: Increased incidence of hypothyroidism and TPO antibodies in patients with rheumatoid disease compared to healthy subjects, and an increase in the degree of disease activity in patients with rheumatoid disease diagnosed with hypothyroidism compared to patients with rheumatoid disease without hypothyroidism.

Keywords: Hypothyroidism, Rheumatoid Arthritis, DAS28-ESR

Introductory Part

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, and it is considered one of the most common systemic inflammatory diseases that affect the synovial joints and many other organs and tissues.

Extra-articular manifestations occur in approximately 40% of

patients, such as interstitial lung diseases, pleural effusions, vasculitis, thyroid disorders, and others.

Immune thyroid disorders (AITD) are considered one of the most common immune disorders in patients with rheumatoid disease, manifesting as a disorder of thyroid function and an increase in the production of anti-TPO, anti-TG antibodies. Therefore, several studies have focused on studying the relationship

between rheumatoid disease and thyroid disorders, as many studies have shown. There is a recent study of the existence of a relationship between the presence of hypothyroidism in patients with rheumatoid disease and the degree of effectiveness of the disease, so this research aims to compare the extent of the occurrence of hypothyroidism between a group of patients diagnosed with rheumatoid arthritis from the reviewers and admissions to Al-Assad and Al-Mowasat University Hospitals in Syria and a group of healthy controls from the patients' companions. In addition to studying the existence of a correlation between hypothyroidism on the one hand and disease activity estimated using the effectiveness index (DAS28-ESR) on the other hand, in a sample of patients in both hospitals. Because of the prevalence of hypothyroidism and the absence of similar studies in Syria on this subject, this research was conducted.

Search Limits

The studied sample is taken from two university hospitals in Damascus, and it does not necessarily represent all patients in Syria, just as the relationship was not studied in a scient number of patients who did not receive any disease-modifying treatment, and therefore we cannot neutralize the role of drugs that may affect the thyroid gland. And lead to disturbance of its functions.

Research Methods, Tools and Method of Work

Samples were collected between January 2020 and January 2022 in Al-Assad and Al-Mowasat University Hospitals, by recording patient data and necessary controls according to a questionnaire for our cross-sectional study/case-control, after obtaining the informed consent of the participants.

The study included 134 patients diagnosed with rheumatoid arthritis previously or at entry into the study, regardless of the duration of the disease and the treatments used, according to the classification criteria for rheumatoid arthritis according to the American College of Arthritis and the European Society Against Rheumatism in 2010 [2].

It also included 134 healthy people, through questioning and clinical examination, who were accompanying patients. Patients who are pregnant or in the postpartum period, patients under 16 years of age, patients with autoimmune disease, pre-existing diabetes mellitus, renal insufficiency, chronic liver disease or malignancy, and patients with previous surgical intervention on the thyroid gland or using known medications were also excluded. They disrupt the functions of (lithium, amiodarone, interferonalpha).

All patients participating in the research underwent clinical and laboratory evaluation:

Clinical Evaluation

It included taking a detailed clinical history and documenting the following information: age, gender, current habits, disease diagnosis conditions, current articular complaints, medications used, surgical and pathological antecedents. A general clinical examination was also performed, the thyroid gland was examined, a careful examination of the articular system was carried out, the number of painful joints, the number of swollen joints

were documented, and the patient's selfassessment of his general health status using the visual analogue scale.

Laboratory Evaluation

Venous blood was drawn for all 134 patients, and analyzes were performed.

(TSH-FT4-anti TPO-ESR-CBC)), using the devices in the laboratories of Al-Assad and Al-Mowasat University Hospitals. Only healthy controls (TSH-FT4-anti TPO) were withdrawn.

The normal TSH value ranges from (0.270-4.20 uIU/ml), the normal FT4 value ranges from (0.932-1.7 ng/dl) and the normal anti-TPO value ranges from (0.0-34 IU/L).

After completing the previous steps, the patients were divided into four groups according to the indicator (DAS28-ESR) as follows: the group of patients with high activity (DAS28 > 5.1), the group of patients with moderate activity (DAS28 >3.2 to 5.1) and the group of patients with mild activity (DAS28). from 2.6 to 3.2) and the recumbent patient group (DAS28<2.6).

In the first arm, the presence of hypothyroidism and TPO antibodies were compared between patients and controls in both hospitals.

While in the second arm, hypothyroidism was compared with the degree of disease activity in each of the two hospitals.

After completing the data collection, it was entered into the computer and analyzed using the Statistical Package for Social Sciences (SPSS) (version 24) (IBM Corporation, Armonk, New York, USA) and Excel 2016. A predictive value less than 0.05 (P value < 0.05) was considered statistically significant.

Introduction

Rheumatoid arthritis is a chronic inflammatory autoimmune systemic disease that is the most common joint disease affecting 0.5-1% of adults in the United States of America That is about one and a half million people annually, The disease is more common in women and can start at any age, but its peak incidence is between 40-60 years [3, 4].

Despite the prevalence of rheumatoid disease worldwide, regardless of race and geographic location, there are some exceptions, with a low prevalence observed in Africa and a higher prevalence in North America 5%.

The most common clinical manifestation is symmetric polyarthritis affecting the small joints, especially of the hands, feet and wrists, Clinical extra-articular manifestations occur in approximately 40% of patients and are associated with poor prognosis and increased morbidity and mortality. Also commonly seen in severe disease associated with RF positivity, ACPA and/or HLA DR4 positivity Most patients suffer from systemic symptoms such as general fatigue, low-grade fever, weight loss, skin injury, ocular injury, heart, chest, blood, vasculitis, thyroid injury, and others [5].

An increase in the incidence of thyroid disorders has been recorded in patients with immune diseases, and this may be explained by a number of mechanisms, including HLA-dependent genetic factors and other factors [6].

Several recent studies have shown a higher incidence of auto-immune thyroid disease in patients with rheumatoid disease compared to other connective tissue diseases. Hypothyroidism is considered the most happening thyroid disorder in rheumatoid disease, with a predominance of females in most of the research, where observed. The prevalence of hypothyroidism is three times higher in women with rheumatoid disease compared to non-inflammatory diseases such as myalgia and osteoporosis. Where genetic and environmental risk factors shared between the two diseases have been described, as the presence of genes (PTPN22, HLA-DRB1, CD40,CTLA4) which increase the risk of autoimmune thyroid lesions and are the same genes that contribute to the pathological mechanism of rheumatoid disease. Several common environmental risk factors, as smoking, have also been studied. And advanced age, females, and an increase in body mass, which are considered as predisposing risk factors for rheumatoid disease and thyroid disease [7-9].

In addition, recent studies have shown the role of thyroid hormones in causing inflammation, as they stimulate the production of oxygen radicals in neutrophils. It increases the expression of MHC2 and stimulates the secretion of inflammatory cytokines IL12, IL6, IL8, from cells. It activates the proliferation of lymphocytes, natural killer cells, and the production of super-oxidation [10, 11].

An association between rheumatoid arthritis and thyroid lesions has been reported. Where the occurrence rate of hypothyroidism with or without an immune cause was 0.05%-34% of the patients with rheumatoid disease [12-15]. The percentage rises to 38% when thyroid antibodies are positive, and these rates are significantly higher when compared to the general population [16-18].

The relationship between rheumatoid disease and its effectiveness and hypothyroidism has been studied in many studies. In a study conducted by Joshi in 2017 in India on 52 patients with rheumatoid disease, it was found that there was hypothyroidism in 38.4% of patients with rheumatoid disease, and there was an important relationship between high levels of TSH and disease activity (ESR)-DAS28 [19].

And in the study of Qian li et al in 2019 in China on 65 patients with rheumatoid disease and 550 of the controls, it confirmed an increased risk of hypothyroidism in rheumatoid patients compared to the controls with a value of (0.001}P-value) [20].

In the study of Hiatham Azeem in Egypt in 2019, which he conducted on 1000 rheumatoid patients and 200 of the controls, and the study lasted for about a year and a half, the prevalence of hypothyroidism was 28% of patients, and TPO antibodies were positive in 5.6% of patients, compared to 2% of the controls. A positive correlation between high TSH numbers and rheumatoid disease activity (DAS28-ESR) [21].

In a case control study conducted by Nazary and colleagues in the United States of America in 2021 (51) including 400 patients with rheumatoid disease and 400 controls, the incidence of hypothyroidism was 7.75% of patients compared to 2.5% of the controls with a P-value=0.0007, and the percentage of antibodies Positive TPO in 13% of rheumatoid patients compared to 5.5% of controls.

In a recent study conducted by Hung Ming in Taiwan in 2022 on 16,714 rheumatoid disease patients and 66,856 controls, it showed an increased risk of developing hypothyroidism in the context of rheumatoid disease, where the incidence was 1.67 times higher than the controls, and the effectiveness of rheumatoid disease was higher in patients with hypothyroidism compared to patients without [22].

There are more studies on the relationship between hypothyroidism and rheumatoid disease and its effectiveness, which will be detailed now and compared later with the results of our study.

Evaluation of Disease Activity

Disease control and remission are evaluated by several approved international standards, some of which are based on data taken from the patient only, while some of them require careful clinical examination by the doctor and laboratory analysis.

It is important to use one of these scales to assess disease activity, and it is not important which scale is used [23].

According to the American College of Rheumatology (ACR), eleven measures of disease effectiveness have been approved and seven measures have been recommended (Table 4), which are [24].

1-Disease Activity Score in 28 joints with Erythrocyte Sedimentation Rate or C-Reactive Protein Level (DAS28-ESR or DAS28-CRP).

2-Clinical Disease Activity Index (CDAI).

3-Simplified Disease Activity Index (SDAI).

4-Routine Assessment of Patient Data 3 (RAPID3).

5- Patient Activity Scale-II (PAS-II).

Table 1: The American College of Rheumatology’s Recommended Rheumatoid Disease Effectiveness Measures and Cut-Off Values for Each. Excerpted from the Article

Anderson J, Caplan L, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res(Hoboken)*. 2012 May;64(5):640-7.

| Table 1. Disease activity cutoffs for each American College of Rheumatology–recommended disease activity measure* | | | | | |
|---|-------|-----------|---------------|---------------|-------------|
| Disease activity measure | Scale | Remission | Low/minimal | Moderate | High/severe |
| Patient-driven composite tools | | | | | |
| PAS | 0–10 | 0.00–0.25 | 0.26–3.70 | 3.71 to < 8.0 | 8.00–10.00 |
| PAS-II | 0–10 | 0.00–0.25 | 0.26–3.70 | 3.71 to < 8.0 | 8.00–10.00 |
| RAPID-3 | 0–10 | 0–1.0 | >1.0 to 2.0 | >2.0 to 4.0 | >4.0 to 10 |
| Patient and provider composite tool | | | | | |
| CDAI | 0–76 | ≤ 2.8 | >2.8 to 10.0 | >10.0 to 22.0 | >22.0 |
| Patient, provider, and laboratory composite tools | | | | | |
| DAS28 (ESR or CRP) | 0–9.4 | < 2.6 | ≥2.6 to < 3.2 | ≥3.2 to ≤5.1 | >5.1 |
| SDAI | 0–86 | ≤ 3.3 | >3.3 to ≤11.0 | >11.0 to ≤26 | >26 |

* PAS Patient Activity Scale; RAPID-3 Routine Assessment of Patient Index Data with 3 measures; CDAI Clinical Disease Activity Index; DAS28 Disease Activity Score with 28-joint counts; ESR erythrocyte sedimentation rate; CRP C-reactive protein; SDAI Simplified Disease Activity Index.

The DAS28 scale is easy to calculate and can be used in clinical practice, as it is based on the evaluation of 28 joints without giving a specific score for each joint, as the number of painful joints and the number of swollen joints are entered in addition to the sepsis number or C-reactive protein, and the general evaluation by the patient (Patient Global Assessment) in a mathematical equation. Patients are divided according to the result into severe activity when the DAS28 is greater than 5.1, moderate effectiveness when it is greater than 3.2 and less than 5.1, low effectiveness when it is greater than or equal to 2.6 and less than or equal to 5.1, while it is considered recumbent when the DAS28 is less from 2.6.

Practical Section

The First Chapter: The Aim of The Research and the Method of Conducting it Research Objective

Finding out the extent of hypothyroidism in patients with rheumatoid disease attending Al-Assad and AlMowasat University Hospitals, and linking that to the effectiveness of rheumatoid disease.

Study Materials and Methods

- **Study style:** Cross Sectional / Case Control.
- **Place of study:** Al-Assad University Hospital and Al-Mowasat University Hospital in Damascus.
- **The time and duration of the study:** starting from September 2020 AD until March 2022 AD, when the sample size was completed.
- **Sample Size:** The sample size was calculated using (Raosoft.com) website and it consisted of (134) patients and (134) controls with a confidence interval (95%).

The Inclusion Criteria

Patients who have previously or currently diagnosed rheumatoid disease according to the classification criteria for rheumatoid arthritis according to the American College of Arthritis and the European Society Against Rheumatism for the year 2010. In addition to a group of healthy controls, through interrogation and detailed clinical examination, from the patients’ companions.

Exclusion Criteria

- Patients who are pregnant or in the postpartum period.
- Patients under 16 years of age.
- Patients who have another autoimmune inflammatory disease, diabetes mellitus, renal insufficiency or chronic liver disease.
- Patients with co-infections.
- Patients with malignancy.
- Patients who are using drugs known to cause disruption of thyroid function (lithium, amiodarone, interferon-alpha).

Study Tools

- The classification criteria for rheumatoid arthritis according to the American College of Rheumatology and the European Society Against Rheumatism 2010 [25, 26]
- Rheumatoid Arthritis Effectiveness Index (DAS28-ESR) [27].
- Criteria for the diagnosis of hypothyroidism according to the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) [28].

The study was divided into two arms. The first: to compare the presence of hypothyroidism and TPO antibodies between patients with rheumatoid disease and normal people, and the second: to compare the presence of hypothyroidism among patients with low, medium, and severe activity, and to determine the type of relationship between hypothyroidism and the indicator of disease activity (DAS28-ESR).

Informed consent was taken from all (268) research participants.

All patients participating in the research underwent a clinical and laboratory evaluation, and the results were recorded in a questionnaire. The questionnaire form was presented in the appendices at the end of the research.

Clinical Evaluation

It included taking a detailed clinical history and documenting the following information: age, gender, current habits, diagnostic conditions, current articular complaints, medications used, and surgical history. A careful clinical examination of the articular system was also conducted, documenting the number of painful joints and the number of swollen joints, and the patient's self-assessment of his general health status using the visual analogue scale [29].

Laboratory Evaluation

Venous blood was drawn for all 134 patients, and analyzes (antiTPO-ESR-FT4-TSH-CBC) were performed using the automated analyzer device located in the laboratory of Al-Assad University Hospital Cobas e 601 (Elecsys TSH) in Al-Assad Hospital. And the automatic analyzer device located in the laboratory of Al-Mowasat University Hospital (IMMULITE SIEMENS), and FT4-TSH-antiTPO analyzes were withdrawn only for healthy controls.

The normal value of TSH is between (0.270-4.2 IU/ml) according to the laboratory of Al-Assad Hospital and between (0.3-5.0 mic IU/ml) according to the laboratory of Al-Mowasat Hospital, and the normal value of FT4 is between (0.932-1.71 ng/dl) according to the laboratory of Al-Assad Hospital and between (0.8-1.8 ng/dl) according to the Mouwasat Hospital laboratory. The normal value of TPO antibodies ranged between 0.0-34 IU/ml) according to the laboratory of Al-Assad Hospital and between (1.0-16.0 IU/L) according to the laboratory of Al-Mowasat Hospital.

After completing the previous steps, the patients were divided into three groups according to the index (DAS28-ESR) as follows: the group of patients with high activity (DAS28 > 5.1), the group of patients with moderate activity (DAS28 > 3.2 to 5.1), and the group of patients with mild activity (DAS28 from 2.6 to 3.2).

The patients were divided according to the presence of hypothyroidism into two groups: the group of patients with hypothyroidism, and the group of patients without hypothyroidism. In the first arm, the presence of hypothyroidism and the positivity of TPO antibodies were compared between patients and controls in each of the two hospitals. In the second arm, the presence of hypothyroidism was compared with the degree of disease activity in each of the two hospitals.

Statistical Methods Used

The analysis was carried out using the Statistical Package for Social Sciences (SPSS) (version 25) (IBM Corporation, Armonk, New York, USA) and Excel 2016. The predictive value less than 0.05 (P value < 0.05) was considered statistically significant.

A-Descriptive Statistics

For categorical variables: we relied on percentages and bar charts.

For continuous variables: measures of central tendency (the mean and the standard deviation) were used.

B-Inferential Statistical

To test the statistical relationships between the basal characteristics, we used the following statistical methods:

- Student's t-test, expressed as "t" for comparison of continuous variables.

- Chi-square test and expressed as "X²" to compare categorical variables with a normal distribution.

- Pearson's test to assess the association between hypothyroidism and disease activity.

Ethical Considerations

Scientific research ethics requires respecting the rights, opinions, and dignity of others, whether they are fellow researchers, research participants, or research targets. The principles of scientific research ethics generally adopt the values of armative action and avoidance of harm, and these two values must be the pillars of ethical considerations during the research process. In our research, the ethical considerations of credibility, trust, and commitment to confidentiality of information will be adhered to through consent.

The questionnaire and the form that was used in the research are included in the appendices at the end of the research.

Research Results

The Studied Sample

The study included 134 patients with rheumatoid disease and 134 controls. The occurrence of hypothyroidism was compared between the patients and controls group. The patients were divided into three groups according to the effectiveness index (DAS28-ESR). The three groups were compared with hypothyroidism in the context of rheumatoid disease, where the presence of hypothyroidism was proven as a diagnosis. Confirmed in 43 of the 134 patients with rheumatoid disease included in the study.

The Research Sample (Patients and Controls) is Distributed According to Age

The ages of patients and controls ranged between 20 and 80 years, with the mean age of patients (50.6 ± 3.9) and the mean age of controls (44.3 ± 2.01), as shown in Table (2)

Table 2: Research sample (patients and controls) by age:

| mean age + standard deviation | The number | Sample (n) |
|-------------------------------|------------|--|
| 44.3±2.01 | 134 | Sample |
| 50.6±3.6 | 134 | Rheumatoid patients |
| 49.2±4.9 | 43 | Rheumatoid patients with hypothyroidism |
| 50.14±4.43 | 91 | Rheumatoid patients without hypothyroidism |

The Research Sample (Patients and Controls) is Distributed According to Gender

The sample of patients with rheumatoid disease was distributed according to sex to (84.3%) females and (19.4%) males. The percentage of female controls was (80.6%) and males (19.4%). The percentage of patients with hypothyroidism was (88.4%) fe-

males and (11.6%) males. The distribution of patients without hypothyroidism was (82.4%) females and (17.6%) males. The reason is due to female dominance due to the prevalence of rheumatoid disease and hypothyroidism in women more than in men [30, 31]. As shown in Table(3).

Table (3): Distribution of the research sample, patients and controls, according to gender:

| Sex | | Sample (n) |
|-----------|------------|--|
| Male | Female | |
| 26(19.4%) | 108(80.6%) | Control (134) |
| 21(15.7%) | 113(84.3%) | Rheumatoid patients (134) |
| 5(11.6%) | 38(88.4%) | Rheumatoid patients with hypothyroidism |
| 16(17.6%) | 75(82.4%) | Rheumatoid patients without hypothyroidism |

To study the presence of a difference in the ratio of males and females between controls and rheumatoid patients, the Pearson Chi-Square test was performed:

p-value=0.422>0.05

Thus, there is no statistically significant difference in sex between controls and rheumatoid patients.

In order to study the existence of a difference in the ratio of males and females between rheumatoid patients with hypothyroidism and without hypothyroidism, the Pearson Chi-Square test was performed:

p-value=0.376>0.05

Thus, there is no statistically significant difference in gender between the presence or absence of hypothyroidism in rheumatoid patients

The Research Sample (Patients and Controls) is Distributed According to The Presence of Hypothyroidism

Hypothyroidism was proven in 43 patients with rheumatoid disease (32%) compared to 10 controls (7.5%), where we notice a higher prevalence of hypothyroidism among patients with rheumatoid disease compared to controls, as shown in Table No. (4).

Table (4): The distribution of the research sample (patients and controls) according to the presence of hypothyroidism:

| Patients sample (134) | | control sample (134) | | Sample (n) |
|-----------------------|--------|----------------------|--------|------------------------|
| percentage | Sample | percentage | Sample | |
| 32% | 43 | 7.5% | 10 | with hypothyroidism |
| 67% | 91 | 92.5% | 124 | without hypothyroidism |

In order to study the importance of the difference in the percentage of hypothyroidism between a sample of patients and a sample of controls, the Pearson Chi-Square test was conducted:

p-value=0.000<0.05

Hence, there is a statistically significant difference in the percentage of hypothyroidism between patients with rheumatoid disease and controls, as it is more prevalent in patients with rheumatoid disease.

Odd ratio = 5.86

That is, the likelihood of developing hypothyroidism increased by 5.86 times if a person had rheumatoid disease compared to those without.

Distribution of Patients with Hypothyroidism According to the Type of Hypothyroidism (Clinical /Subclinical)

The incidence of clinical hypothyroidism was higher in patients with rheumatoid disease than in the subclinical form, as it was diagnosed in 29 patients with rheumatoid disease at a rate of 67.44% compared to 6 subjects with a rate of 60%, and subclinical hypothyroidism was diagnosed in 14 patients with rheumatoid disease at a rate of 32.56% compared to 32.56% vs. 4 persons of the witnesses, at a rate of 40%. As shown in Table No. (5)

Table (5): The distribution of patients with hypothyroidism according to the type of hypothyroidism (clinical / subclinical):

| A sample of patients with | | A sample of controls with | | Sample(n) |
|---------------------------|------------|---------------------------|------------|----------------------------|
| percentag | The number | percentag | The number | hypothyroidism (10) |
| 67.44% | 29 | 60% | 6 | Clinical hypothyroidism |
| 32.56% | 14 | 40% | 4 | Subclinical hypothyroidism |

In order to study the importance of the difference in the prevalence of clinical hypothyroidism between a sample of patients and a sample of controls, the Pearson Chi-Square test was conducted:

p-value=0.719>0.05

Hence, there is no statistically significant difference in the type of hypothyroidism between the two groups of controls and patients with rheumatoid disease.

The Research Sample (Patients And Controls) was Distributed According to the TPO Antibodies

We note that the positivity of TPO antibodies was significantly higher in patients with rheumatoid disease compared to controls, as it was positive in 33 patients with a rate of 24.6% compared to 8 controls with a rate of 6%. As shown in Table No. (6)

Table (6): Distribution of the research sample (patients and controls) according to TPO antibodies:

| Sample patients (134) | | Sample control (134) | | Sample (n) |
|-----------------------|------------|----------------------|------------|-----------------------------|
| percentag | The number | percentag | The number | |
| 24.6 % | 33 | 6 % | 8 | TPOantibodies are positive |
| 75.4 % | 101 | 94 % | 126 | TPO antibodies are negative |

To study the importance of the difference in the percentage of positivity for TPO antibodies between a sample of patients and a sample of controls, the Pearson Chi-Square test was conducted: p-value=0.000<0.05

Hence, there is a statistically significant difference in the percentage of positivity of TPO antibodies between patients with rheumatoid disease and controls, as it is more prevalent in patients with rheumatoid disease. Odd ratio = 5.15

That is, the likelihood of developing TPO antibody positivity is 5.15 times greater if a person has rheumatoid disease compared to those without.

Distribution of Rheumatoid Disease Patients According to Disease Activity DAS28-ESR

The patients were distributed according to the degree of effectiveness of the disease, where the percentage of patients with low effectiveness was (20.8%), and patients with medium effectiveness (40.4%), which is the highest percentage of patients, while the percentage of patients with high effectiveness was (38.8%). As shown in Table No. (7)

Table (7): Distribution of rheumatoid disease patients according to disease activity DAS28-ESR:

| mean age + standard deviation DAS ESR 28 | percentag | The number | disease eacy |
|--|-----------|------------|------------------|
| 2.24±0.5 | 8.9% | 12 | Slumber <2.6 |
| 2.9±0.15 | 11.9% | 16 | Low (2.6-3.2) |
| 4.1±0.5 | 40.4% | 54 | Middle (3.2-5.1) |
| 5.8±0.55 | 38.8% | 52 | High >5.1 |

Distribution of Rheumatoid Disease Patients with or Without Hypothyroidism According to Disease Activity DAS28-ESR

We note that the percentage of high-eacy patients with rheumatoid disease with hypothyroidism was the highest (60.5%). Patients with low eacy constituted the lowest percentage (9.3%),

and patients with medium eacy (30.2%). As for patients with rheumatoid disease without hypothyroidism, the patients formed Those with medium eacy had the highest percentage (45.1), patients with low eacy (26.3%), and patients with high eacy (28.6%). As shown in Table No. (8)

Table (8): Distribution of patients with or without hypothyroidism according to disease activity DAS28-ESR:

| Rheumatoid patients without | | Rheumatoid patients with hypothyroidism | | disease eacy |
|-----------------------------|------------|---|------------|------------------|
| percentag | The number | percentag | The number | |
| DAS ESR 28 | | | | |
| 12.1%<2.6 | 11 | 2.32% | 1 | Slumber |
| 14.3% | 13 | 6.98% | 3 | Low (2.6-3.2) |
| 45.1% | 41 | 30.2% | 13 | Middle (3.2-5.1) |
| 28.6% | 26 | 60.5% | 26 | High >5.1 |

To study the existence of a relationship between disease activity and hypothyroidism, the Independent samples T-test was conducted:

| | | |
|--------------------|-------------|-----------------------------|
| standard deviation | average DAS | Rheumatoid disease patients |
| 1.08 | 5.54 | with hypothyroidism |
| 1.30 | 4.15 | Without hypothyroidism |

From it, we note that the average degree of disease effectiveness was greater in patients with hypothyroidism compared to non-hypothyroidism patients

p-value=0.000<0.05

Hence, there is a statistically significant difference in disease activity between the presence or absence of hypothyroidism, i.e. disease activity increases if patients have hypothyroidism.

By conducting the logistic regression test, they were:

Odd ratio=2.5

That is, with every increase in the incidence of hypothyroidism in patients, the probability of disease activity increases by 2.5 times.

Comparison Table of Patients with Rheumatoid Disease With or Without Hypothyroidism

A comparison was made between patients with hypothyroidism and patients without hypothyroidism, where hypothyroidism was diagnosed in 43 patients with rheumatoid disease compared to 91 patients with rheumatoid disease without hypothyroidism, and the average age of the patients was almost similar in the two groups with female control, and the effectiveness of the disease was higher in patients with hypothyroidism compared to patients without thyroid disease. As shown in Table No. (9)

Table (9): Comparison of patients with rheumatoid disease with or without hypothyroidism:

| Rheumatoid patients without hypothyroidism | Rheumatoid patients with hypothyroidism | Sample (n) |
|--|---|-----------------------------|
| 91 | 43 | number of patients |
| 50.1 ±4.43 | 49.2 ±4.9 | average age (years) |
| 82.4% female | 88.4% female, | The ratio % |
| 17.6% Male | 11.6%. Male | |
| Female > Male | Female > Male | Sex |
| 13 (39.4%) | 20 (60.6%) | Positive for TPO antibodies |
| 0.4 ±3.8 DAS28-ESR | 0.4 ±4.3 | Disease activity |

Discussion and Comparison With International Studies

The research included 134 patients with rheumatoid disease and 134 healthy controls through clinical examination and interrogation, where the ages of patients and controls ranged between 16 and 80 years, and the mean age of patients was (50.6 ± 3.9) and the mean age of controls was (44.3 ± 2.01). The percentage of females in the patient sample was (84.3%) and the percentage of males (15.7%). The percentage of females with hypothyroidism was (88.4%) and the percentage of males was (11.6%). This is explained by the prevalence of rheumatoid disease and hypothyroidism in women more than in men. The percentage of females in the control sample was (80.6%) and the percentage of males (19.4%). The number of patients with hypothyroidism was 43 patients with a rate of ((32%), and the number of people with hypothyroidism among the controls was 10 people with a percentage ((7.5%), P-value<0.000. It was classified The pattern of hypothyroidism in patients with hypothyroidism was divided into clinical hypothyroidism with a rate of (67.44%) and sub-clinical hypothyroidism with a rate of (32.56%). The percentage of TPO antibody positivity in patients (24.6%) and the percentage of TPO antibody positivity in controls (6%), P-value < 0.000 This shows that the prevalence of hypothyroidism and TPO antibody positivity was higher in patients with rheumatoid disease than in controls.

As for the distribution of patients according to the degree of activity of the disease, our study showed that about (20.8%) of the patients were in a state of low activity, (40.4%) in a state of

moderate activity, and (38.8%) in a state of severe activity.

By comparing the presence of hypothyroidism among the groups of patients divided according to the degree of activity, the percentage of patients with low activity was (9.3%), (30.2%) with moderate activity, and (60.5%) with severe activity. This shows that hypothyroidism is associated with an increase in the severity of rheumatoid disease.

After conducting the necessary statistical tests, our study showed that there is a significant relationship between hypothyroidism and the degree of disease activity (DAS28-ESR). Finally, after comparing the presence of hypothyroidism among patients and controls, it was found that there were statistically significant differences between the occurrence of hypothyroidism in patients and hypothyroidism in controls.

As a result of our study, hypothyroidism is positively and statistically significant with disease activity in patients with rheumatoid disease, and early detection of its presence may be useful in predicting disease activity.

Our study must be compared with several international studies conducted in this context.

In a study by Enas A. Elattar and his colleagues in 2014 in Egypt, on 150 patients with rheumatoid disease and 50 controls, whose ages ranged from 62-35 years, the average age was (45.2 ± 7.8), with females controlling by 90%, as the incidence of hypothy-

roidism was among 36 patients (24%) of the patients compared to only one patient (2%) of the controls, and TPO antibodies were positive in 14 patients (9.3%) compared to 3 of the controls (6%), and by comparing the effectiveness of the disease, there were statistically significant differences between patients with TPO deficiency Thyroid and disease activity (DAS28-ESR, HAQ).

In a study by Joshi and his colleagues in 2017 in India on 52 patients with rheumatoid disease, the average age of patients was 41.4 ± 10 years, and the percentage of females was 75% and males 25%, and the number of patients with hypothyroidism was 20 patients, with a rate of (38.4%), and the study showed There was a significant correlation between elevated serum TSH levels and disease activity index (DAS28-ESR) [32].

In another study in India conducted by Joseph Anoop in 2017 on 100 patients with rheumatoid disease, the average age of patients was 43.9 ± 11.96 , with the disease controlling females by 81%, and the percentage of patients with hypothyroidism was 20% (15% of them were hypothyroidism) [33]. clinical and 5% subclinical hypothyroidism), and TPO antibody was positive in 31% of patients. The study did not address the effect of hypothyroidism on the effectiveness of rheumatoid disease.

In a case-control study in China conducted by Qian Li and colleagues in 2019 on 65 patients with rheumatoid disease and 550 controls, an increased risk of developing hypothyroidism was shown compared to controls (P-value < 0.0074), where the incidence of hypothyroidism was 26.2% vs. 13.5% of controls, hypothyroidism was classified as 10.8% clinical and 15.4 subclinical [34].

In the study of Hiatham Azeem in 2019 in Egypt, which lasted for a year and a half, and was conducted on 1000 patients with rheumatoid disease, the infection rate for females was 85% and males 15%, and the average age of patients was (40.75 ± 5) , and the incidence of hypothyroidism was 28%, and the percentage of subclinical hypothyroidism was the largest percentage compared to the clinical form, and TPO antibodies were positive in 5.6% of patients compared to 2% of controls, and with regard to the effectiveness of the disease, there was a positive correlation between high TSH numbers and the effectiveness of rheumatoid disease (DAS28-ESR) [35].

In a study by Wassem Mir in India in 2019 that included 250 patients with rheumatoid disease, the average age of the patients was (49.2 ± 12.1) years, and the infection rate was 86.8% for females and 13.2% for males [36]. The prevalence of TPO antibodies was studied in patients, as it was positive by 22.5%. Of the patients, the incidence of hypothyroidism was 42.2%, and the highest percentage at the expense of the subclinical pattern was 38.3%, and this contradicts our study. The study also compared disease efficacy, where disease efficacy was higher in rheumatoid disease patients with hypothyroidism compared to non-hypothyroidism, and there was a positive correlation between hypothyroidism and (Vas, DAS28-ESR) numbers with a P-value = 0.0002.

In the study of Nazary and his colleagues in 2021 in the United States of America, the study pattern was a witness case, and the study lasted for a year. The study included 400 newly diagnosed rheumatoid disease patients and 400 controls [37]. The incidence of hypothyroidism was 7.75% of patients compared to 2.5% of controls, with P-value = 0.0007.

In a recent study conducted by Hung-Ming Huang and his colleagues in the first month of 2022 in Taiwan, which included 16,714 patients with rheumatoid disease and 66,856 controls, the average age of the patients was 51.5, with the disease controlling females by 75%, and the study showed an increased risk of infection [38]. Hypothyroidism in patients with rheumatoid disease, where the incidence of hypothyroidism was 1.74 times higher in patients with rheumatoid disease compared to the control group, and the effectiveness of the disease was clearly higher in patients with hypothyroidism compared to non-infected patients.

In contrast to our current study, the study was conducted by Emamifar and colleagues in Denmark in 2017 on 439 patients with rheumatoid disease. The percentage of hypothyroidism was (30.4%) of the patients [39]. There is no statistically significant difference between the effectiveness of rheumatoid disease and between the two groups of patients with hypothyroidism and non-hypothyroidism, and this may be explained by the difference in race, geographical location, and environmental variables.

In the study of Posselt and colleagues in 2017 in Brazil, which was conducted on 210 patients with rheumatoid disease and 141 controls, the incidence of hypothyroidism was 16.1% of patients and 11.3% of controls, and TPO antibodies were positive in 11.4% of patients compared to 5.6% of controls [40]. Controls: Then the study showed that there was no significant difference between the two groups of patients and controls in terms of the prevalence of hypothyroidism and TPO antibodies, and the study did not show any relationship between hypothyroidism and the effectiveness of rheumatoid disease.

In another Swedish study conducted by Waldenlind K and colleagues in 2020, which lasted from 2006 to 2016, patients were monitored over a period of 3-6 months after the start of treatment with methotrexate [41-69]. The study included 9004 patients with rheumatoid disease, and the percentage of hypothyroidism was 11% of the patients, and the percentage of antibody positivity was not studied. The study also showed a similarity in disease efficacy between the two groups of patients with hypothyroidism and non-hypothyroidism. This may be explained by environmental variables. Methotrexate treatment and patients' follow-up may have a role in increasing disease efficacy.

Limitations and Obstacles

The studied sample is taken from two university hospitals in Damascus, and it does not necessarily represent all patients in Syria, and it is preferable to conduct the study in all Syrian governorates. Patients who did not receive any disease-modifying treatment such as sulfasalazine and leunomide, whose effect on thyroid function has been shown in recent studies, and we did not study the effect of disease duration on it.

Conclusion and Proposals

Our study showed that there is a positive correlation between the presence of hypothyroidism and the degree of activity of rheumatoid disease estimated by (DAS28-ESR). It also showed that there are statistically significant differences between the presence of hypothyroidism and anti-TPO positivity in patients with rheumatoid disease and in controls, where early detection of hypothyroidism in the context of rheumatoid disease and its treatment may help reduce the effectiveness of the disease. Therefore, screening of thyroid function and TPO antibodies is recommended for all patients with rheumatoid disease, but more comprehensive studies are needed in order to generalize the results.

Declarations

The author asserts that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Specifically, ethics committee approval was not required as all subjects provided written Informed Consent prior to participation in the study.

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