# Common Autoimmune Diseases among Yemeni Patients in Sana'a City, Yemen

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**ABSTRACT**

**Objective:** To determine the most common autoimmune diseases (ADs) among Yemeni patients in Sana'a city.

**Methods:** This cross-sectional study was conducted in six health facilities in Sana'a city from January 2014 to July 2017. It prospectively recruited 131 patients with ADs and retrospectively included 1786 records of patients with ADs, totaling the sample size to 1917. Data about gender and age of prospective patients and as well as the gender, age and the type of AD from patients' records were collected using a pre-designed data collection sheet. Sera from patients' sera were investigated for autoantibodies to diagnose ADs using immunological techniques. Data were then analyzed and expressed using descriptive statistics.

**Results:** The majority of approximately two-thirds of patients with ADs attending the health facilities or record-retrieved were females, with a mean age of 32.35 ± 13.72 years (range: 1–89). Approximately half of the patients had a single type of either systemic or organ-specific ADs, while less than 1% had concurrent ADs. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) were the most frequent systemic ADs, being higher among females than males with male:female ratios of 1:4, 1:6 and 1:7, respectively. On the other hand, autoimmune hepatitis (AIH), Graves' disease, Hashimoto's disease and celiac disease (CD) were the most frequent organ-specific ADs. AIH was higher among males than females with a male:female ratio of 2:1, while Graves' and Hashimoto's diseases and CD were higher among females with a male:female ratio of 1:2–1:5. The most frequent concurrence between ADs was between SLE and RA (55.6%) as well as AIH and AIG (16.7%), being higher among females than males with male:female ratios of 1:9 and 1:2, respectively. SLE and AIH were equally concurrent between males and females, while the concurrence of other types of ADs was observed among females only.

**Conclusions:** AIH, RA and SLE are the most frequent ADs among Yemeni patients with a steady rise in the frequency of ADs over the period 2014-2017 in Sana'a city. Systemic and organ-specific ADs are comparably equal in distribution and concurrently present among approximately 1.0% of cases, with predominance among females compared to males. Population-based studies for the assessment of incidence/prevalence of ADs and the environmental factors associated with the trending increase in the prevalence of ADs in Yemen are issues for further studies.

**Keywords:** Autoimmune diseases, Autoimmune hepatitis, Rheumatoid arthritis, Systemic lupus erythematosus, Yemen

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## 1. Introduction

Autoimmune diseases (ADs) are a heterogeneous group of systemic or organ-specific disorders initiated by the loss of immunotolerance to self-antigens.[1, 2] The organ-specific ADs affect single body organs and include autoimmune thyroid diseases (AITD), multiple sclerosis (MS) and type 1 diabetes (T1D), while systemic ADs affect multiple body organs and include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic vasculitis.[3] There are more than 80 different types of ADs, which are more frequent among females than males (75% *vs.* 25%).[4, 5] Some ADs cluster within families and individuals such as SLE and MS, with many individuals developing more than one AD leading to polyautoimmunity.[6] For instance, multiple autoimmune syndrome occurs when a patient has three or more ADs.[7, 8]

Although the exact causes of ADs are not yet known, many factors can trigger ADs, including a familial genetic predisposition towards autoimmunity, epigenetics, gender and environmental triggers such as viruses, bacteria, drugs, sunlight, pollutants or stress.[7, 9] Immunological factors can also lead to the activation of autoreactive B and T cells.[10] ADs are characterized by a breakdown of central and peripheral immunotolerance mechanisms that allow the immune system to distinguish between self- and non-self antigens. Such mechanisms include polyclonal activation, cross-reactivity and tissue injury or infection.[11] There are three mechanisms of pathogenesis of ADs. The first mechanism involves autoantibodies directed against unmodified or modified intracellular or cell surface structures as occurs in Graves' disease, myasthenia gravis (MG) and Goodpasture's syndrome. The second mechanism involves the formation of autoantigen-autoantibody immune complexes in intercellular fluids or in the general circulation that ultimately mediate tissue damage as occurs in SLE and RA. The third mechanism involves the activation of cytotoxic T-cells as occurs in Hashimoto's thyroiditis, MS and T1D.[12, 13]

Diagnosis of ADs depends on clinical criteria and diagnostic tests to identify autoantibodies in the serum. However, the definitive diagnosis of ADs can be a lengthy process that requires repeated evaluation and monitoring.[14, 15] The prevalence of ADs is different across countries and varies from very rare like in MG to common like in AITD, SLE and RA.[16] To the best of our knowledge, no studies on the frequency of ADs have been published in Yemen except for few studies about single types of ADs. Therefore, this study was conducted to determine the most common ADs among Yemeni patients in Sana'a city – Yemen over the period 2014–2017.

## 2. Methods

### 2.1. Study design, setting and population

This cross-sectional study was conducted in six health facilities in Sana'a city from January 2014 to July 2017. It prospectively recruited 131 patients with ADs and retrospectively included 1786 records of patients with ADs, totaling the sample size to 1917. Four public health facilities (Al-Thawra Modern General Hospital, Kuwait University Hospital, Al-Sabeen Maternity and Childhood Hospital and National Center of Central Public Health Laboratories) and two private health facilities (University of Science and Technology Hospital and Al-Aulaqi Specialized Medical Laboratories) were included in the study.

### 2.2. Data and blood collection

After clinical examinations, data about the gender and age of prospective patients were collected using a standard data collection sheet and blood samples were collected by venipuncture. Data about the gender, age and the type of ADs were retrieved from the records of patients for retrospective analysis. Sera of patients were separated and investigated for autoantibodies by enzyme-linked immunosorbent assay (ELISA) and immunofluorescent assay (IFA) using commercially available

kits (Inova Diagnostics, Inc., San Diego, CA, USA) and by an automated Cobas e411 system with electrochemiluminescence immunoassay (ECLIA) using a commercially available kit provided (Roche Diagnostics GmbH, Mannheim, Germany.

The autoantibodies measured by ELISA included anti-dsDNA antibodies for SLE; cyclic citrullinated peptide (CCP) antibodies for RA; anti-phospholipid (APL) antibodies, anti-cardiolipin antibodies (ACA) and anti-β2 glycoprotein (β2GP) for antiphospholipid syndrome (APS); liver/kidney/microsomal (LKM) antibodies for the diagnosis of autoimmune hepatitis (AIH); mitochondrial (M2) antibodies for primary biliary cirrhosis (PBC); proteinase (PR3) antibodies Wegener's granulomatosis; myeloperoxidase (MPO) antibodies for vasculitis; anti-*Saccharomyces cerevisiae* antibodies (ASCA) for Crohn's disease and ulcerative colitis; centromere antibodies for calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia (CREST) syndrome; Jo-1 antibodies for the diagnosis of polymyositis (PM); scleroderma-70 (Scl-70) antibodies for systemic sclerosis (SSc); SS-A and SS-B antibodies for Sjogren's syndrome (SS); ribonucleoprotein (RNP) antibodies for mixed connective tissue disease (MCTD); anti-tissue transglutaminase (tTG) antibodies (IgG and IgA) and anti-gliadin (IgG and IgA) antibodies for celiac disease (CD) and anti-acetylcholine antibodies for MG.

The autoantibodies measured by IFA included anti-nuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) for AIH; anti-mitochondrial antibodies (AMA) for PBC; endomysial antibodies (EMA) for CD; anti-neutrophil cytoplasmic antibodies (ANCA) for vasculitis, inflammatory bowel diseases (IBD) and Wegner's granulomatosis; anti-gastric parietal cell antibodies (AGPA) for autoimmune gastritis (AIG); anti-islet antibodies for T1D.

The autoantibodies measured by ECLIA included anti-thyroglobulin (Tg), anti-thyroid stimulation hormone (TSH) receptor and anti-thyroperoxidase (TPO) antibody for Hashimoto's and Graves' diseases.

## 2.3. Statistical analysis

Data were analyzed using IBM SPSS Statistics, version 21.0 21 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation (SD), while qualitative variables were presented as frequencies and proportions.

## 3. Results

### 3.1. Characteristics of patients with ADs

Table (1) shows that the majority of approximately two-thirds of patients with ADs attending the health facilities or record-retrieved were females, with a mean age of 32.35 ± 13.72 years (range: 1–89). In addition, most patients with ADs attending health facilities and those record-retrieved were aged 16-30 years (37.4% *vs.* 47.2%) and 31-45 years (35.1% *vs.* 29.8%), respectively.

**Table 1.** Characteristics of patients with ADs attending and record-retrieved from six health facilities in Sana'a city, Yemen (2014–2017)

| Characteristic | Study patients (N = 131) | | Record-retrieved patients (N = 1786) | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Gender** | | | | |
| Male | 40 | (**30.5**) | 570 | (**31.9**) |
| Female | 91 | (**69.5**) | 1216 | (**68.1**) |
| **Age** (years) | | | | |
| Mean ± SD: | 32.35 ± 13.72 | | | |
| Range: 1–89 | | | | |
| ≤15 | 13 | (**9.9**) | 134 | (**7.5**) |
| 16-30 | 49 | (**37.4**) | 843 | (**47.2**) |
| 31-45 | 46 | (**35.1**) | 533 | (**29.8**) |
| 46-60 | 19 | (**14.5**) | 222 | (**12.5**) |
| 61-75 | 4 | (**3.1**) | 49 | (**2.7**) |
| >75 | 0 | (**0.0**) | 5 | (**0.3**) |

SD, standard division.

### 3.2. Annual trend of diagnosed ADs

Table (2) shows that the ADs were most frequently diagnosed from August 2016 to the end of the same year. However, the least frequent proportions of ADs were diagnosed from the beginning of 2017 until July of the same year.

**Table 2.** Trend of diagnosed ADs in six health facilities in Sana'a city over the period 2014–2017

| Year of diagnosis | Patients with ADs attending health facilities and record-retrieved | |
|---|---|---|
| | n | (%) |
| 2014 | 505 | (**26.34**) |
| 2015 | 570 | (**29.74**) |
| 2016* | 753 | (**39.28**) |
| 2017* | 89 | (**4.64**) |
| **Total** | 1917 | (**100.0**) |

ADs, autoimmune diseases; * From August 2016 to July 2017.

### 3.3. Types of ADs among Yemeni patients

Table (3) shows that a half of ADs diagnosed among patients attending or record-retrieved from health facilities in Sana'a city had systemic ADs followed by those having organ-specific ADs (48.88%). However, less than 1% had concurrent disorders.

**Table 3.** Types of ADs among patients attending and record-retrieved from six health facilities in Sana'a city, Yemen (2014–2017)

| Types of ADs | n | (%) |
|---|---|---|
| Systemic | 962 | (**50.18**) |
| Organ-specific | 937 | (**48.88**) |
| Concurrent ADs | 18 | (**0.94**) |
| **Total** | **1917** | (**100.00**) |

ADs, autoimmune diseases.

### 3.4. Distribution of individual ADs among Yemeni patients by gender

Table (4) shows that RA (39.2%), SLE (36.9%) and APS (16.4%) were the most frequent systemic ADs, being higher among females than males with male:female ratios of 1:4, 1:6 and 1:7, respectively. On the other hand, AIH (50.7%), Graves' disease (16.0%), Hashimoto's disease (10.7%) and CD (10.7%) were the most frequent organ-specific ADs. AIH was higher among males than females with a male:female ratio of 2:1, while Graves' and Hashimoto's diseases and CD were higher among females with a male:female ratio of 1:2–1:5. The most frequent concurrence between ADs was between SLE and RA (55.6%) as well as AIH and AIG (16.7%), being higher among females than males with male:female ratios of 1:9 and 1:2, respectively. SLE and AIH were equally concurrent between

males and females, while the concurrence of other types of ADs was observed among females only.

**Table 4.** Age-distribution of different types of ADs among patients attending or record-retrieved from six health facilities in Sana'a city, Yemen (2014–2017)

| Type of ADs | Gender | | | Male:female ratio |
|---|---|---|---|---|
| | **Male** n (%) | **Female** n (%) | **Total** n (%) | |
| **Systemic ADs** (N = 962) | | | | |
| RA | 73 (**7.6**) | 304 (**31.6**) | 377 (**39.2**) | 1:4 |
| SLE | 55 (**5.7**) | 300 (**31.2**) | 355 (**36.9**) | 1:6 |
| APS | 19 (**2.0**) | 139 (**14.4**) | 158 (**16.4**) | 1:7 |
| SS | 3 (**0.3**) | 22 (**2.3**) | 25 (**2.6**) | 1:7 |
| MCTD | 2 (**0.2**) | 15 (**1.6**) | 17 (**1.8**) | 1:8 |
| SSc | 1 (**0.1**) | 14 (**1.5**) | 15 (**1.6**) | 1:7 |
| Vasculitis | 3 (**0.3**) | 4 (**0.4**) | 7 (**0.7**) | 1:1 |
| PM | 3 (**0.3**) | 2 (**0.2**) | 5 (**0.5**) | 1:1 |
| Wegner's granulomatosis | 2 (**0.2**) | 0 (**0.0**) | 2 (**0.2**) | - |
| CREST syndrome | 0 (**0.0**) | 1 (**0.1**) | 1 (**0.1**) | - |
| **Organ-specific ADs** (N = 937) | | | | |
| AIH | 322 (**34.8**) | 153 (**16.3**) | 475 (**50.7**) | 2:1 |
| Graves' disease | 27 (**2.9**) | 123 (**13.1**) | 150 (**16.0**) | 1:5 |
| Hashimoto's disease | 18 (**1.9**) | 82 (**8.8**) | 100 (**10.7**) | 1:5 |
| CD | 36 (**3.8**) | 64 (**6.8**) | 100 (**10.7**) | 1:2 |
| MG | 17 (**1.8**) | 30 (**3.2**) | 47 (**5.0**) | 1:2 |
| PBC | 10 (**1.1**) | 16 (**1.7**) | 26 (**2.8**) | 1:2 |
| AIG | 5 (**0.5**) | 6 (**0.6**) | 11 (**1.2**) | 1:1 |
| Crohn's disease | 4 (**0.4**) | 6 (**0.6**) | 10 (**1.1**) | 1:2 |
| T1D | 4 (**0.4**) | 5 (**0.5**) | 9 (**1.0**) | 1:1 |
| Ulcerative colitis | 3 (**0.3**) | 6 (**0.6**) | 9 (**1.0**) | 1:2 |
| **Concurrent ADs** (N =18) | | | | |
| SLE-RA | 1 (**5.6**) | 9 (**50.0**) | 10 (**55.6**) | 1:9 |
| AIH-AIG | 1 (**5.6**) | 2 (**11.1**) | 3 (**16.7**) | 1:2 |
| SLE-AIH | 1 (**5.6**) | 1 (**5.6**) | 2 (**11.1**) | - |
| SLE-SS | 0 (**0.0**) | 1 (**5.6**) | 1 (**5.6**) | - |
| SLE-MCTD | 0 (**0.0**) | 1 (**5.6**) | 1 (**5.6**) | - |
| APL-SS | 0 (**0.0**) | 1 (**5.6**) | 1 (**5.6**) | - |

ADs, autoimmune diseases; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; SS, Sjogren's syndrome; MCTD, mixed connective tissue diseases; SSc, systemic sclerosis; PM, polymyositis; CREST, calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; AIH, autoimmune hepatitis; CD, celiac disease; MG, myasthenia gravis; PBC, primary biliary cirrhosis; AIG, autoimmune gastritis; T1D, type 1 diabetes.

## 4. Discussion

ADs include a wide spectrum of chronic conditions that may affect specific organs or multiple systems with a significant burden on the quality of life.[17] These are initiated by the loss of immunotolerance and mediated through T- or B-cell activation, leading to tissue damage. ADs are on the rise worldwide in the past decades, particularly in developed countries,[18] but limited information on their prevalence is available from developing countries, including Yemen.

The present study revealed a steady rise in the frequency of ADs in the past few years in Sana'a city between 2014 and mid2017. This finding is consistent with that reported elsewhere in the developing and developed countries about the accumulating rise in the frequency of ADs in the last decades.[18-21] The rise of patients with ADs can be explained by socioeconomic factors, particularly in selected migrant populations, in addition to environmental, racial, geographical and genetic factors as well as the increased public/professional awareness and the improved diagnostic techniques of ADs.[14, 18, 20, 22, 23]

The study revealed that approximately 99% of patients had one type of ADs, while the remaining 1% were affected by two different ADs. This result is consistent with those reported from Denmark and Italy.[24, 25] The proportions of systemic and organ-specific ADs were comparably equal, accounting to half of the patients each. This finding disagrees with that reported elsewhere, where organ-specific ADs were the most frequent.[18, 22, 24, 26]

RA, SLE and APS were the most frequent systemic ADs, which were different from those reported from some western countries such as USA, Denmark and Italy as well as among the US veterans in Iraq and Afghanistan.[18, 24, 25, 27] The higher frequency of ADs in females compared to males in the present study is in agreement with that reported elsewhere.[22, 25–27] The predominance of ADs in females may be explained by the effect of sex hormones on the immune system leading to its dimorphism with females having higher immunoglobulin levels and mounting stronger humoral immune responses than males. Genetic differences in genetic factors between males and females had led researchers to think that the genetic background of ADs is also related to the genetic determinants of gender.[5, 23, 28–30]

The majority of patients with ADs in the present study were adults, and this is in line with that reported from Western countries.[18, 19] This may be explained by the fact that increased sex hormones may play an important role in triggering the disease and/or more exposure to risk factors of ADs in adulthood.[28]

## 5. Conclusions

AIH, RA and SLE are the most frequent ADs among Yemeni patients with a steady rise in the frequency of ADs over the period 2014- mid-2017 in Sana'a city. Systemic and organ-specific ADs are comparably equal in distribution and concurrently present among approximately 1.0% of cases, with predominance among females compared to males. Population-based studies for the assessment of incidence/prevalence of ADs and the environmental factors associated with the trending increase in the prevalence of ADs in Yemen are issues for further studies.

## Ethical considerations

This study was approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen. Written informed consent was obtained from all patients who voluntarily agreed to participate in the study.

## Acknowledgments

## Authors' contributions

All authors contributed equally to the design, implementation, statistical analysis and manuscript drafting. They also read and approved the final version of the submitted manuscript.

## Competing interests

The authors declare that they have no competing interests associated with this article.

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