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Original Article

Ultrasonographic evaluation of gastrointestinal system involvement in chronic inflammatory rheumatic diseases

Okan Kucukakkas[1], Teoman Aydin[1], Mehmet Ali Gultekin[2]

[1]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey
[2]Department of Radiology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey

Abstract

Aim: Although chronic inflammatory rheumatic diseases (CIRDs) primarily affect the joints due to arthritis; involvement of other systems and organs is not rare. Ultrasound evaluations are particularly useful in the detection of pathologies observed in the gastrointestinal tract. The aim of this study was to investigate and compare the results of abdominal ultrasonography in gastrointestinal system of some common chronic inflammatory rheumatic diseases.

Material and Methods: 96 patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis were included in the study. The data of patients were retrospectively reviewed from patient files and hospital database. Patients with abdominal ultrasound performed for the check-up indication in the last 6 months and updated laboratory tests in the last 1 month were included in the study. The patients were divided into three groups according to the diagnosis and the results were compared.

Results: No gastrointestinal system involvement was observed in the patients except liver and gallbladder pathologies. The most frequent liver pathologies were hepatosteatosis (49.0%) and hepatomegaly (41.7%), respectively. The rate of patients with cholecystectomy was 8.3% and 6.3% of the patients had gallstones. When the results were compared between the groups, it was seen that only the incidence of gallstones was significantly higher in the psoriatic arthritis group than in other groups.

Conclusion: In the course of chronic inflammatory rheumatic diseases, many organ and system involvement may be observed. Abdominal ultrasound imaging, especially in patients with additional risk factors, may be useful for early detection of many intra-abdominal organ pathologies, especially the gastrointestinal tract.

Keywords: Gastrointestinal system; rheumatic diseases; ultrasound

INTRODUCTION

Rheumatology covers a wide range of diseases affecting several organ systems. These diseases develop due to various pathogenic mechanisms and cause limitations in functionality, reduced quality of life, and increased mortality. With some of them being more common and others being very rare, there are over 200 chronic inflammatory rheumatic diseases (CIRD) worldwide. Rheumatoid arthritis (RA), spondyloarthropathies (SPA), systemic lupus erythematosus (SLE) and gout are the most well-known and frequently observed ones of these diseases. In a study conducted in the USA, the risk of developing CIRD for lifetime was calculated to be 1/12 in women and 1/20 in men. Although CIRDs primarily affect the joints due to arthritis, involvement of other systems and organs is not rare (1).

RA is the most common of all CIRDs. Erosion that develops in cartilage and bone together with inflammation of the joint sheath leads to joint deformities and progressive physical disability. It affects approximately one in every 100 people around the world and is 2 times more common in women than in men (2). Axial spondyloarthropathy (AxSPA) is a chronic inflammatory disease that primarily affects the spine and the joint connections of the spine and pelvis and may cause bone formation, leading to spinal fusion. In addition to inflammation of the joints and tendons, psoriasis, inflammatory bowel disease and ocular findings (uveitis, etc.) may accompany. The disease has two stages. In non-radiographic AxSPA, joint is observed to be normal in radiographs. Radiographic findings develop in its following form and are called ankylosing spondylitis (AS). Approximately 0.9% of people in the world are affected by AS (3). Psoriatic arthritis (PSA), another member of the spondyloarthropathy family, is a chronic inflammatory disease characterized by inflammation of the synovial tissue, tendons and skin (14). In 40-60% of PSA patients, erosive and deformity-inducing joint complications are observed. PSA-induced joint damage can affect a person's work and social relationships (4).

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Corresponding Author: Okan Kucukakkas, Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey **E-mail:** okan4494@yahoo.com

Although the management of existing CIRDs may facilitate suppression of disease activity and improvement of function, comorbidities such as cardiovascular diseases, renal diseases, lung diseases, infection, malignancy, osteoporosis, gastrointestinal diseases, hemopoietic system problems and depression remain an important issue (5). Failure to notice these involvements can lead to many damages and disabilities (1).

Ultrasound (US) imaging is the most widely used non-invasive imaging method in radiology departments and has been used in clinical practice since the early 1970s. It is recognized as a valuable tool in the diagnosis and follow-up of many conditions, including the initial evaluation of hepatobiliary system and pancreatic disorders, renal colics, gynaecological diseases, especially ovarian masses (6). In this respect, a detailed abdominal examination with US in terms of intraabdominal pathologies associated with gastrointestinal system (GIS), which may be observed in the course of CIRDs, can be very useful for early diagnosis and treatment.

This study aimed to analyse intraabdominal GIS pathologies by total abdominal US in some of the most frequently observed CIRDs, to compare the incidence of these pathologies in different rheumatic diseases and to investigate their possible relationships with other clinical and laboratory parameters.

MATERIAL and METHODS

This study was approved by the Bezmialem Vakıf University Faculty of Medicine Ethics Committee. The study was conducted in accordance with the ethical principles described by the Declaration of Helsinki. A total of 96 CIRD patients (32 male, 64 female) who were followed up at the Physical Medicine and Rehabilitation Clinic of Bezmialem Vakıf University were included in the study. The patients were divided into three groups by the diagnoses of RA, AS and PSA as three most common CIRDs in our clinic practice. The patients who met the 2010 ACR/EULAR classification criteria for the RA group (7), the 2006 CASPAR classification criteria for the PSA group, (8) and the ASAS classification criteria for the AS group (9) were included in the study. Other inclusion criteria for the patients were to be between the ages of 18-65, to have been diagnosed with the disease for at least 3 years, to have the clear and detailed results of total abdominal US, which was performed in the last 6 months and requested for check-up purposes in the hospital records, and to have updated laboratory and demographic data in the last 1 month. Patients with other autoimmune or rheumatic diseases, malignancies, signs of active infection, and insufficient data records were excluded from the study. The files of the patients were retrospectively reviewed, and their demographic data (age, sex, body mass index (BMI), smoking, alcohol use, comorbid diseases, duration of disease diagnosis), laboratory results [C-reactive protein (CRP), sedimentation, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglyceride, haemoglobin (HGB), haematocrit (HCT), white blood cell (WBC), platelet (PLT), aspartate transaminase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP)], drug utilization history, and disease activity scores were recorded. When reviewing the drug utilization history, patients who had received their current treatment for at least 6 months were included in the study for a more significant correlation between drug utilization and clinical and US findings. Disease activity levels were calculated using the Disease Activity Score-28 (DAS28) based on evaluation of 28 joints for RA, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for AS, and the Disease Activity Score in Psoriatic Arthritis (DAPSA) for PSA. Existing comorbid diseases were obtained from the anamnesis information of the patients.

Ultrasound

Total abdominal US imaging was performed according to the local protocols of the hospital. Patients requesting check-up for rheumatic disease as indication were included. The procedure was performed by radiologists who are experienced in abdominal US and know the diagnosis of the disease. Images that were requested for other preliminary diagnoses (appendicitis, cholecystitis, etc.) other than the check-up indication were not included in the study. Patients with US results that were not optimally evaluated, especially gas artefact, were also excluded from the study too. All findings related to GIS from US reports were noted in detail. The staging of the patients with hepatosteatosis was performed as follows: Grade 1: Minimal diffuse increase in echogenicity, with normal diaphragm and intrahepatic vessel walls; Grade 2: Moderate diffuse increase in echogenicity, slight deterioration in the visualization of the diaphragm and intrahepatic vessel walls, Grade 3: Marked increase in echogenicity, severe or complete deterioration in the visualization of diaphragm, intrahepatic vessel walls and posterior segment of the right lobe (10).

Statistical Analysis

The data were analysed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA) statistical software package for Windows. For the descriptive statistics of the study, the continuous variables were expressed as mean±standard deviation, and frequencies and percentages were used for the categorical variables. Shapiro-Wilks test was performed for the distribution conformity of the data, and homogeneous distribution of variances were analysed using Levene's test. When comparing the groups, one-way ANOVA test was used for the data with normal distribution. If significant differences were observed, post-hoc analysis was performed to observe between which subgroups there were differences. The data with no normal distribution were compared using Kruskal-Wallis test. If there was a significant difference, Mann-Whitney U test was performed with Bonferroni correction to observe between which subgroups there were differences. The chi-square test was performed to determine whether the nominal variables differed by the groups. Correlations

of the data were evaluated with Spearman's Correlation Coefficient. The p<0.05 values were considered statistically significant.

RESULTS

A total of 96 patients (32 RA, 33 AS and 31 PSA patients) were included in the study. The number of women in the PSA group was significantly higher than in the AS group. The number of comorbidity observed in the AS patients was significantly lower than in the other groups. The use of non-steroidal anti-inflammatory drugs (NSAIDs) and biologic disease-modifying drugs (bDMARDs) was significantly higher in the AS patients than in other groups, while the use of conventional synthetic disease-modifying drugs (csDMARDs) was lower. Corticosteroid use was higher in the RA group compared to other groups. Detailed nominal demographic data of the patients and comparison of these data between groups are shown in Table 1.

Table 1. Comparison of groups in terms of nominal demographic data

	RA n (%)	AS n (%)	PSA n (%)	TOTAL n (%)	p
Gender					
Male	10 (10.4%) [a,b]	18 (18.8%) [b]	4 (4.2%) [a]	32 (33.3%)	
Female	22 (22.9%) [a,b]	15 (15.6%) [b]	27 (28.1%) [a]	64 (66.7%)	**0.002[q]**
Cigarette					
Yes	10 (10.4%)	10 (10.4%)	11 (11.5%)	31 (32.3%)	
No	22 (22.9%)	23 (24.0%)	20 (20.8%)	65 (67.7%)	0.896[q]
Alcohol					
Yes	1 (1.0%)	2 (2.1%)	4 (4.2%)	7 (7.3%)	
No	31 (32.3%)	31 (32.3%)	27 (28.1%)	89 (92.7%)	0.310[q]
Comorbidities					
Yes	19 (19.8%) [a]	5 (5.2%) [b]	17 (17.7%) [a]	40 (41.7%)	
No	13 (13.5%) [a]	28 (29.2%) [b]	14 (14.6%) [a]	56 (58.3%)	**0.000[q]**
NSAIDs					
Yes	16 (16.7%) [a,b]	23 (24.0%) [b]	11 (11.5%) [a]	50 (52.1%)	
No	16 (16.7%) [a,b]	10 (10.4%) [b]	20 (20.8%) [a]	46 (47.9%)	**0.023[q]**
Corticosteroids					
Yes	25 (26.0%) [a]	2 (2.1%) [b]	7 (7.3%) [b]	34 (35.4%)	
No	7 (7.3%) [a]	31 (32.3%) [b]	24 (25.0%) [b]	62 (64.6%)	**0.000[q]**
DMARDs					
Yes	30 (31.3%) [a]	6 (6.3%) [b]	26 (27.1%) [a]	62 (64.6%)	
No	2 (2.1%) [a]	27 (28.1%) [b]	5 (5.2%) [a]	34 (35.4%)	**0.000[q]**
Biologics					
Yes	11 (11.5%) [a]	28 (29.2%) [b]	12 (12.5%) [a]	55 (57.3%)	
No	21 (21.9%) [a]	5 (5.2%) [b]	19 (19.8%) [a]	41 (42.7%)	**0.000[q]**

[q]: Chi-square test; NSAID: Non-Steroidal Anti-Inflammatory Drug; DMARD: Disease-Modifying Anti-Rheumatic Drug; ***Each superscript letter ([a,b]) denotes a subset of disease categories whose column proportions do not differ significantly from each other at the 0,05 level

The mean age of the AS patients was significantly lower than the other groups. There was no significant differences in other demographic data such as BMI and disease duration. In the laboratory tests, HGB and HCT levels were significantly lower in the PSA patients than in the AS patients. Numerical demographic data and comparison of all laboratory measurements between groups are shown in Table 2 in detail.

Comorbid diseases were compared between groups. Renal dysfunction [glomerular filtration rate (eGFR) <60 ml/min/1.73 m2] was significantly more frequent in the PSA paitents than in the AS patients, and so was HT in the RA patients than in the PSA patients, DM in the PSA patients than in the AS patients, and osteoporosis in the RA patients than in the AS patients. A detailed comparison of comorbid diseases between groups is shown in Table 3.

Table 2. Comparison of numerical demographic data and laboratory results of the groups

	RA n=32 Mean ± SD	AS n=33 Mean ± SD	PSA n=31 Mean ± SD	TOTAL n=96 Mean ± SD	p	Difference between groups
Age	49.3 ± 8.2	40.4 ± 11.9	49.1 ± 11.3	46.18 ± 11.2	**0.01***	**RA vs. AS: 0.03[b]** **RA vs. PSA: 1.000[b]** **AS vs. PSA: 0.04[b]**
BMI (kg/m^2)	27.0 ± 3.1	27.5 ± 3.0	27.6 ± 4.3	27.3 ± 3.5	0.746*	
Disease Duration (years)	10.0 ± 5.7	8.8 ± 6.0	10.2 ± 6.9	9.6 ± 6.1	0.628[k]	
Sedimentation (mm/h)	17.0 ± 10.7	13.5 ± 10.3	18.8 ± 13.6	16.3 ± 11.6	0.169[k]	
CRP(mg/L)	12.8 ± 16.4	9.6 ± 12.9	7.7 ± 14.2	10.0 ± 14.5	0.729[k]	
HGB (gr/dl)	12.9 ± 1.8	13.6 ± 1.5	12.5 ± 2.0	13.0 ± 1.81	**0.034***	RA vs. AS:0.350[b] RA vs. PSA:0.950[b] **AS vs. PSA:0.031[b]**
HCT (%)	40.0 ± 4.5	41.6 ± 4.2	38.5 ± 5.1	40.0 ± 4.7	**0.029***	RA vs. AS:0.490[b] RA vs. PSA:0.585[b] **AS vs. PSA:0.024[b]**
WBC (10^3/ul)	7.9 ± 1.8	7.9 ± 1.9	7.3 ± 2.1	7.72 ± 1.9	0.315*	
PLT (10^3/ul)	247.0 ± 66.0	271.9 ± 74.1	253.2 ± 61.7	257.5 ± 67.6	0.306*	
ALT (U/L)	20.0 ± 7.6	25.2 ± 13.4	26.2 ± 17.2	23.7 ± 13.4	0.360[k]	
AST (U/L)	18.8 ± 5.2	18.9 ± 4.6	21.9 ± 7.7	19.8 ± 6.04	0.298[k]	
GGT (U/L)	31.0 ± 21.3	31.4 ± 14.6	28.6 ± 13.5	30.3 ± 16.6	0.471[k]	
ALP (U/L)	83.8 ± 26.4	87.5 ± 24.1	84.9 ± 26.0	85.4 ± 25.3	0.638[k]	
LDL (mg/dl)	117.5 ± 29.7	128.9 ± 37.0	126.0 ± 31.3	124.1 ± 32.8	0.405[k]	
HDL (mg/dl)	45.8 ± 9.7	46.7 ± 10.5	48.3 ± 13.7)	46.8 ± 11.32	0.746[k]	
Total Cholesterole (mg/dl)	188.7 ± 32.8	201.1 ± 39.2	201.2 ± 38.1	196.9 ± 32.8	0.396[k]	
Triglycerides (mg/dl)	145.9 ± 57.9	149.8 ± 58.7	129.8 ± 43.0	142.0 ± 53.9	0.438[k]	

***: One way anova test, [k]: Kruskal Wallis test, [b]: bonferroni test, [m]: Mann Whitney U test**
The groups were compared with one way anova test for normal distributed data. Post hoc analysis was performed to observe which subgroups differed if there was a significant difference.
Data without normal distribution were compared with Kruskal Wallis test. If there was a significant difference, mann whitney u test was performed with bonferroni correction in order to observe the difference between the subgroups.
BMI; Body Mass Index, CRP; C-Reactive Protein, HDL; High-Density Lipoprotein, LDL; Low-Density Lipoprotein, HGB; Hemoglobin, HCT; Hemotacrit, WBC; White Blood Cell, PLT; Platelet, AST; Aspartate Transaminase, ALT; Alanine Aminotransferase, GGT; Gamma Glutamyl Transpeptidase, ALP; Alkaline Phosphatase

Concerning the disease activity levels, the mean DAS28 score was 4.10±1.34 for RA patients, the mean BASDAI score was 5.06±1.92 for AS patients, and the mean DAPSA score was 17.86±11.38 for PSA patients. The correlation between disease activity levels and demographic data and laboratory tests was examined using Spearman's correlation coefficient. There was a strong positive correlation between DAS28 and CRP in the RA patients. There were moderate correlations with age and sedimentation, weak positive correlations with corticosteroid use, WBC, ALP and LDL levels. In the AS patients, there was a strong positive correlation with CRP, a moderate positive correlation with sedimentation, and weak positive correlations with BMI and corticosteroid use. In the PSA patients, there was a strong positive correlation with CRP, a moderate positive correlation with sedimentation, and weak positive correlations with age, female gender, BMI and disease duration. There was also a weak negative correlation with HGB in the PSA patients. The detailed correlation analysis between disease activity and clinical and laboratory parameters is shown in Table 4.

Analysis of Ultrasound Results

US results of the patients were evaluated. No GIS involvement was observed in the patients except liver and gallbladder pathologies. The most frequent liver pathologies were hepatosteatosis (49.0%) and hepatomegaly (41.7%), respectively. The rate of patients with cholecystectomy was 8.3% while and 6.3% of the patients had gallstones. When the results were examined between the groups, only the incidence of gallstones was significantly higher in the PSA group than in the other groups. The distribution of ultrasound results among the 3 groups is shown in Table 5.

Table 3. Comparison of comorbid diseases between groups

	RA n (%)	AS n (%)	PSA n (%)	PSA n (%)	P
Lipid Metabolism Disorder					
Yes	18 (18.8%)	23 (24.0%)	22 (22.9%)	63 (65.6%)	
No	14 (14.6%)	10 (10.4%)	9 (9.4%)	33 (34.4%)	0.390[q]
Renal Dysfunction					
Yes	7 (7.3%) [a,b]	3 (3.1%) [b]	13 (13.5%) [a]	23 (24.0%)	
No	25 (26.0%) [a,b]	30 (31.3%) [b]	18 (18.8%) [a]	73 (76.0%)	**0.008**[q]
Hypertension					
Yes	12 (12.5%) [a]	3 (3.1%) [b]	11 (11.5%) [a]	26 (27.1%)	
No	20 (20.8%) [a]	30 (31.3%) [b]	20 (20.8%) [a]	70 (72.9%)	**0.016**[q]
Diabetes					
Yes	7 (7.3%) [a,b]	2 (2.1%) [b]	10 (10.4%) [a]	19 (19.8%)	
No	25 (26.0%) [a,b]	31 (32.3%) [b]	21 (21.9%) [a]	77 (80.2%)	**0.030**[q]
Osteoporosis					
Yes	8 (8.3%) [a]	0 (0.0%) [b]	3 (3.1%)[a,b]	11 (11.5%)	
No	24 (25.0%) [a]	22 (34.4%) [b]	28 (29.2%) [a,b]	85 (88.5%)	**0.006**[q]
Thyroid Metabolism Disorder					
Yes	2 (2.1%)	1 (1.0%)	1 (1.0%)	4 (4.2%)	
No	30 (31.3%)	32 (33.3%)	30 (31.3%)	92 (95.8%)	0.770[q]
Heart failure					
Yes	3(3.1%)	2 (2.1%)	0 (0.0%)	5 (5.2%)	
No	29 (30.2%)	31 (32.3%)	31 (32.3%)	91 (94.8%)	0.237[q]

[q]: Chi-square test, Each superscript letter ([a,b]) denotes a subset of disease categories whose column proportions do not differ significantly from each other at the 0,05 level

Table 4. Spearman correlation analysis between disease activity levels and demographic / laboratory parameters

	DAS28 (RA)	BASDAI (AS)	DAPSA (PSA)
Age	**.557****	-.011	**.670****
Gender	.288	-.087	**.409***
BMI	.312	**.375***	**.458****
Disease Duration	.223	.183	**.415***
Corticosteroid use	**.409***	**.387***	.125
Sedimentation	**.633****	**.680****	**.556****
CRP(mg/L)	**.859****	**.861****	**.803****
HGB (gr/dl)	-.296	-.276	**-.368***
WBC (103/ul)	**.357***	.116	.283
ALP (U/L)	**.443***	-.122	.342
LDL (mg/dl)	**.381***	.222	,188

*:p<0.05, **:p<0.01
Other clinical and laboratory data showed no statistically significant correlation. BMI; body mass index, CRP; C-Reactive Protein, LDL; Low-Density Lipoprotein, HGB; Hemoglobin, WBC; White Blood Cell, ALP; Alkaline Phosphatase

The relationship between the US results and demographic data and laboratory results of the patients were also examined. For a more understandable and statistically significant analysis, ultrasound results were grouped and analysed as liver and gallbladder pathology separately. The most remarkable findings were that DAS28, one of the disease activity parameters, was moderately correlated with the presence of any liver US pathology, and strongly correlated with the presence of hepatomegaly, and that the DAPSA score was moderately correlated with the presence of liver pathology. No correlation was observed between BASDAI score and US findings. There were no significant correlations between US findings and sex, presence of asthma, presence of osteoporosis, methotrexate / sulphasalazine / hydroxychloroquine / NSAIDs / corticosteroid / bDMARD use, WBC and PLT count, and AST, ALT, HDL levels.

The correlation analysis of US groups with demographic and laboratory parameters is shown in Table 6.

Table 5. Distribution of abdominal USG scans between patient groups in terms of GIS findings

	RA (n=32) n (%)	AS (n=33) n (%)	PSA (n=31) n (%)	TOTAL (n=96) n (%)	p
Hepatosteatosis					
Yes	12 (12.5%)	17 (17.7%)	18 (18.8%)	47 (49.0%)	
Grade 1	7 (7.3%)	9 (9.4%)	11 (11.5%)	27 (28.1%)	
Grade 2	5 (5.2%)	7 (7.3%)	5 (5.2%)	17 (17.7%)	
Grade 3	0 (0.0%)	1 (1.0%)	2 (2.1%)	3 (3.1%)	
No	20 (20.8%)	16 (16.7%)	13 (13.5%)	49 (51.0%)	0.561[q]
Hepatomegalia					
Yes	12 (12.5%)	14 (14.6%)	14 (14.6%)	40 (41.7%)	
No	20 (20.8%)	19 (19.8%)	17 (17.7%)	56 (58.3%)	0.822[q]
Liver calcific granuloma					
Yes	2 (2.1%)	0 (0.0%)	1 (1.0%)	3 (3.1%)	
No	30 (31.3%)	33 (34.4%)	30 (31.3%)	93 (96.9%)	0.350[q]
Liver Cyst					
Yes	2 (2.1%)	0 (0.1%)	2 (2.1%)	4 (4.2%)	
No	30 (31.3%)	33 (34.4%)	29 (30.2%)	92 (95.8%)	0.335[q]
Gall bladder cyst					
Yes	1 (1.0%)	1 (1.0%)	3 (3.1%)	5 (5.2%)	
No	31 (32.3%)	32 (33.3%)	28 (29.2%)	91 (94.8%)	0.396[q]
Cholecystectomi					
Yes	1 (1.0%)	3 (3.1%)	4 (4.2%)	8 (8.3%)	
No	31 (32.3%)	30 (31.3%)	27 (28.1%)	88 (91.7%)	0.366[q]
Gall bladder stone					
Yes	0 (0.0%) [a]	0 (0.0%) [a]	6 (6.3%) [b]	6 (6.3%)	
No	32 (33.3%) [a]	33 (34.4%) [a]	25 (26.0%) [b]	90 (93.8%)	**0.001[q]**
Gall bladder wall enlargment					
Yes	1 (1.0%)	0 (0.0%)	4 (4.2%)	5 (5.2%)	
No	31 (32.3%)	33 (34.4%)	27 (28.1%)	91 (64.8%)	0.055[q]

[q]: Chi-square test, Each superscript letter (a,b) denotes a subset of disease categories whose column proportions do not differ significantly from each other at the 0,05 level

Table 6. Spearman correlation analysis between USG findings and clinical/laboratory parameters

	All pathologies of liver	All pathologies of the gallbladder	NAFLD	Hepatomegaly	Cholecystectomy	Gallstone
Age	**.407****	**.300****	**.293****	**.435****	.169	.180
BMI	**.397****	**.203***	**.395****	**.374****	**.209***	.084
Disease duration	**.325****	.097	**.269****	**.436****	.136	-.037
Cigarette	**-.261***	-.070	-.142	-.177	-.047	.006
Alcohol	**.346****	.125	**.275****	**.237***	.085	.072
≥ 1 comorbidities	**.268****	.179	**.208***	**.338****	-.032	**.212***
Hypertension	**.206***	.168	.153	**.293****	.071	.133
Diabetes	.135	**.269****	.089	.164	.039	.196
Hypothyroidism	.169	.187	**.213***	**.247***	.126	.162
Heart failure	.190	.021	.146	**.277****	.099	-.061
Hyperlipidemia	**.221***	**.265****	.138	**.211***	.139	.187
Renal dysfunction	**.305****	**.404****	**.231***	**.417****	.007	**.460****
The use of leflunomide	**.242***	.085	.071	.383	.000	-.098
CRP(mg/L)	**.222***	-.015	.052	**.321****	-.025	-.022
Sedimentation (mm/h)	**.306****	.160	.061	**.411****	.046	.094

HGB (gr/dl)	-.271**	-.230*	-.039	-.270**	-.177	-.113
HCT (%)	-.257*	-.238*	-.027	-.238*	-.218*	-.081
GGT (U/L)	.235*	-.108	.369**	.253*	-.116	.075
ALP (U/L)	.334**	.139	.357**	.340**	.127	.167
LDL (mg/dl)	.293**	.294**	.383**	.270**	.201*	.286**
Total cholesterol (mg/dl)	.283**	.319**	.386**	.249	.205*	.263**
Triglycerides(mg/dl)	.157	.221*	.041	.342**	.103	.130
DAS28	.727**	.122	.420*	.706**	.049	-
DAPSA	.540**	.035	.336	.486**	.140	-.078

BMI; Body Mass Index, HT; Hypertension, DM; Diabetes, CRP; C-Reactive Protein, HGB; Hemoglobin, HCl; Hemotacrit GGT; Gamma Glutamyl Transferase, ALP; Alkaline Phosphatase, LDL; Low Density Lipoprotein, DAS28; Disease Activity Score-28, DAPSA; Disease Activity Score In Psoriatic Arthritis, *** Parameters that do not show any correlation were not added to the table

Table 7. Comparison of groups in terms of hepatic enzyme levels

	RA	AS	PSA	TOTAL	p
Increased TA (AST/ALT)					
Yes (n)	5	8	10	23	
% within TA	21.7%	34.8%	43.5%	100.0%	
%within disease	15.6%	24.2%	32.3%	24.0%	
% of Total	5.2%	8.3%	10.4%	24.0%	0.302[q]
No (n)	27	25	21	73	
% within TA	37.0%	34.2%	28.8%	100.0%	
% within disease	84.4%	75.8%	67.7%	76.0%	
% of Total	28.1%	26.0%	21.9%	76.0%	
Increased GGT					
Yes (n)	9	8	7	24	
% within GGT	37.5%	33.3%	29.2%	100.0%	
%within disease	28.1%	24.2%	22.6%	25.0%	
% of Total	9.4%	8.3%	7.3%	25.0%	0.872[q]
No (n)	23	25	24	72	
% within GGT	31.9%	34.7%	33.3%	100.0%	
% within disease	71.9%	75.8%	77.4%	75.0%	
% of Total	24.0%	26.0%	25.0%	75.0%	
Increased ALP					
Yes (n)	4	3	3	10	
% within ALP	40.0%	30.0%	30.0%	100.0%	
% within disease	12.5%	9.1%	9.1%	10.4%	
% of Total	4.2%	3.1%	3.1%	10.4%	0.892[q]
No (n)	28	30	28	86	
% within ALP	32.6%	34.9%	32.6%	100.0%	
%within disease	87.5%	90.9%	90.3%	89.6%	
% of Total	29.2%	31.3%	29.2%	89.6%	

[q]: chi-square test
TA; transaminases, AST; aspartate transaminase, ALT; alanine aminotransferase, GGT; gamma glutamyl transferase, ALP; alkaline phosphatase

DISCUSSION

CIRDs are characterized by different etiopathogenesis, clinical and radiological findings. Although the pathogenesis of these diseases, which are a heterogeneous group, is not clear, it is thought that they develop on a genetic basis due to immune system dysregulation and under the influence of environmental factors (11). The autoimmune inflammatory response leads to different clinical and laboratory findings (12). Our main objectives in this study were (1) to examine in detail the comorbidities and laboratory abnormalities observed in patients of RA, AS and PSA, which are the 3 CIRDs we frequently encounter in our clinical practice, (2) to detect possible GIS pathologies including liver and gallbladder by means of total abdominal US, and (3) to analyze the relationships of the detected involvement and abnormalities with disease activation, demographic data and other laboratory results. According to the analysis of the US results, all GIS pathologies were on liver and gallbladder. Thus, it would be more understandable to analyse the results at the level of these two organs.

Liver

When a liver pathology is detected in a rheumatic disease, it can be difficult to distinguish whether it is a hepatic manifestation of the disease, a condition associated with primary liver disease, or related the drugs given for the treatment of rheumatic disease. The literature offers changeable data on the prevalence, importance and specificity of liver damage in autoimmune rheumatic diseases (13).

Rigby et al. believe that liver damage is usually not a hepatic symptom of RA (14). However, other authors think that the hepatic manifestation of RA is present in 6-74% of RA patients (15,16). A slight elevation of aminotransferases (ALT/AST) and/or elevation of ALP and GGT due to unknown aetiology are sometimes referred to as hepatic manifestation of RA. Currently, there is a great deal of evidence confirming the important role of the liver in modulating the immune response in autoimmune and chronic inflammatory disorders. Nevertheless, the pathogenesis of liver injury is still unclear.

The fact that patients with an autoimmune disease have a higher susceptibility to other autoimmune diseases has also been confirmed for RA patients. The most common autoimmune liver disease in RA patients is primary biliary cirrhosis (PBC) followed by autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC). PSC should be considered in all RA patients with ALP and GGT elevation (13).

Non-alcoholic fatty liver disease (NAFLD) covers a wide spectrum of pathological changes from simple steatosis [non-alcoholic fatty liver (NAFL)] to the more progressive form of NAFLD, namely, non-alcoholic steatohepatitis (NASH). Obesity, diabetes, hyperlipidaemia, hypertension, hyperuricemia and metabolic syndrome have been accepted as risk factors for NAFLD (17). Approximately 31% of RA patients are at risk for NAFLD development, and only 1.4% have advanced disease. RA and NAFLD are thought to share some common risk factors associated with inflammation. Specific inflammatory cytokines, such as RA-specific inflammation-associated tumour necrosis factor alpha, can lead to fibrogenic and apoptotic responses in the liver. In addition, the use of drugs such as methotrexate (MTX), NSAIDs, and corticosteroids is associated with an increased risk for NAFLD, and it is recommended to monitor patients more closely in particular. The use of biological therapy is associated with a low risk for NAFLD (13).

As for the SPA group, it is difficult to distinguish disease-related hepatic abnormalities from adverse reactions associated with SpA treatment. NAFLD is more common in psoriasis and psoriatic arthritis than in the general population. Arthritis that has more disease activity exhibits high-grade steatosis. Minor transaminase increase was identified in 26% of the AS patients. Some authors have reported a higher rate of hepatobiliary disease in UC compared to CD disease (18). Recently, hospital-based observational studies have shown that patients with psoriasis are 1.5 to 3 times more likely to undergo NAFLD. This increased risk of NAFLD and subsequent risk of liver injury have been explained by the increased prevalence of NAFLD risk factors such as obesity, diabetes mellitus and alcohol consumption in patients with psoriasis (8). Furthermore, among the various pathways that contribute to the development of hepatosteatosis, circulating inflammatory cytokine concentrations are thought to be the most important factor in causing and sustaining insulin resistance (IR) (19).

In our study, mean levels of aminotransferases, GGT and ALP were within normal limits in all 3 patient groups. Regarding the patients with increased enzyme levels, 24% of the patients had transaminase, 25% had GGT, and 10.4% had ALP elevation. There were no significant differences between the groups by enzyme elevations, but the correlation analysis concluded that especially GGT and ALP levels were more correlated with liver pathology. The closest association with liver injury was observed as the disease activity level in RA and PSA patients. Although we observed a remarkable GGT and ALP elevations in our study, no image suggestive of PSC was detected in US findings. Nevertheless, since endoscopic retrograde cholangio-pancreatography (ERCP) is the gold-standard method in the diagnosis of PSC, it would be appropriate to evaluate these patients with this method for definitive diagnosis. The distribution of the patients with elevated enzyme levels is shown in Table 7 in detail.

According to our data, NAFLD was observed in 47 patients (49%). NAFLD was present in 37.5% of RA patients, 51.5% of AS patients and 58.1% of PSA patients. There were no significant differences between the groups. While the correlation analysis showed a significant correlation with parameters such as advanced age, high BMI, prolonged disease duration, alcohol use, presence of additional

comorbidity, high GGT / ALP / LDL / total cholesterol levels, the correlation level was poor. Of the disease activity scores, only DAS28 correlated with NAFLD. As for other liver pathologies, 40 (41.7%) patients had hepatomegaly, 3 (3.1%) had liver calcified granuloma and 4 (4.2%) had liver cyst. There were no significant differences between the patient groups by liver pathologies. When the groups were examined in themselves, the group with the most common liver pathology was the PSA group by 67.7%. This rate was 57.6% for AS and 56.3% for RA.

Gall bladder

Gallbladder disease is a common digestive disorder worldwide and manifests itself as gallstone disease most commonly. Although there are different types of gallstone depending on their compositions, most biliary stones are made of cholesterol in western societies. Although gallstone disease is a multifactorial disease derived from complex interactions among many genetic and environmental factors, impaired cholesterol metabolism has been one of the mechanisms involved in the formation of cholesterol gallstones (20).

Due to inflammation, the hypothesis that the endothelial function of the gallbladder is altered, and thus the recovery of lipids may be reduced, forms the basis of the disorder in cholesterol metabolism, and the development of cholesterol stones constituting 80% of the stones can be explained by this mechanism. Hence, patients with chronic inflammatory disease may show a higher prevalence of gallstones. In fact, few studies have demonstrated a higher prevalence of gallstones in patients with systemic lupus, anti-phospholipid syndrome, and rheumatoid arthritis (21,22).

The prevalence of gallbladder disease in female RA patients was higher than in previous studies. General population studies have shown that female gender, advanced age, sedentary lifestyle, and possibly nonsteroidal anti-inflammatory drugs (NSAIDs), which are more common in RA, are some of the most important risk factors for gallbladder diseases development (23).

Genetic studies have identified possible risk alleles shared among primary biliary cirrhosis, primary sclerosing cholangitis, psoriasis and AS (24). However, only a few case reports have clinically demonstrated this association (25). Considering the common risk factors shared with RA, it would not be surprising to see increased gallbladder diseases in SPA patients, especially PSA.

In our study, 16 patients (16.7%) had at least one gallbladder pathology on US. 10 (10.4%) of these patients were in the PSA group and were significantly higher than in the other groups (p=0.018). All 6 (6.3%) patients with gallstones were also in the PSA group and were statistically higher than in the other groups. Although other pathologies such as cholecystectomy, gallbladder cyst or wall thickening were observed more frequently in the PSA group, there was no significant difference between groups. An interesting result of our study was that the gallbladder pathologies, which are closely associated with PSA, did not correlate with the DAPSA score. Although US results showed significant correlation with many clinical and laboratory parameters, correlation levels were poor for all data (Table 6).

Although a number of previous studies have shown that most of the liver and gallbladder pathologies increase in CIRDs, a comparative study has not been performed among the most frequent CIRDs before. We think that our study is the first in this respect. It was a noteworthy result that gallstone disease was observed at a higher rate in PSA compared to other rheumatic diseases. While the relatively small number of patients is the greatest limitation of our study, we think that its results will contribute to the literature.

CONCLUSION

It is thought that various aetiologies may cause GIS involvement during the course of CIRD. In CIRD patients, regular laboratory checks are required to detect these involvement, especially of liver and gallbladder. Timely estimation of the origin of the damage is very important for advanced treatment plan and prognosis of CIRD. Accurate and timely use of anamnesis, clinical examination, laboratory and imaging methods is very important to make this determination.

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REFERENCES

1. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81
2. Baillet A, Gossec L, Carmona L, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis 2016;75:965-73.
3. Balato N, Napolitano M, Ayala F, et al. Nonalcoholic fatty liver disease, spleen and psoriasis: new aspects of low-grade chronic inflammation. World J Gastroenterol 2015;21:6892-97.
4. Caplan L, Kuhn KA. Gastrointestinal and hepatic disease in spondyloarthritis. Rheum Dis Clin N Am 2018;44:153-64.
5. Cojocaru M, Cojocaru IM, Silosi I, et al. Liver involvement in patients with systemic autoimmune diseases. Maedica 2013;8:394-7.
6. Dissaneevate K. Results of Lower Abdominal Ultrasound as Part of Whole Abdominal Ultrasound in Patients with and without Indications Related to Lower Abdomen. J Med Assoc Thai 2017;100:177-82.

7. García-Gómez MC, de Lama E, Ordoñez-Palau S, et al. High prevalence of gallstone disease in rheumatoid arthritis: A new comorbidity related to dyslipidemia? Reumatol Clin (English Edition) 2019;15:84-9.
8. Hirschfield GM, Chapman RW, Karlsen TH, et al. The genetics of complex cholestatic disorders. Gastroenterology 2013;144:1357-74.
9. Ito S, Hasegawa H, Nozawa S, et al. Gallstones in patients with rheumatoid arthritis. J Rheumatol 1999;26:1458-66.
10. Liu J-T, Yeh H-M, Liu S-Y, et al. Psoriatic arthritis: epidemiology, diagnosis, and treatment. World J Orthop 2014;5:537-43.
11. Mori S, Arima N, Ito M, et al. Non-alcoholic steatohepatitis-like pattern in liver biopsy of rheumatoid arthritis patients with persistent transaminitis during low-dose methotrexate treatment. PloS one 2018;13:e0203084.
12. Mosca M, Neri R, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. Clin Exp Rheumatol 1999;17:615-20.
13. Pamuk O, Umit H, Unlu E, et al. An increased frequency of gallbladder stones in rheumatoid arthritis patients. Factors related to gallbladder stone formation. Clin Exp Rheumatol 2006;24:317-20.
14. Radovanović-Dinić B, Tešić-Rajković S, Zivkovic V, et al. Clinical connection between rheumatoid arthritis and liver damage. Rheumatol Int 2018;38:715-24.
15. Rigby WF, Lampl K, Low JM, et al. Review of routine laboratory monitoring for patients with rheumatoid arthritis receiving biologic or nonbiologic DMARDs. J Rheumatol 2017;2017:9614241.
16. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002;123:745-50.
17. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376:1094-108.
18. Sieper J, Braun J, Rudwaleit M, et al. Ankylosing spondylitis: an overview. Ann Rheum Dis 2002;61:8-18.
19. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68:1-44.
20. Soultati A, Dourakis S. Hepatic manifestations of autoimmune rheumatic diseases. Ann Gastroenterol 2005;18:309-24.
21. Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. Gastroenterol Clin N 2010;39:157-69.
22. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
23. Van Der Heijde D, Daikh DI, Betteridge N, et al. Common language description of the term rheumatic and musculoskeletal diseases (RMDs) for use in communication with the lay public, healthcare providers and other stakeholders endorsed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). Ann Rheum Dis 2018;77:829-32.
24. Vargas CA, Medina R, Rubio CE, et al. Primary biliary cirrhosis associated with ankylosing spondylitis. J Clin Gastroenterol 1994;18:263-4.
25. Yang X, Mardekian J, Sanders KN, et al. Prevalence of pulmonary arterial hypertension in patients with connective tissue diseases: a systematic review of the literature. Clin Rheumatol 2013;32:1519-31.