Clinical Trial/Experimental Study

Medicine®

OPEN

Correlation between high-frequency ultrasonography of patients with early rheumatoid arthritis and anti-CCP antibody

Jie Yang, MM, Qinghe Shao, MM, Jieyan Wu, MM*

Abstract

Objectives: To study the correlation between high-frequency ultrasonography of patients with early rheumatoid arthritis (RA) and anti-cyclic citrullinated peptide (CCP) antibody.

Methods: Two wrists, 1st to 5th metacarpal phalangeal (MCP) and 1st to 5th proximal interphalangeal (PIP) joints of 53 early RA patients treated from October 2015 to October 2017 and 30 healthy subjects were examined by high-frequency ultrasonography. The thicknesses of synovial membrane, sheaths of 1st to 5th extensor tendons, flexor tendons and ulnar wrist extensor tendons were measured. Related pathological changes were observed.

Results: RA and control groups had significantly different thicknesses of synovium, extensor and flexor tendon sheaths ($P < .001$). In RA group, 14.15% of joints had cavity fluid, 5.23% had cartilage destruction, and 2.32% of bone cortices had tendon sheath effusion. The detection rates of tendon sheath effusion and tendon adhesion were 19.81% and 16.30% respectively. Anti-CCP antibody positive group had significantly different DAS28, Health Assessment Questionnaire score and rheumatoid factor positive rate from those of negative group ($P < .05$). Synovitis, cartilage destruction, bone erosion, tendon sheath effusion, and joint effusion were significantly positively correlated with these values ($P < .05$). Besides, 8.92% of joints had blood flow signals of thickening synovium, of which joints with signals in the active phase accounted for 4.37%. The resistance index (RI) of synovial artery was (0.58 ± 0.07). However, 0.94% of joints had synovial blood flow signals in the inactive phase, and RI of synovial artery was (0.67 ± 0.03). Anti-CCP antibody positive group was significantly more prone to bone erosion than negative group ($P < .05$).

Conclusions: For patients with early RA, high-frequency ultrasonography was more likely to detect articular cartilage destruction and bone erosion changes when anti-CCP antibody was positive. Combining anti-CCP antibody with ultrasonography can provide valuable evidence for the development of clinical treatment regimens.

Abbreviations: CCP = anti-cyclic citrullinated peptide, CDE = color Doppler energy, CDFI = color Doppler flow imaging, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire, MCP = metacarpal phalangeal, PIP = proximal interphalangeal, Psv = peak systolic velocity, RA = rheumatoid arthritis, RF = rheumatoid factor, RI = resistance index, SJC = swollen joint count, TJC = tender joint count.

Keywords: finger joint, rheumatoid arthritis, ultrasonography

1. Introduction

Rheumatoid arthritis (RA) is a systemic disease mainly manifested as chronic inflammatory joint lesions. The pathological changes mainly include chronic non-suppurative synovitis, synovial congestion, edema, exudation, inflammatory cell infiltration, and granulation tissue formation, then eroding articular cartilage through attenuation and damage. As a result, the subchondral bone is further eroded, leading to joint dysfunction. RA affects joints symmetrically at multiple sites, usually involving wrists, fingers (toes), and knees.[1,2] Several biochemical assays have reference values for the diagnosis of RA. Anti-cyclic citrullinated peptide (CCP) antibody, as a polypeptide fragment of cyclic filaggrin, is mainly IgG-type. With high sensitivity and specificity to RA, it can be used as an ideal serological marker for diagnosis.[3,4]

At present, non-invasive imaging methods for osteoarticular lesions have gradually increased, mostly using MRI and ultrasonography. MRI is ideal for soft tissue resolution, with the advantages of multi-parametric imaging and arbitrary plane imaging, as well as good contrast for soft tissues under normal and pathological conditions. Therefore, MRI can be used to diagnose early RA lesions and synovial changes before and after treatment by observing the thickness of synovial membrane,[5] but it has not been popularized due to long time, high cost, and hardly acceptable conditions and environment of examination. Compared with MRI, ultrasonography is safe, non-invasive, easily operable, free from ionizing radiation, and low-cost, so it is

Editor: Jenn-Haung Lai.

JY and QS contributed equally to this work.

The authors have no conflicts of interest to disclose.

Department of Ultrasound Medicine, Gansu Provincial People's Hospital, Lanzhou, Gansu Province, P. R. China.

* Correspondence: Jieyan Wu, Department of Ultrasound Medicine, Gansu Provincial People's Hospital, No. 204 West Dong-gang Road, Lanzhou 730000, Gansu Province, P. R. China (e-mail: wujieyangpph@aliyun.com).

Medicine (2019) 98:6(e14083)

Received: 15 July 2018 / Received in final form: 6 December 2018 / Accepted: 19 December 2018

http://dx.doi.org/10.1097/MD.0000000000014083

relatively popular among patients. High-frequency ultrasonography can distinguish the fine structure of tissues and is suitable for the observation of interior and exterior joints and soft tissue lesions. Doppler ultrasonography can show the blood flow signals in hyperplastic synovial membrane, which is thus more suitable for the dynamic observation of hyperplastic blood vessels in the synovium of RA lesions and related hemodynamic changes. Nevertheless, Doppler ultrasonography is limited in detecting blood microcirculation in organs and affected by the detection angle. In recent years, with the rapid development of ultrasound imaging technology, the nonlinear effects of contrast agent and special imaging mode can help display the microvascular structures in organs and lesions sensitively, benefiting the observation of synovial vascular hyperplasia in RA lesions.[6] The aim of this study was to perform high-frequency ultrasonography for early effusion of metacarpal phalangeal (MCP), proximal interphalangeal (PIP), and wrist joints, synovial hyperplasia, vasospasm formation, cartilage and bone destruction together with tendon lesions, to analyze the correlation with anti-CCP antibody, and to verify the value of ultrasonography in assessing RA joint damage, providing valuable evidence for RA diagnosis, treatment, and prognosis evaluation.

2. Methods

2.1. Subjects

Fifty-three RA patients who were treated in our hospital from October 2015 to October 2017 were selected, including 9 males and 44 females aged between 21 and 63 years old, (42.4 ± 12.4) on average. The mean disease course was (11.2 ± 7.5) months. This study has been approved by the ethics committee of our hospital, and written consent has been obtained from all patients.

Inclusion criteria: In accordance with the 1987 revised RA classification and diagnostic criteria by the American College of Rheumatology and/or the 2010 ACR/EULAR classification criteria for RA including anti-CCP antibody testing.[7] Exclusion criteria: Patients complicated with other rheumatoid immune diseases or bone joint diseases; pregnant or lactating women; patients with a history of wrist injury or surgery.

Meanwhile, 30 healthy subjects comprising medical workers and volunteers were selected as a control group, without history of developmental abnormalities, joint swelling or history of hereditary RA. Before examination, written consent has been obtained from all subjects, including 7 males and 23 females aged between 24 and 65 years old, (41.9 ± 12.5) on average.

2.2. Apparatus

GE Logiq 9 color Doppler ultrasound system was used, with real-time linear-array high-frequency probe at the frequency of 6.0 to 15.0 MHz. The musculoskeletal ultrasonographic conditions, including depth, gain, and focused site, were optimized according to lesions. The distribution of articular synovial blood flow was observed by color Doppler flow imaging (CDFI) and color Doppler energy (CDE) imaging. Ultrasonography was performed for the MCP, PIP, and wrist joints of both hands in the 2 groups by the same physician.

2.3. Ultrasonographic conditions

Each subject received examinations of 1st to 5th PIP, 1st to 5th MCP and bilateral wrist joints. According to the specifications for ultrasonic examination of muscles and bone joints formulated by the American Institute of Ultrasound in Medicine and ACR, all subjects were examined in the sitting position, with the palms placed flat on the examination table, a pillow underneath and 5 fingers separated slightly. For palm surface examination, the palm was placed upwards, with the wrist slightly stretched. For examination on the dorsal side of hand, the palm was placed downwards and slightly bent. Transverse and longitudinal scans were performed for the dorsal and palmar sides of wrist, MCP and PIP joints respectively, and the measured values were recorded. Each section was measured 3 times, and the results were averaged. The detection indices included articular cavity fluid, synovial thickness, synovial blood flow, blood flow spectrum, destruction of articular cartilage, subchondral bone erosion, and periarticular tendon lesions.

2.3.1. Ultrasonographic measurement of wrist joint. Observation was conducted from the dorsal sagittal plane of joint. The longitudinal section of radio-carpal joint was selected, of which the bony structure was the lower end of the radius and the lunate bone. The thickness of echoless area in front of the lunate bone was not measured.

2.3.2. Ultrasonographic measurement of MCP and PIP joints. The dorsal sagittal plane of joint was selected to measure the thickness of hypoechoic area between the tendon and bone surface. According to the method of Conaghan et al,[8] when the synovial membrane underwent inflammatory changes, the thickness of the hypoechoic area between finger extensor tendon and metacarpal cortex was measured for MCP joint, and that of the dorsal surface of the first phalanx was measured for PIP joint. Synovial tissue was measured perpendicularly to the bone surface at the thickest point.

2.3.3. Measurement of thicknesses of 1st to 5th finger extensor tendons, flexor tendons, and ulnar wrist extensor tendons. For extensor tendon, the thickness at the midpoint of MCP and PIP joints on the dorsal sagittal plane was measured. For flexor tendon, the thickness at the midpoint of MCP and PIP joints on the palmar sagittal plane was measured. Both measurements were performed perpendicularly to the skin. For ulnar wrist extensor tendon, the thickness approximately 2.0 cm away from the capitulum ulnae of hand dorsal side was measured.

2.4. Determination of measurement indices

2.4.1. Joint effusion. According to the diagnostic criteria of Conaghan et al,[8] joint effusion was determined when the thickness of echoless area between MCP and PIP joints was >1 mm. Tendon sheath effusion was determined based on the appearance of an irregular echoless area.

2.4.2. Synovium and tendon. Currently, there are no globally accepted normal reference thicknesses for joint synovium or tendon sheath. In this study, the method of Schmidt et al was used,[9] that is, the measured synovial and tendon sheath thicknesses of the healthy control group were employed as the reference standards.

2.4.3. Determination criteria for tendon adhesion. The boundaries between tendon, tendon sheath and surrounding tissues were fuzzy. In the motion state, local parts could move passively along with surrounding tissues.

2.4.4. Blood flow distribution. According to the criteria of Adler et al,[10] blood flow grading was conducted for joint synovium:

grade 0: no blood flow signal in the synovial membrane; grade I: mild blood flow signals in the synovial membrane, with 1 to 2 sites of dotted signals; grade II: moderate blood flow signals, with a major blood vessel or 2 to 3 small blood vessels; grade III: rich blood flow signals, with over 4 blood vessels or vascular network. The blood flow signals above grade I was determined as hyperplasia of synovial blood vessels.

2.4.5. Blood flow spectra. Pulsed-wave Doppler sampling was conducted for color blood flow in hyperplastic synovial artery. The peak systolic velocity (Psv, Vmax) and end diastole velocity (Vmin) were measured when the blood flow spectrum of synovial artery was clearly shown, and the automatically calculated resistance index (RI) was recorded: RI = (Vmax–Vmin)/Vmax. RI was measured twice and averaged.

2.5. Detection of biochemical indices

Fasting venous blood was collected from patients on the morning of the second day after hospitalization, and all subjects were tested for anti-CCP antibody by ELISA. The normal value was <25 mg/L.

Rheumatoid factor (RF) was detected by rate nephelometry with a kit purchased from Beckman Coulter Inc. (CA). An RF value of >20 IU/mL was considered positive.

2.6. Determination criteria for active RA

The inclusion criteria for active RA were based on the study of Van Der Kooij et al:[11] 1) Swollen joint count (SJC) ≥6 (66 joints); 2) tender joint count (TJC) ≥6 (68 joints); 3) erythrocyte sedimentation rate (ESR) ≥28 mm/h. The patients who met the above 3 criteria simultaneously were identified as active RA.

2.7. Evaluation by Health Assessment Questionnaire (HAQ) and DAS28

The daily activities of RA patients were evaluated by HAQ, and each question was scored from 0 to 3 points, with 0 being "without any difficulty" and 3 being "inability to do". The RA disease activity was assessed by DAS28. A DAS28 of >5.1 means active disease, <3.2 means low disease activity, and <2.6 indicates remission.

2.8. Statistical analysis

All data were analyzed by SPSS16.0 software. Clinical variables were expressed as mean ± standard deviation and percentage (%). The categorical data conforming to normal distribution were subjected to the *t* test, and those not underwent the Mann–Whitney *U* test. Dichotomous or polytomous numerical data were subjected to the χ^2 test and ordered ranked data underwent the Mann–Whitney *U* test. The correlations of data conforming to normal distribution were subjected to the Pearson's correlation analysis, and data with non-normal distribution and ranked data were given the Spearman's correlation analysis and Pearson's χ^2 test. $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline clinical data

A total of 53 RA patients and 30 healthy subjects were included in this study. The RA group comprised 9 males and 44 females aged between 21 and 63 years old, (42.4 ± 12.4) on average. The mean disease course was (11.2 ± 7.5) months. The control group consisted of 7 males and 23 females aged between 24 and 65 years old, (41.9 ± 12.5) on average. The 2 groups had comparable gender, age, height, and body weight (Table 1). For the RA group, 1166 MCP, PIP, and bilateral wrist joints were examined.

Table 1

Baseline clinical data.

Clinical data	RA group	Healthy control group	χ^2/t	*P*
Gender, male/female	9/44	7/23	0.497	.481
Age, yr	42.4 ± 12.4	41.9 ± 12.5	0.106	.916
Height, cm	162.00 ± 8.26	160.18 ± 7.92	0.979	.331
Body weight, kg	58.19 ± 5.42	58.12 ± 4.98	0.058	.954

RA = rheumatoid arthritis.

3.2. Effusion distribution in joints of RA patients

Of the 1166 joints in the 53 RA patients, 165 joints in 40 cases had cavity fluid. Particularly, MCP joints in these patients were most vulnerable with the effusion thicknesses of 0.16 to 0.90 mm (Table 2).

3.3. Synovial membrane thickening and synovial blood flow distribution

The synovial membranes of different joints in the RA group were all significantly thicker than those of the healthy control group ($P < .001$).

The synovial membranes of RA patients obviously thickened, especially at 2nd and 3rd MCP as well as 3rd PIP joints. Of all tested joints, 104 (8.92%) had blood flow signals of thickening synovium, with 28 (2.40%) at grade I, 67 (5.75%) at grade II and 9 (0.78%) at grade III (Table 3). Contrarily, none joint of the healthy control group had such signal.

3.4. Cartilage destruction and bone erosion

Of all tested joints, 61 (5.23%) had cartilage destruction, mostly at MCP joints (2.49%). Besides, 27 joints (2. 32%) underwent bone erosion, especially at PIP and MCP joints (0.86%) (Table 4).

3.5. Tendon thickening and tenosynovitis

The tendons of fingers and wrists in the RA group were all significantly thicker than those of the healthy control group ($P < .05$).

The RA group had the thickest extensor tendon (about 1.50 mm) at the 3rd finger of the right hand, and the thickest ulnar wrist extensor tendon (approximately 1.80 mm) on the right side.

Table 2

Effusion distribution in joints of RA patients.

Joint	Number of involved cases (% of total cases)	Number of joints with effusion (% of total joints)
Wrist	10 (18.87%)	30 (2.57%)
MCP	18 (33.96%)	83 (7.12%)
PIP	12 (22.62%)	52 (4.46%)
Total	40 (75.48%)	165 (14.15%)

MCP = metacarpal phalangeal, PIP = proximal interphalangeal, RA = rheumatoid arthritis.

Table 3

Synovial blood flow distribution.

Blood flow grading	Number of involved joints (% of total joints)	PIP (% of total joints)	MCP (% of total joints)	Wrist (% of total joints)
I	28 (2.40%)	10 (0.86%)	12 (1.03%)	6 (0.51%)
II	67 (5.75%)	12 (1.03%)	39 (3.34%)	16 (1.37%)
III	9 (0.78%)	0 (0.00%)	3 (0.26%)	6 (0.51%)
Total	104 (8.92%)	22 (1.89%)	54 (4.63%)	28 (2.40%)

MCP = metacarpal phalangeal, PIP = proximal interphalangeal.

Table 4

Cartilage destruction and bone erosion of different joints.

Blood flow grading	Number of involved cases (% of total cases)	Number of involved joints (% of total joints)	PIP (% of total joints)	MCP (% of total joints)	Wrist (% of total joints)
Cartilage destruction	24 (45.28%)	61 (5.23%)	21 (1.80%)	29 (2.49%)	11 (0.94%)
Bone erosion	15 (28.30%)	27 (2.32%)	10 (0.86%)	10 (0.86%)	7 (0.60%)
Total	39 (73.58%)	88 (7.55%)	31 (2.66%)	39 (3.35%)	18 (1.54%)

MCP = metacarpal phalangeal, PIP = proximal interphalangeal.

In addition, the RA group had significantly higher flexor tendon thicknesses than those of the healthy control group ($P < .05$).

The RA group had the thickest flexor tendon (about 2.30 mm) at the 2nd finger of the right hand. Of all joints, the detection rates of tendon sheath effusion and tendon adhesion were 19.81% and 16.30% respectively (Table 5). Tendon sheath effusion and tendon adhesion mostly occurred at MCP joints. In contrast, the healthy control group did not suffer from these symptoms.

3.6. Clinical and biochemical indices of anti-CCP antibody positive and negative groups

The anti-CCP antibody positive group had significantly different DAS28, HAQ score, and RF positive rate from those of negative group ($P < .05$), but their age, morning stiffness time, ESR, and CRP level were similar ($P > .05$) (Table 6).

3.7. Correlations between ultrasonographic results and DAS28, HAQ score, and RF positive rate

Synovitis, cartilage destruction, bone erosion, tendon sheath effusion, and joint effusion were significantly positively correlated with DAS28, HAQ score, and RF positive rate ($P < .05$) (Table 7).

3.8. Ultrasonographic results of anti-CCP antibody positive and negative groups

Of the 53 RA patients, 29 were anti-CCP antibody positive and the other 24 were negative. In the anti-CCP antibody positive group, there were 23 cases of joint cavity fluid, 20 cases of synovitis (synovial membrane thickening and blood flow grade > I), 19 cases of cartilage destruction, 12 cases of bone erosion and 21 cases of tendon sheath effusion. In the negative group, there

Table 5

Distribution of tendon pathological changes.

Blood flow grading	Number of involved cases (% of total cases)	Number of involved joints (% of total joints)	MCP (% of total joints)	Wrist (% of total joints)
Tendon sheath effusion	39 (73.58%)	231 (19.81%)	183 (15.69%)	48 (4.12%)
Tendon adhesion	32 (60.38%)	190 (16.30%)	116 (9.95%)	21 (1.80%)

MCP = metacarpal phalangeal.

Table 6

Clinical and biochemical indices of anti-CCP antibody positive and negative groups.

Index	Anti-CCP antibody positive group (n = 29)	Anti-CCP antibody negative group (n = 24)	Fisher's exact test/t	P
HAQ score, point	1.69 ± 0.32	1.41 ± 0.28	3.523	.001
DAS28	5.45 ± 0.43	5.02 ± 0.38	3.817	.000
RF positive rate	29 (100.00%)	3 (12.50%)	Fisher's exact test	.000
Age, yr	42.7 ± 12.0	42.1 ± 12.9	0.175	.862
Height, cm	163.26 ± 8.29	160.02 ± 8.21	1.422	.161
Body weight, kg	58.11 ± 5.41	58.24 ± 5.48	0.087	.931
Morning stiffness time, min	71.93 ± 12.18	69.64 ± 10.93	0.713	.479
ESR, mm/h	60.18 ± 5.11	58.17 ± 4.97	1.443	.155
CRP level, mg/L	46.73 ± 4.54	47.92 ± 5.01	0.906	.369

CCP = anti-cyclic citrullinated peptide, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire, RF = rheumatoid factor.

Table 7

Correlations between ultrasonographic results and DAS28, HAQ score and RF positive rate.

	DAS28		HAQ score		RF positive rate	
	r	*P*	r	*P*	r	*P*
Synovitis	0.512	.021	0.443	.029	0.416	.033
Cartilage destruction	0.492	.025	0.509	.020	0.495	.024
Bone erosion	0.631	.000	0.587	.009	0.553	.011
Tendon sheath effusion	0.438	.031	0.602	.000	0539	.014
Joint effusion	0.397	.039	0.594	.000	0.531	.017

HAQ = Health Assessment Questionnaire, RF = rheumatoid factor.

Table 8

Ultrasonographic results of anti-CCP antibody positive and negative groups.

	Synovitis		Cartilage destruction		Bone erosion		Tendon sheath effusion		Joint effusion	
Group	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Anti-CCP antibody positive	20	9	19	10	12	17	21	9	23	6
Anti-CCP antibody negative	16	8	5	19	3	21	18	6	17	7
χ^2	0.032		10.582		5.397		0.166		0.510	
P	>.05		<.001		<.05		>.05		>.05	

CCP = anti-cyclic citrullinated peptide.

were 17 cases of joint cavity fluid, 16 cases of synovitis, 5 cases of cartilage destruction, 3 cases of bone erosion and 18 cases of tendon sheath effusion. Spearman's correlation analysis showed that the 2 groups were correlated in cartilage destruction ($\chi^2 = 10.582$, $P < .001$) and bone erosion ($\chi^2 = 5.397$, $P < .05$), and the anti-CCP antibody positive group was more vulnerable. However, the 2 groups had no correlation in synovitis, tendon sheath effusion or joint effusion ($P > .05$) (Table 8).

3.9. Blood flow indices of RA patients in active and inactive phases

The joints with synovial blood flow signals in the active phase accounted for 4.37% (51 joints). RI of synovial artery was (0.58 ± 0.07), and Psv was (6.94 ± 1.41). However, only 0.94% of joints had synovial blood flow signals in the inactive phase (11 joints), and RI of synovial artery was (0.67 ± 0.03). Meanwhile, Psv was (6.92 ± 0.96). RI of RA patients in the active phase was significantly lower than that of the inactive phase ($t = 4.251$, $P < .05$). Nevertheless, they had similar Psv values ($P > .05$) (Table 9).

4. Discussion

RA is a systemic autoimmune disease characterized by chronic destructive joint disease, with the incidence of 0.01% to 0.05% in different populations. RA can occur at any age, with the peak age of 30 to 50 years old, and it usually occurs in women.60% to 70% of RA patients have a slow onset. The main clinical manifestation is systemic polyarticular inflammation, and painful and stiff limb joints such as MCP and wrist joints gradually develop within weeks or months. Its onset is often accompanied by systemic discomforts such as fatigue, loss of appetite, weight loss, and fever, as well as affected performance in lung, heart, nervous system, blood, and eyes.[1] The early diagnosis and early treatment of RA are closely related to the prognosis and quality of life of patients, but it is still difficult for early diagnosis currently. We herein aimed to study the pathological changes of hand joints in patients with early RA, observe the occurrence of various lesions of the synovial membrane, cartilage, cortical bone surface, and muscle bonds by ultrasonography, and summarize the characteristics, so as to provide more imaging evidence for an early clinical diagnosis.

Table 9

Blood flow indices of RA patients in active and inactive phases.

	Active phase	Inactive phase	*t*	*P*
Case number	23	30		
Number of joints with blood flow spectra	51	11		
Psv	6.94 ± 1.41	6.92 ± 0.96	0.051	>.05
RI	0.58 ± 0.07	0.67 ± 0.03	4.251	<.001

Psv = peak systolic velocity, RI = resistance index.

RA can affect multiple joints throughout the body, of which the hand PIP, MCP or wrist joints are the earliest susceptible joints, and also the most characteristic affected joints. Joint pain and pressing pain are often the earliest manifestations of the disease, which are often continuous and symmetric, and their degree varies among individuals.[12] To a certain extent, it is related to the site of inflammation, the rate and amount of effusion formation. Most patients are accompanied by swelling of the joints. In terms of joint swelling, PIP, MCP, and wrist joints in both hands are the most commonly affected, and can also occur in any joint. In the early stage, edema of peri-articular synovial tissues and exudation of inflammatory cells were predominant; in the middle and late stages of the disease, periarticular capsule may appear due to hyperplasia and hypertrophy of the synovial membrane.[13] In RA patients, effusion and irregularly thickened synovial tissue were seen in the swollen joint cavity. In addition, morning stiffness, also one of the early manifestations of RA, refers to a patient's apparent tightness and stiffness at the joints in the early morning, which can be improved after turning them. Morning stiffness can be seen in a variety of arthritis, but it is most prominent in RA.

Joint effusion is a common lesion in early RA joints and is caused by increased synovial fluid secretion from synovitis. The amount of joint effusion is related to the degree of synovitis, and joint effusion is an index of synovial activity.[14] Ultrasonography is the best way to examine effusion in the joints. About 1 mL of effusion can be found at minimum. Articular effusion in the 2-dimensional gray-scale ultrasonography is manifested as joint cavity widening, and the joint cavity within the echo-free zone can be deformed after extrusion. In this study, among 53 patients with early RA, 40 cases had effusions in the joint cavity, with 165 affected joints, which was one of the most common manifestations of joint disease, and the effusion thickness was about 1.0 to 9.0 mm. In the normal control group, 2 cases were found with the effusion of >1.0 mm in 2 joint cavities, respectively located in the right middle finger PIP (about 1.2 mm of thickness) and the right index finger MCP (about 1.5 mm of thickness), without synovial thickening. Upon inquiry, both of the subjects were frequent computer users, and the effusion may be caused by chronic strain. This study found that in some patients with incomplete swelling of the knuckles or wrist joints, it is difficult to find positive signs of joint inflammation in clinical examinations. However, ultrasonography can detect effusions in multiple joint cavities and can clinically provide a certain basis for the diagnosis in the early stage.

Synovitis, as the main pathological change of RA, is manifested as synovial thickening and the formation of neovascularization of the synovial membrane, that is, pannus formation. The gray-scale ultrasonography of synovial thickening is manifested as dark area widening within the joint cavity, synovial structure with visible low-medium echo thickening in liquid dark areas, featuring extrusion non-deformation, uneven surface, and nodular projection.[15] In this study, 53 patients had significantly thicker synovial membrane than normal healthy individuals, and the thickened synovium was marked in index finger MCP, PIP, middle finger MCP, and PIP, with the thickest one at 2.3 mm. When RA inflammation is active, the thickened synovial pannus has abundant blood flow signal that is often associated with clinical symptoms. The color flow imaging methods mainly include CDFI and CDE imaging, both of which can detect increased blood flow signals in the thickened synovium and bone surface, and the blood flow can be displayed as spots, star spots, or short rods.[16,17] In this study, increased blood flow signals in the thick synovium and cartilage surface were detected by CDFI and CDE imaging, and a total of 104 joints in 36 cases were observed to have pannus. The results showed that the synovial blood flow signal was mainly graded I-II, and grade III blood flow signals were mostly common in wrist joints, which was probably because the synovial hyperplasia area of the finger joints was small compared with the wrist joints, with thin hyperplastic synovial blood vessels, so abundant blood flow signals could be seen in the wrist joints.

The fibrous tissue of RA with rich capillary can invade the articular cartilage, forming pannus, which in turn causes cartilage degeneration and destruction, joint space narrowing, and destruction of bony joint surface in a successive way. Articular subchondral cystic degeneration and bone erosion are more characteristic and objective signs of RA, with distinctive diagnostic significance.[18] Recently, Möller et al measured the articular cartilage of MCP and PIP in the second to fifth finger of RA patients and compared the results with the X-ray ones.[19] It was found that in the early RA, cartilage could be reduced and the cartilage layer thinned; and the extent of cartilage changes detected by ultrasonography was related to the duration of progressive disease. In the 53 RA patients, cartilage destruction was found in 24 cases and 61 joints, with high incidence of PIP, and bone erosion in 15 cases and 27 joints, mainly distributed in the PIP and MCP joints. Bone erosion in wrist joints was not found, considering that the lesions were still in an early stage, the wrist articular surface area was relatively large, and the cartilage layer was thicker than the finger joints, so bone erosion occurred relatively late.

Tendon and tendon sheath lesions can occur in early RA, and muscle-tendon lesions are the main cause of functional disability in patients. Wang et al found that in the comparison of the tendon lesions positive rate, there was no statistically significant difference between the group of disease duration <2 years and the group of disease course ≥2 years,[20] indicating that obvious muscle tendon lesions could appear in the early stage of RA. However, it is difficult to examine tendon lesions in clinical examinations and laboratory tests. Therefore, the importance to ultrasonography on tendon lesions can not only make up for the shortcomings of clinical examination, and benefit the early diagnosis of the disease, but also help clinicians in the patients' disease progression and prognosis, so as to promptly give active treatment to reduce the disability rate. Wakefield et al showed that high-frequency ultrasonography in the detection of flexor and extensor tendon lesions has a high specificity and positive predictive value,[21] which can be used as an effective means to detect tendon lesions. Tenosynovitis is considered to be one of the earliest features of arthritis, and its ultrasonographic manifestations include effusion in and thickening of the tendon sheath, and reduction of echo, and the tendon boundary blurs and the fiber structure disappears with the course of the disease. In this study, the extensor and flexor tendon sheaths were significantly thickened compared with the normal control group, and the incidence of tendon sheath effusion was high. Flexor tendon sheath effusion was relatively common and easier to show, and the ulnar extensor tendon sheath effusion was also more common, which may be caused by no sheath in extensor tendon and blurred edges.

At present, in all imaging examinations, only ultrasonography has real-time dynamic monitoring capabilities and can observe the relationship between tissues in motion, such as the relationship between tendons and tendon sheaths and surrounding tissues. Normal people have clear boundaries between tendon sheaths and periarticular tissues, which can exercise independently without any passive traction. The tendon adhesions caused by RA joint inflammation showed blurred boundary between tendons and tendon sheaths, and with the surrounding tissues. Under the state of motion, the local tendons could be passively moved together with the surrounding tissues. Adhesion of tendon sheath to the surrounding tissue can also be considered as one of the manifestations of tendinitis, and the severity of adhesions is often closely related to the impaired function of the diseased joint. Therefore, tendon adhesion may be the manifestation of the earliest joint damage, but there is no relevant research reported at home and abroad. Herein, there were 32 cases and 190 joint extensor tendons with tendon adhesions, most of which occurred in the tendons of the finger joints. In patients with severe adhesions, the function of finger joints was limited, passively bent or stretched. However, there is no grading standard for the severity of tendon adhesion at home and abroad. Therefore, future studies will further discuss the establishment of tendon adhesion and its grading criteria by ultrasonography. In this study, neither rupture nor breakage of extensor or flexor tendons nor tendon synovial cyst was found in the case group. It

is considered that the above lesions did not appear because tendons were not severely damaged during the early course of the disease.

Disease activity refers to the systemic and local inflammatory manifestations of RA. Its main clinical manifestation is synovitis. Some clinical indices can be used to assess the disease activity, such as SJC, TJC, patients' assessment of pain and overall severity, the assessment of dysfunction and the acute-phase response.[22] In imaging examinations, ultrasonography is a sensitive method to detect the activity of joint inflammation, and it is also one of the research hotspots worldwide in recent years. High-frequency ultrasonography can show thickening of synovium at different degrees and increased blood flow signals in the synovium. Increased blood flow signals in the synovium are a sign of relative increase in blood flow, and it also suggests the phase of active inflammation. However, when the condition is stable, the color flow signal in the synovium can be weakened or disappear. Strunk et al found that the Doppler grading of the wrist joint synovial blood flow in RA patients is highly correlated with the degree of synovitis assessed by clinical examination.[23] It is thus considered that power Doppler is a sensitive method to distinguish the degree of inflammatory activity of pannus. The results of this study also showed that even for small finger joints, color Doppler could also find in the thickened synovial blood flow. In the thickened synovium of wrist joints, it is easier to find more abundant blood flow signals.

Zhu et al used high-frequency ultrasonography to measure the wrist joints of 31 patients in an active stage and 36 patients in an inactive stage and found that the RI value of the intra-articular artery could be used as an index to clinically reflect the synovial inflammatory lesions of RA.[24] Herein, based on the active RA inclusion criteria, 23 active patients in 53 patients were examined, all of which were examined with synovial blood flow signals, with an average Psv of (6.94 ± 1.41) and RI of (0.58 ± 0.07). In the remaining 30 inactive RA patients, 8 patients had synovial blood flow signals with an average Psv of (6.92 ± 0.96) and RI of (0.67 ± 0.03). The detection rate of synovial blood flow signal in RA patients was higher than that in inactive patients, suggesting that the richness of synovial blood flow signal is associated with disease activity.

High-frequency ultrasonography can detect the joint cavity fluid in hand MCP, PIP and wrist, synovial inflammation (including synovial hyperplasia and synovial pannus formation), destruction of joint cartilage and bone erosion, in the early stage of RA, with advantages in early diagnosis. In addition, it can also detect the joint surrounding tendon lesions that cannot be found in clinical examination, including tenosynovitis, tendon sheath effusion, and tendon adhesions. Synovial blood flow signals detected by color ultrasonography and RI values of the synovial arteries are associated with RA activity.

In summary, for patients with early RA, high-frequency ultrasonography was more likely to detect articular cartilage destruction and bone erosion changes when anti-CCP antibody was positive. Combining anti-CCP antibody with ultrasonography can provide valuable evidence for developing clinical treatment regimens.

Author contributions

Conceptualization: Jie Yang, Qinghe Shao, Jieyan Wu.
Investigation: Qinghe Shao.
Methodology: Jie Yang, Qinghe Shao.
Supervision: Jieyan Wu.
Writing – original draft: Jie Yang, Qinghe Shao.
Writing – review & editing: Jieyan Wu.

References

[1] Bartlett SJ, Bykerk VP, Cooksey R, et al. Feasibility and domain validation of rheumatoid arthritis (RA) flare core domain set: report of the OMERACT 2014 RA Flare Group Plenary. J Rheumatol 2015;42:2185–9.

[2] Miner JJ, Aw-Yeang HX, Fox JM, et al. Brief report: chikungunya viral arthritis in the United States: a mimic of seronegative rheumatoid arthritis. Arthritis Rheumatol 2015;67:1214–20.

[3] Wagner CA, Sokolove J, Lahey LJ, et al. Identification of anticitrullinated protein antibody reactivities in a subset of anti-CCP-negative rheumatoid arthritis: association with cigarette smoking and HLA-DRB1 'shared epitope' alleles. Ann Rheum Dis 2015;74:579–86.

[4] Takeuchi T, Miyasaka N, Inui T, et al. High titers of both rheumatoid factor and anti-CCP antibodies at baseline in patients with rheumatoid arthritis are associated with increased circulating baseline TNF level, low drug levels, and reduced clinical responses: a post hoc analysis of the RISING study. Arthritis Res Ther 2017;19:194–204.

[5] Conaghan PG, Østergaard M, Bowes MA, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. Ann Rheum Dis 2016;75:1024–33.

[6] D'Agostino MA, Wakefield RJ, Berner-Hammer H, et al. Value of ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results from the APPRAISE study. Ann Rheum Dis 2016;75:1763–9.

[7] Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.

[8] Conaghan PG, McGonagle D, Wakefield R, et al. New approaches to imaging of early rheumatoid arthritis. Clin Exp Rheumatol 1999;17: S37–42.

[9] Schmidt WA, Schmidt H, Schicke B, et al. Standard reference values for musculoskeletal ultrasonography. Ann Rheum Dis 2004;63:988–94.

[10] Adler DD, Carson PL, Rubin JM, et al. Doppler ultrasound color flow imaging in the study of breast cancer: preliminary findings. Ultrasound Med Biol 1990;16:553–9.

[11] Van Der Kooij SM, Goekoop-Ruiterman YP, De Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 2009;68:914–21.

[12] Myasoedova E, Crowson CS, Davis JM, et al. THU0144 understanding fatigue in patients with rheumatoid arthritis (RA): the role of RA disease activity flares. Ann Rheum Dis 2015;74:245.

[13] Yoshimi R, Toyota Y, Tsuchida N, et al. AB0973 the 8-joint ultrasound score is useful for monitoring response to treatment for rheumatoid arthritis. Ann Rheum Dis 2016;75:1234.

[14] Mancarella L, Addimanda O, Cavallari C, et al. Synovial inflammation drives structural damage in hand osteoarthritis: a narrative literature review. Curr Rheumatol Rev 2017;13:43–50.

[15] Sudoł-Szopińska I, Zaniewicz-Kaniewska K, Saied F, et al. The role of ultrasonography in the diagnosis of rheumatoid arthritis and peripheral spondyloarthropathies. Pol J Radiol 2014;79:59–63.

[16] Cai XH, Yang SP, Shen HL, et al. Application of contrast-enhanced ultrasonography and ultrasonography scores in rheumatoid arthritis. Int J Clin Exp Med 2015;8:20056–64.

[17] Xiao H, Yuan J, Zhu H. Application and study on knees joint of ultrasonography in the diagnosis and treatment of rheumatoid arthritis. Life Sci J 2016;13:100–7.

[18] Hayer S, Bauer G, Willburger M, et al. Cartilage damage and bone erosion are more prominent determinants of functional impairment in longstanding experimental arthritis than synovial inflammation. Dis Model Mech 2016;9:1329–38.

[19] Möller B, Bonel H, Rotzetter M, et al. Measuring finger joint cartilage by ultrasound as a promising alternative to conventional radiograph imaging. Arthritis Rheum 2009;61:435–41.

[20] Wang SK, Yuan WL, Li XF, et al. High frequency ultrasonography in the early diagnosis of rheumatoid arthritis. Chin J Rheumatol 2007;11: 544–6.

[21] Wakefield RJ, O'connor PJ, Conaghan PG, et al. Finger tendon disease in untreated early rheumatoid arthritis: a comparison of ultrasound and magnetic resonance imaging. Arthritis Rheum 2007;57:1158–64.
[22] Sromova L, Busek P, Sedova L, et al. Intraindividual changes of dipeptidyl peptidase-IV in peripheral blood of patients with rheumatoid arthritis are associated with the disease activity. BMC Musculoskelet Disord 2015;16:244–50.
[23] Strunk J, Heinemann E, Neeck G, et al. A new approach to studying angiogenesis in rheumatoid arthritis by means of power Doppler ultrasonography and measurement of serum vascular endothelial growth factor. Rheumatology 2004;43:1480–3.
[24] Zhu J, Zhang WY, Fang QM, et al. Synovial membrane thickness and arterial resistance index of wrist in assessing the activity of rheumatoid arthritis. Chin J Med Imaging Technol 2010;26:124–6.