Quest Diagnostics®

Clinical Focus

Osteoarthritis and Rheumatoid Arthritis

Laboratory Markers for Diagnosis and Prognosis

Clinical Background

Osteoarthritis (OA) is the most common form of arthritis in the United States, affecting 13.9% of adults over 25 years of age.[1] It is characterized by loss of hyaline cartilage in the joints and radiographic changes, such as decreased joint space and osteophytes. Rheumatoid arthritis (RA) is much less common and affects different joint tissues. It occurs in 0.5% to 1% of people in the United States, with prevalence being 2 to 3 times higher in women than men.[2,3] RA is an autoimmune disease characterized by chronic, systemic inflammation, which predominantly affects the synovial membranes and articular structures in joints but may damage organs such as the heart and lungs.[4] Both diseases appear to have a genetic component, but the exact causes are unknown.

Differentiating OA and RA is important because treatments differ. OA is often treated with drugs that alleviate symptoms but do not change the disease course, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs may also be used to treat the symptoms of RA, but other options are available that can change the disease course. Disease-modifying anti-rheumatic drugs (DMARDs) (eg, methotrexate, leflunomide) or biological therapies (eg, adalimumab, etanercept, infliximab) can often ameliorate RA, improve the clinical outcome, and in some cases achieve remission. Treatment of RA early in the course of the disease can prevent or minimize irreversible joint damage.[5]

Many symptoms of OA and RA overlap, including pain, swelling, and stiffness in the joints. These similarities can cause difficultly when differentiating the diseases. However, some symptoms and laboratory markers can assist with differentiation. For example, joint stiffness is less common in OA patients, and joint swelling is hard and bony in OA but soft and tender in RA.[6] In addition, some laboratory markers are elevated in RA patients but normal in OA patients.

This *Clinical Focus* discusses laboratory tests available to assist in differentiating RA from OA and other conditions that manifest with polyarthritis. The associations between test results and disease progression are also discussed.

Disease Classification Criteria

The American College of Rheumatology has published guidelines for the classification of OA in different joints.[7,8,9] Depending on the joint, classification criteria may include joint symptoms (pain, stiffness, swelling, enlargement, deformation), age, erythrocyte sedimentation rate, radiological criteria (presence of osteophytes or narrowing of joint space), synovial fluid tests (color, appearance, white blood cell count), or the sensation of crackling in the joint called crepitus (Table 1). Sensitivity and specificity for diagnosis vary based on 1) the joint (knee, hand, hip); 2) the classification method (traditional vs classification tree); and 3) the criteria (clinical vs clinical and radiographic vs clinical and laboratory).

Diagnosis of RA relies on patient history, physical examination, laboratory testing, and radiographic evidence of joint damage. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 Rheumatoid Arthritis Classification Criteria are based on clinical presentation (synovitis, joint swelling), serology, acute-phase reactants, and duration of symptoms. The criteria are designed to identify early-stage patients who are at high risk of persistent and/or erosive disease.[5] Once other conditions such as OA, systemic lupus erythematosus, psoriatic arthritis, gout, and arthritis caused by viral infection (eg, parvovirus B19, rubella, hepatitis C virus) have been ruled out, a patient is classified as having RA if a score of ≥6 out of a possible 10 is reached. Details of the scoring system and classification criteria can be found in the Figure and reference 5.

Table 1. Criteria for Diagnosis of Osteoarthritis in Different Joints

Knee (Clinical and Laboratory)[a,7]	Hand[a,8]	Hip (Clinical and Radiographic)[a,9]
• Knee pain Plus ≥5 of the following • Age >50 years • Joint stiffness <30 minutes • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth • ESR <40 mm/hour • RF <1:40 • Synovial fluid clear, viscous, or white blood cell count <2,000/mm^3	• Hand pain, aching, or stiffness Plus ≥3 of the following • Hard tissue enlargement of ≥2 of 10 selected joints[b] • Hard tissue enlargement of ≥2 distal interphalangeal joints • <3 swollen metacarophalangeal joints • Deformity of ≥1 of 10 selected joints[b]	• Hip pain Plus ≥2 of the following • ESR <20 mm/hour • Osteophytes (femoral or acetabular) • Joint space narrowing (superior, axial, and/or medial)
Sensitivity: 92% Specificity: 75%	Sensitivity: 94% Specificity: 87%	Sensitivity: 89% Specificity: 91%

[a] Schema presented are in traditional format. Depending on the joint, schema may also be available in traditional or classification tree format for clinical criteria alone or in combination with radiographic criteria.[7-9] Other schema have different sensitivities (86% to 95%) and specificities (69% to 98%).
[b] Selected joints include 1st carpometacarpal and 2nd and 3rd distal and proximal interphalangeal joints of each hand.

This table is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

Individuals Suitable for Testing

- Individuals with symptoms of arthritis not attributed to diagnosed conditions
- Individuals with arthritis requiring differential diagnosis of OA from RA
- Individuals with established RA

Test Availability

A list of tests that may be useful in RA diagnosis, assessment of prognosis, and follow-up is provided in Table 2. Diagnosis of RA can help differentiate OA from RA.

Test Selection

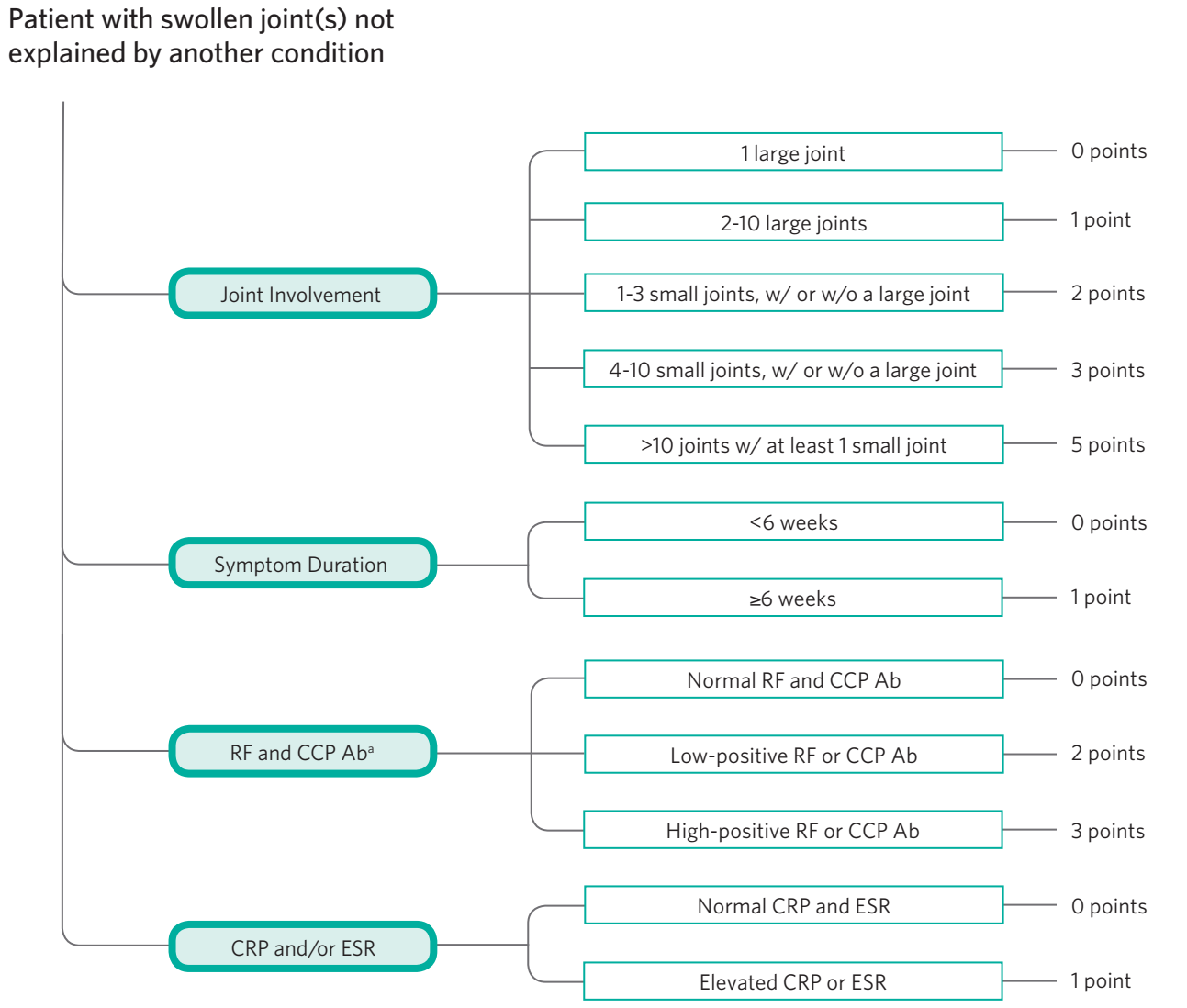
Diagnosis

Laboratory testing can help differentiate RA from other conditions that manifest with polyarthritis, such as OA, mainly by assisting with the diagnosis of RA. These tests can be especially useful early in the disease course for establishing diagnosis.

Rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody are established biomarkers that are integrated into ACR/EULAR criteria for RA classification.[5] 14-3-3η protein is a newer marker for RA that has higher sensitivity in early RA than either RF or CCP and can thus identify RA in some cases that are not identified using RF or CCP. Together, these 3 markers can help differentiate RA from conditions that present with arthritis because they are positive less often in many non-RA conditions, such as OA. These markers may also alert clinicians to the coexistence of RA in a patient with OA.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are serological acute-phase markers of inflammation that are also integrated into the ACR/EULAR criteria for RA classification.[5] ESR can also help classify OA (Table 1).[7,9]

Figure. ACR/EULAR Classification Criteria for Rheumatoid Arthritis



ACR/EULAR indicates American College of Rheumatology/European League Against Rheumatism; RF, rheumatoid factor; CCP Ab, cyclic citrullinated peptide antibody; CRP, C-reactive protein; and ESR, erythrocyte sedimentation rate.

[a] These classification criteria are weighted for RF and CCP. However, 14-3-3η adds diagnostic sensitivity to the traditional markers of RF and CCP.[10]

This figure was developed by Quest Diagnostics based on reference 5. It is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient. Criteria are designed to identify early-stage patients who are at high risk of persistent and/or erosive disease. Criteria have been designed to facilitate study of people with early-stage disease; they are not intended as diagnostic criteria.[5]

Table 2. Tests Available to Support Diagnosis, Prognosis, and Follow-up of Rheumatoid Arthritis

Test Code	Assay	Method	Clinical Use
91472	Rheumatoid Arthritis Diagnostic Panel IdentRA™ with 14-3-3 eta[a] Includes RF IgM, CCP IgG, and 14-3-3 eta protein	Immunoturbidimetry (RF) ELISA (CCP antibody and 14-3-3 eta protein)	Provides additional diagnostic and prognostic value relative to each assay alone
19878	Rheumatoid Arthritis Diagnostic Panel, Comprehensive Includes RF (IgG), RF (IgA), RF (IgM), CCP antibody (IgG), Sjögren's antibody (SS-A), Sjögren's antibody (SS-B)	ELISA (RF IgG/A/M, CCP) Immunobead based enzyme immunoassay (SS-A, SS-B)	Assist in diagnosis and determining prognosis of RA; may help differentiate RA from primary Sjögren's syndrome versus RA with secondary Sjögren's syndrome
TBD	RA and Sjögren's Diagnostic Panel with 14-3-3 eta Includes RF (IgG), RF (IgA), RF (IgM), CCP antibody (IgG), 14-3-3 eta protein, Sjögren's antibody (SS-A), Sjögren's antibody (SS-B)	ELISA (RF IgG/A/M, CCP, 14-3-3 eta) Immunobead based enzyme immunoassay (SS-A, SS-B)	Assist in diagnosis and determining prognosis of RA; may help differentiate RA from primary Sjögren's syndrome versus RA with secondary Sjögren's syndrome
90071	ANA, IFA Rheumatoid Arthritis Diagnostic Panel with Reflex to Titer/Pattern Includes ANA screen, IFA with Reflex to Titer and Pattern, IFA; RF; CCP antibody IgG	Immunofluorescence assay (ANA, Titer and Pattern) Immunoturbidimetry (RF) ELISA (CCP antibody)	Assist in diagnosis of RA
TBD	ANA, IFA Rheumatoid Arthritis Diagnostic Panel (with Reflex to Titer/Pattern) with 14-3-3 eta Includes ANA screen, IFA with Reflex to Titer and Pattern, IFA; RF; CCP antibody IgG; 14-3-3 eta protein	Immunofluorescence assay (ANA, Titer and Pattern) Immunoturbidimetry (RF) ELISA (CCP antibody, 14-3-3 eta protein)	Assist in diagnosis of RA
4418(X)	Rheumatoid Factor	Latex agglutination/ immunoturbidimetry	Assist in diagnosis and determining prognosis of RA; detects primarily IgM RF
15682	Rheumatoid Factor (IgA)	ELISA	Provides added specificity when used in combination with other RF or CCP antibody assays; may help predict severity of disease course

(*continued*)

Table 2. Tests Available to Support Diagnosis, Prognosis, and Follow-up of Rheumatoid Arthritis (*continued*)

Test Code	Assay	Method	Clinical Use
15683	Rheumatoid Factor (IgG)	ELISA	Provides added specificity when used in combination with other RF or CCP antibody assays
19705(X)	Rheumatoid Factor (IgA, IgG, IgM)	ELISA	Assist in diagnosis of RA; detecting all 3 isotypes improves the specificity and predictive value
11173	Cyclic Citrullinated Peptide (CCP) Antibody (IgG)	ELISA	Assist in diagnosis and determining prognosis of RA; more specific than RF
91455	14-3-3 eta Protein[a]	ELISA	Assist in diagnosis of RA; more sensitive than either RF or CCP for early RA[10]
809	Erythrocyte Sedimentation Rate (ESR)	Modified Westergren	Assist in diagnosis of RA and assess disease activity
4420	C-Reactive Protein (CRP)	Nephelometry	Assist in diagnosis of RA and assess disease activity
15384	Rheumatoid Factor Screen with Reflex to Titer, Synovial Fluid	Latex agglutination	Assist in diagnosis and prognosis of RA
6398	Synovial Fluid Analysis, Complete Includes color, appearance, microscopic cell differential, crystals, and mucin clot	Microscopy/polarized light	Assist in diagnosis of disorders of the joints and joint fluid
4562	Cell Count and Differential, Synovial Fluid Includes color, appearance, total nucleated cell count, and percentage of neutrophils, lymphocytes, monocytes/macrophages, eosinophils, and synoviocytes	Microscopic visualization	Assist in diagnosis of disorders of the joints and joint fluid
4563	Crystals, Synovial Fluid	Microscopy/polarized light	Exclude pathologic crystals
17658	LD, Synovial Fluid	Ultraviolet kinetic	Differentiate OA from RA, infectious arthritis, and gout

(*continued*)

Table 2. Tests Available to Support Diagnosis, Prognosis, and Follow-up of Rheumatoid Arthritis (*continued*)

Test Code	Assay	Method	Clinical Use
657	Mucin Clot, Synovial Fluid	Macroscopic examination/ Ropes test	Assist in differential diagnosis of diseases of joints and joint fluid
4446	Culture, Aerobic and Anaerobic[b] Includes aerobic culture, anaerobic culture, and Gram stain	Direct microscopy, bacterial culture, aerobic and anaerobic isolation	
6641	Susceptibility Panel, Aerobic Bacterium[b]	Varies	
6642	Susceptibility Panel, Anaerobic Organism[b]	Microdilution panel	
17597	Complement Component C3, Synovial Fluid	Immunoturbidimetry	Assist in diagnosis of immunologic disorders
17598	Complement Component C4, Synovial Fluid	Immunoturbidimetry	
4943	C4d Fragment, EIA	Enzyme immunoassay (EIA)	

ELISA, enzyme-linked immunosorbent assay; LD, lactate dehydrogenase.
[a] This test was developed and its performance characteristics have been determined by Quest Diagnostics Nichols Institute. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.
[b] Indicate synovial fluid as sample type.

RF and CCP

Rheumatoid factor is a widely used laboratory marker of RA. The reported sensitivity of RF is 57% for early RA[10] and ranges from 60% to 86% for established RA.[11,12] Specificity is relatively low (70%-85%) for early and established RA,[10,12-14] and patients with other rheumatic diseases or conditions that present with polyarthritis often have positive RF results (Table 3).

RF titer is most often assessed using latex agglutination or immunoturbidimetry, which primarily detects IgM RF. IgM RF, as well as IgA RF and IgG RF, can also be measured individually with specific immunoassays. The presence of IgA RF, IgG RF, or both in patients with IgM RF and joint disease markedly increases the likelihood that the patient has RA; these combinations are not typically found in patients with other rheumatic diseases that may be accompanied by IgM RF. However, IgA RF and IgG RF are not highly sensitive and are not widely used in the initial diagnosis of RA.

CCP antibody is assessed by immunoassay. The sensitivity of CCP antibody is comparable to that of RF in early (59%)[10] and established RA (64%-88%).[11,14] However, CCP antibody is also highly specific (90%-98%) for early and established RA.[10,13,15,16] Patients who are healthy or have other rheumatic diseases test positive for CCP antibody less often than for RF (Table 3). For example, 2 studies (n=40 and n=30) showed that approximately 7% of patients with OA tested positive for CCP antibody versus 12.5% to 17% for RF.[10,13] In addition, most side-by-side comparisons demonstrate that CCP antibody is at least as sensitive as and more specific than RF in various clinical situations.[11-14,17,18]

The combination of RF and CCP antibody appears to provide greater sensitivity than either assay alone[11,12,18] and is commonly used in the diagnostic evaluation of suspected RA. In addition, RF and especially CCP antibody can be detected years before the onset of symptoms. In studies of blood donors, the sensitivity of CCP antibody detection for future development of RA ranged from 29% to 37%, with a specificity of ≥98%.[19-21] Sensitivity increased as the time to disease onset decreased.[21,22] CCP antibody testing may also predict a future diagnosis of RA in patients with a diagnosis of undifferentiated arthritis.[23]

14-3-3η

The 14-3-3η protein is elevated in serum and synovial fluid during joint inflammation.[24] 14-3-3η provides higher sensitivity for early RA than RF or CCP antibody testing. In a side-by-side comparison, 14-3-3η sensitivity (64%) was higher than that of RF (57%) or CCP antibody (59%).[10] In patients with established RA, the sensitivity of 14-3-3η (77%) was comparable to that of RF or CCP antibody and specificity (93%) fell between that of RF and CCP antibody.[10]

The addition of serum 14-3-3η measurement to RF and CCP antibody testing provides greater sensitivity for early RA: 78% with 14-3-3η versus 72% without 14-3-3η.[10] Improvement of sensitivity is important because 28% to 44% of patients with early disease test negative for RF and CCP antibody.[3,25] In seronegative patients, 14-3-3η detects 21% of patients with early RA and 67% of patients with established RA.[10] This increased sensitivity may translate into treatment earlier in the course of disease, which can minimize irreversible joint damage.

14-3-3η results may also help differentiate RA from OA. One study showed that median serum levels were higher in early RA patients (0.76 ng/mL) than in OA patients (0.00 ng/mL).[10]

CRP and ESR

CRP and ESR measurement can be used in combination with other laboratory and clinical results to identify patients with RA (Figure). CRP is produced by the liver in response to tissue injury, infection, and inflammation. Levels increase during periods of heightened RA disease activity, but elevations may also reflect inflammation due to other causes such as infection or injury. The ESR typically rises 24 to 48 hours after an inflammatory stimulus and returns to normal levels gradually thereafter. ESR measurement may help assess disease activity when other clinical and laboratory studies yield equivocal results.[26] These acute-phase markers of inflammation are also sometimes used to monitor RA disease activity.

According to the American College of Rheumatology criteria for the classification and reporting of OA (Table 2), ESR can help classify OA. ESR thresholds vary by joint: ≤20 mm/hour for hip, <40 mm/hour for knee; ESR is not recommended for the classification of OA in the hand.[7-9]

Prognosis

The clinical course of OA is variable, and patient characteristics (eg, joint deformity, osteophyte formation) and disease characteristics (eg, generalized OA) are useful for assessing OA progression.[27] Though some evidence suggests that increased serum levels of hyaluronic acid may be associated with OA progression, laboratory markers are not typically used to determine prognosis.[27]

Like OA, RA has a variable clinical course. Some patients have self-limiting disease whereas others develop progressive joint damage. Predicting which RA patients will experience progressive disease may help direct aggressive treatment with DMARDs and/or biological agents to patients who need it most, and spare others from unnecessary exposure to the potential adverse effects of these drugs.[5]

RF and CCP antibody testing are useful for determining the prognosis of RA. A positive RF test result is predictive of long term radiographic progression and more severe joint damage.[28-30] CCP antibody testing is predictive of disease progression at 3 to 10 years after disease onset. In most studies, CCP antibody positivity at baseline correlates with poor prognosis in terms of radiographic and functional outcome.[28,29,31]

14-3-3η testing may also be useful for RA prognosis. Elevated levels of 14-3-3η have been associated with radiographic progression. In a study that included 33 early RA patients, median baseline 14-3-3η levels were higher in patients with radiographic progression (2.68 ng/mL, IQR 0.12 to 15.94) after 30 months than patients without progression (0.09 ng/mL, IQR 0.06 to 12.59).[25] 14-3-3η may also inform response to therapy. A decrease in 14-3-3η marks response to DMARDs and anti-TNF drugs, and decreases have been associated with better clinical outcomes.[32,33]

Supportive Testing

Laboratory tests are not typically used in supportive testing for OA.

A complete blood count with white blood cell differential can help document the mild anemia, leukocytosis, and other hematologic abnormalities sometimes associated with RA. More severe anemia may reflect gastrointestinal bleeding resulting from steroidal and non-steroidal

anti-inflammatory drugs. Urinalysis typically yields normal results. Liver and kidney function should be assessed before starting therapy with non-steroidal anti-inflammatory drugs and/or DMARDs, to establish baseline values, and at intervals thereafter.

Test Interpretation

The result of each assay should be evaluated in conjunction with clinical and radiographic findings and other serological test results.

Diagnosis

In patients requiring differential diagnosis of OA from RA, a positive/elevated result of RF, CCP, or 14-3-3η is suggestive of inflammatory arthritis, such as RA. However, RA may coexist with OA.

RF

Positive RF results are suggestive of RA, but the low specificity precludes a definitive diagnosis.[10,15,18] Positive results are also common in patients with other rheumatic diseases and conditions that can mimic RA (Table 3). Very high titers may be associated with more severe joint disease, Felty's syndrome, rheumatoid nodules, peripheral neuropathy, skin ulcers, scleritis, and vasculitis. Negative results are consistent with conditions other than RA but do not rule out RA; 14% to 43% of patients with RA are seronegative.[10-12] Though rare, seroconversion of RF-negative patients can occur[34]; thus, follow-up testing at intervals until disease pattern and activity stabilize may be useful if the initial result is negative. IgA RF and IgG RF are both highly specific for RA, but negative results do not rule out RA due to the relatively low sensitivity of IgA RF and IgG RF.[18]

CCP Antibody

Positive CCP antibody results are suggestive of RA.[10,13,15,16] Though this assay is generally more specific than RF, patients with other rheumatic diseases may have elevated titers (Table 3). Negative results suggest that other rheumatic diseases may be responsible for the patient's symptoms but do not rule out a diagnosis of RA; 12% to 41% of patients with RA are seronegative.[10,14]

14-3-3η

Positive 14-3-3η results are suggestive of RA.[10] However, negative results do not rule out RA; 23% to 36% of patients with RA are seronegative.[12] In the setting of a personal history of psoriasis, family history of psoriasis, nail changes, back pain or heel pain along with peripheral joint polyarthritis, a positive 14-3-3η result may suggest a diagnosis of psoriatic arthritis.

Combination of RF, CCP Antibody, and 14-3-3η Protein

The combination of a positive IgM RF *and* CCP antibody result is highly suggestive of RA (~90%-100%). However, this test result may be found in some patients with other rheumatic diseases such as SLE, scleroderma, and psoriatic arthritis. Patients with positive CCP antibody and *negative* RF results are also likely to have RA. Patients with positive RF and negative CCP results are less likely to have RA, but RA remains a possibility. Negative results on both assays indicate a low likelihood of RA but do not exclude the diagnosis. Between 28% and 44% of patients with early disease test negative for RF and CCP antibody.[3,25] In RF-positive patients with chronic HCV or other infections associated with polyarticular arthritis, a positive CCP antibody result suggests a likely diagnosis of coexisting RA; HCV patients with cryoglobulinemia typically have negative CCP antibody results.[35]

Elevated 14-3-3η is an indication of RA or psoriatic arthritis but not of other diseases such as OA, osteoporosis, gout, psoriasis, Crohn's disease, ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, Sjögren's syndrome, scleroderma, and multiple sclerosis.[10,25]

In patients with suspected RA, a positive/elevated result of RF, CCP antibody, and/or 14-3-3η protein suggests an RA diagnosis. Negative/normal results for all 3 markers indicate that an RA diagnosis is less likely.

CRP and ESR

Elevated levels of CRP or ESR are consistent with an RA diagnosis, if other laboratory and clinical criteria are met (Figure). In patients with RA, elevated levels of CRP or ESR indicate heightened disease activity. However, elevations may also be due to other inflammatory conditions. Normal CRP and ESR results indicate relatively low disease activity. In patients with discordant CRP and ESR results, CRP levels may be the more reliable marker of RA disease activity.[36]

Table 3. Reactivity of Rheumatoid Factor (RF), Cyclic Citrullinated Antibody (CCP Ab), and 14-3-3η Assays in Various Disorders

Population	Sample Size	Percent Positive[a]		
		RF	CCP Ab (≥20 Units)	14-3-3η (>0.2 ng/mL)
Early RA[10]	99	57	59	64
Established RA[10]	124	84	79	77
Healthy individuals/blood donors[18,b]	154	7	1	--[c]
SLE[26]	201	13	6	--[c]
Scleroderma[37]	86	--	12	--[c]
Primary Sjögren's syndrome[38,b]	134	59	8	--[c]
Juvenile RA[39]				
Polyarticular onset	77	18	13	--
Pauciarticular onset	139	7	2	--
Polymyalgia rheumatica[40]	49	7	0	--
Mixed connective tissue disease/vasculitis[18,b]	103	43	7	--
Psoriatic arthritis[41]	160	11	7	--
Non-inflammatory myalgia[13]	52	19	8	--
Osteoarthritis[13]	40	13	8	--[c]
Lyme disease[15,d]	20	--	15	--
Hepatitis C infection (no cryoglobulinemia)[35]	50	44	0	--
HCV-related cryoglobulinemia[35]	29	76	7	--

--, not available.

[a] The percentages shown are based on the specific references cited.

[b] RF tested by IgM RF ELISA.

[c] Though the frequency of 14-3-3η-positive patients with these disorders is not yet available, data related to blood levels of 14-3-3η have been published. Blood levels of 14-3-3η tend to be elevated in patients with RA, but not in other diseases including osteoarthritis, osteoporosis, gout, psoriasis, Crohn's disease, ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, primary Sjögren's syndrome, scleroderma, and multiple sclerosis.[10,25]

[d] First-generation CCP Ab assay.

Prognosis

RF and CCP

A positive RF test result suggests long term radiographic progression and more severe joint damage.[28-30] A positive CCP antibody test result at baseline suggests poor prognosis in terms of radiographic and functional outcome.[28,29,31] The combination of a positive IgM RF and CCP antibody result is also associated with an aggressive disease course.

14-3-3η

Elevated levels of 14-3-3η may be predictive of radiographic progression.[25]

CRP and ESR

Elevated levels of CRP or ESR during early RA may be predictive of long-term (10-year) disease progression.[29]

References

1. Centers for Disease Control and Prevention. Osteoarthritis. http://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Accessed December 17, 2014.
2. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum*. 2006;36:182-188.
3. Jansen AL, van der Horst-Bruinsma I, van Schaardenburg D, et al. Rheumatoid factor and antibodies to cyclic citrullinated Peptide differentiate rheumatoid arthritis from undifferentiated polyarthritis in patients with early arthritis. *J Rheumatol*. 2002;29:2074-2076.
4. Centers for Disease Control and Prevention. Rheumatoid arthritis. http://www.cdc.gov/arthritis/basics/rheumatoid.htm. Accessed December 17, 2014.
5. 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;62:2569-2581.
6. Venables PJW and Maini RN. Diagnosis and differential diagnosis of rheumatoid arthritis. http://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-rheumatoid-arthritis#H16. Accessed December 17, 2014.
7. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum*. 1986;29:1039-1049.
8. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum*. 1990;33:1601-1610.
9. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum*. 1991;34:505-514.
10. Maksymowych WP, Naides SJ, Bykerk V, et al. Serum 14-3-3eta is a Novel Marker that Complements Current Serological Measurements to Enhance Detection of Patients with Rheumatoid Arthritis. *J Rheumatol*. 2014;41:2104-2113.
11. Dubucquoi S, Solau-Gervais E, Lefranc D, et al. Evaluation of anti-citrullinated filaggrin antibodies as hallmarks for the diagnosis of rheumatic diseases. *Ann Rheum Dis*. 2004;63:415-419.
12. Greiner A, Plischke H, Kellner H, et al. Association of anti-cyclic citrullinated peptide antibodies, anti-citrullin antibodies, and IgM and IgA rheumatoid factors with serological parameters of disease activity in rheumatoid arthritis. *Ann N Y Acad Sci*. 2005;1050:295-303.
13. Sauerland U, Becker H, Seidel M, et al. Clinical utility of the anti-CCP assay: experiences with 700 patients. *Ann N Y Acad Sci*. 2005;1050:314-318.
14. Suzuki K, Sawada T, Murakami A, et al. High diagnostic performance of ELISA detection of antibodies to citrullinated antigens in rheumatoid arthritis. *Scand J Rheumatol*. 2003;32:197-204.
15. Bizzaro N, Mazzanti G, Tonutti E, et al. Diagnostic accuracy of the anti-citrulline antibody assay for rheumatoid arthritis. *Clin Chem*. 2001;47:1089-1093.
16. Lee DM, Schur PH. Clinical utility of the anti-CCP assay in patients with rheumatic diseases. *Ann Rheum Dis*. 2003;62:870-874.
17. Forslind K, Ahlmen M, Eberhardt K, et al. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). *Ann Rheum Dis*. 2004;63:1090-1095.
18. Vallbracht I, Rieber J, Oppermann M, et al. Diagnostic and clinical value of anti-cyclic citrullinated peptide antibodies compared with rheumatoid factor isotypes in rheumatoid arthritis. *Ann Rheum Dis*. 2004;63:1079-1084.
19. Berglin E, Padyukov L, Sundin U, et al. A combination of autoantibodies to cyclic citrullinated peptide (CCP) and HLA-DRB1 locus antigens is strongly associated with future onset of rheumatoid arthritis. *Arthritis Res Ther*. 2004;6:R303-R308.
20. Nielen MM, van SD, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum*. 2004;50:380-386.
21. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum*. 2003;48:2741-2749.
22. Chibnik LB, Mandl LA, Costenbader KH, et al. Comparison of threshold cutpoints and continuous measures of anti-cyclic citrullinated peptide antibodies in predicting future rheumatoid arthritis. *J Rheumatol*. 2009;36:706-711.
23. van Gaalen FA, Linn-Rasker SP, Van Venrooij WJ, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum*. 2004;50:709-715.
24. Kilani RT, Maksymowych WP, Aitken A, et al. Detection of high levels of 2 specific isoforms of 14-3-3 proteins in synovial fluid from patients with joint inflammation. *J Rheumatol*. 2007;34:1650-1657.
25. Maksymowych WP, van der Heijde D, Allaart CF, et al. 14-3-3eta is a novel mediator associated with the pathogenesis of rheumatoid arthritis and joint damage. *Arthritis Res Ther*. 2014;16:R99.
26. Hoffman IE, Peene I, Cebecauer L, et al. Presence of rheumatoid factor and antibodies to citrullinated peptides in systemic lupus erythematosus. *Ann Rheum Dis*. 2005;64:330-332.
27. Cheung PP, Gossec L, Dougados M. What are the best markers for disease progression in osteoarthritis (OA)? *Best Pract Res Clin Rheumatol*. 2010;24:81-92.
28. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2007;66:34-45.
29. Lindqvist E, Eberhardt K, Bendtzen K, et al. Prognostic laboratory markers of joint damage in rheumatoid arthritis. *Ann Rheum Dis*. 2005;64:196-201.

30. Vencovsky J, Machacek S, Sedova L, et al. Autoantibodies can be prognostic markers of an erosive disease in early rheumatoid arthritis. *Ann Rheum Dis*. 2003;62:427-430.

31. Kastbom A, Strandberg G, Lindroos A, et al. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). *Ann Rheum Dis*. 2004;63:1085-1089.

32. Maksymowych WP, Marotta A. 14-3-3 eta and its auto-antibodies predict response to anti-TNF therapy [ACR abstract 1315]. *Arthritis Rheum*. 2013;65:S556.

33. Britsemmer K, Maksymowych WP, van Schaardenburg D, et al. 14-3-3 eta is an early RA biomarker that is modifiable with standard DMARDS and corresponds with improvement in clinical variables [EULAR abstract A388]. *Ann.Rheum.Dis*. 2013;72:A388.

34. Gossec L, Paternotte S, Combe B, et al. Repeated anticitrullinated protein antibody and rheumatoid factor assessment is not necessary in early arthritis: results from the ESPOIR cohort. *J Rheumatol*. 2014;41:41-46.

35. Wener MH, Hutchinson K, Morishima C, et al. Absence of antibodies to cyclic citrullinated peptide in sera of patients with hepatitis C virus infection and cryoglobulinemia. *Arthritis Rheum*. 2004;50:2305-2308.

36. Wolfe F. Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. *J Rheumatol*. 1997;24:1477-1485.

37. QUANTA Lite(R) CCP3 IgG ELISA [package insert]. San Diego, CA: Inova Diagnostics; 2010.

38. Gottenberg JE, Mignot S, Nicaise-Rolland P, et al. Prevalence of anti-cyclic citrullinated peptide and anti-keratin antibodies in patients with primary Sjögren's syndrome. *Ann Rheum Dis*. 2005;64:114-117.

39. Ferucci ED, Majka DS, Parrish LA, et al. Antibodies against cyclic citrullinated peptide are associated with HLA-DR4 in simplex and multiplex polyarticular-onset juvenile rheumatoid arthritis. *Arthritis Rheum*. 2005;52:239-246.

40. Lopez-Hoyos M, Ruiz de AC, Blanco R, et al. Clinical utility of anti-CCP antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. *Rheumatology (Oxford)*. 2004;43:655-657.

41. Alenius GM, Berglin E, Rantapaa DS. Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without joint inflammation. *Ann Rheum Dis*. 2006;65:398-400.

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