

Rheumatoid factor

What are rheumatoid factors?^[1]

Rheumatoid factors are antibodies against the Fc portion of IgG (also an antibody). Rheumatoid factors can belong to any isotype of immunoglobulin – eg, IgM, IgG and IgE – and any of these can be detected in the blood test. Enzyme-linked immunosorbent assay (ELISA) can differentiate between the different subtypes of rheumatoid factors.

Following the discovery of rheumatoid factors 80 years ago, the identification of both anti-citrullinated protein antibodies (ACPAs) and anti-carbamylated protein antibodies (anti-CarP Abs) has greatly facilitated early diagnosis and prognosis prediction of rheumatoid arthritis.^[2]

ACPAs are highly specific for RA, whereas RF can also be found among healthy (elderly) individuals and patients with other autoimmune diseases or infection.^[3]

Based on the presence of several autoantibodies like rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPAs), anti-carbamylated protein (anti-CarP) antibodies, and anti-acetylated protein antibodies, RA can be subdivided into seropositive and seronegative disease^[4]

When to measure rheumatoid factor?

Any patient who is suspected of having rheumatoid disease. However, keep in mind it may be negative in rheumatoid disease and thus it is important to refer before serology is available.^[5] Many patients with rheumatoid disease are seronegative to begin with but 80% seroconvert (become positive). Disease severity is often worse in those who are seropositive.

See also the separate [Rheumatoid Arthritis, Management of Rheumatoid Arthritis](#) and [Disease-modifying Antirheumatic Drugs \(DMARDs\)](#) articles.

Rheumatoid factor test

Venous blood is taken in a 'clotted' tube - usually the same one as U&E.

How are the results reported

Rheumatoid factor results can be reported in titres (normal <1:20) but more commonly as units (normal <23 IU/ml but see local guidelines, as this may vary from laboratory to laboratory). The sensitivity and specificity of rheumatoid factor for rheumatoid disease is low and thus it is not a good screening test. However, the predictive value of rheumatoid factor in patients with symmetric polyarticular joint swelling is 80%.

When is it positive?

- Rheumatoid arthritis - sensitivity in established disease is only 60-70% with a specificity of 78%. The higher the level in rheumatoid disease the worse the joint destruction and the greater the chance of systemic involvement.
- False positives occur in 5% of healthy individuals and in any inflammatory condition - eg, Sjögren's syndrome, systemic lupus erythematosus and mixed connective tissue disorder.

NICE guidance

The National Institute for Health and Care Excellence (NICE) recommends the following:^[5]

- Offer to carry out a blood test for rheumatoid factor in adults with suspected rheumatoid arthritis who are found to have synovitis on clinical examination.
- Consider measuring anti-cyclic citrullinated peptide (CCP) antibodies in adults with suspected RA if they are negative for rheumatoid factor.

- Refer for specialist opinion any adult with suspected persistent synovitis of undetermined cause. Refer urgently (even with a normal acute-phase response, negative anti-CCP antibodies or rheumatoid factor) if any of the following apply:
 - The small joints of the hands or feet are affected.
 - More than one joint is affected.
 - There has been a delay of three months or longer between onset of symptoms and seeking medical advice.

Disease associations of rheumatoid factor^[6]

- Arthritis: rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, reactive arthritis.
- Other connective tissue diseases: primary Sjogren's syndrome, mixed connective tissue disease, systemic lupus erythematosus, systemic sclerosis, dermatomyositis/polymyositis, systemic vasculitides (polyarteritis nodosa, granulomatosis with polyangiitis - formerly Wegener's granulomatosis).
- Bacterial infections: bacterial endocarditis, *Chlamydia pneumoniae*, *Klebsiella pneumoniae*, syphilis, tuberculosis.
- Viral infections: Coxsackie B, dengue, EBV, CMV, hepatitis A, B and C, herpes, HIV, measles, parvovirus, rubella.
- Parasitic infections: Chagas, malaria, onchocerciasis, toxoplasmosis.
- Other diseases: mixed cryoglobulinaemia type II, liver cirrhosis, primary biliary cirrhosis, malignancy, after multiple immunisations, chronic sarcoidosis.
- Healthy individuals: frequency increases with age - eg, 5% 50-year-olds, 10-25% 70-year-olds.

Prognostic use of rheumatoid factor

Rheumatoid factor does not generally help in monitoring rheumatoid disease, although it may help with the use of newer agents such as etanercept and infliximab. In patients on etanercept or infliximab and DMARDs the levels of rheumatoid factor reduce, which is associated with reduced clinical disease activity.

One study in Denmark found that people with elevated rheumatoid factor have up to 26-fold greater long-term risk of rheumatoid arthritis, and up to 32% 10-year absolute risk of rheumatoid arthritis.^[7]

Rheumatoid factor can also predict disease outcome in some patients. One example of this is that radiological progression – ie changes in hand X-rays – is worse in those who are seropositive.

Further reading

- [Lab Tests Online - UK](#)
- [Wasserman A](#); Rheumatoid Arthritis: Common Questions About Diagnosis and Management. *Am Fam Physician*. 2018 Apr 1;97(7):455-462.
- [Greenblatt HK, Kim HA, Bettner LF, et al](#); Preclinical rheumatoid arthritis and rheumatoid arthritis prevention. *Curr Opin Rheumatol*. 2020 May;32(3):289-296. doi: 10.1097/BOR.0000000000000708.

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3. [Scherer HU, Haupl T, Burmester GR](#); The etiology of rheumatoid arthritis. *J Autoimmun*. 2020 Jun;110:102400. doi: 10.1016/j.jaut.2019.102400. Epub 2020 Jan 22.
4. [Derksen VFAM, Huizinga TWJ, van der Woude D](#); The role of autoantibodies in the pathophysiology of rheumatoid arthritis. *Semin Immunopathol*. 2017 Jun;39(4):437-446. doi: 10.1007/s00281-017-0627-z. Epub 2017 Apr 27.
5. [Rheumatoid arthritis in adults: management](#); NICE Guideline (July 2018 - last updated October 2020)

6. [Ingegnoli F, Castelli R, Gualtierotti R](#); Rheumatoid factors: clinical applications. Dis Markers. 2013;35(6):727–34. doi: 10.1155/2013/726598. Epub 2013 Nov 13.
7. [Nielsen SF, Bojesen SE, Schnohr P, et al](#); Elevated rheumatoid factor and long term risk of rheumatoid arthritis: a prospective cohort study. BMJ. 2012 Sep 6;345:e5244. doi: 10.1136/bmj.e5244.

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