

Increased diagnostic accuracy and more effective treatment schemes together with new drugs help in tackling one of the most important rheumatic diseases.

Rheumatoid arthritis – an overview

Rheumatic diseases

There are many rheumatic disorders, and their signs and symptoms are often similar and may overlap. As a result, it frequently needs an expert rheumatologist to arrive at a sound diagnosis and initiate adequate treatment. A selection of typical rheumatic conditions is shown below, and rheumatoid arthritis (RA) is an important one of them:

- Rheumatoid arthritis
- Ankylosing spondylitis
- Psoriatic arthritis
- Polymyalgia rheumatica
- Vasculitis
- Systemic lupus erythematosus
- Sjögren's syndrome
- Scleroderma/systemic sclerosis
- Lyme borreliosis
- Osteoporosis
- Fibromyalgia
- Osteoarthritis

Rheumatoid arthritis

RA is a chronic inflammatory autoimmune disease where the patient's immune system attacks the body's own tissues. Typically, joints of the hands and wrists are affected. Symptoms usually include pain, swelling and stiffness with some functional impairment. More general symptoms such

as fatigue, loss of appetite and low-grade fever can also be observed in many patients¹. If the disease is active for some time without adequate control it can typically lead to chronic joint damage and subsequent disability with deformity as you can see in figures 1 and 2.

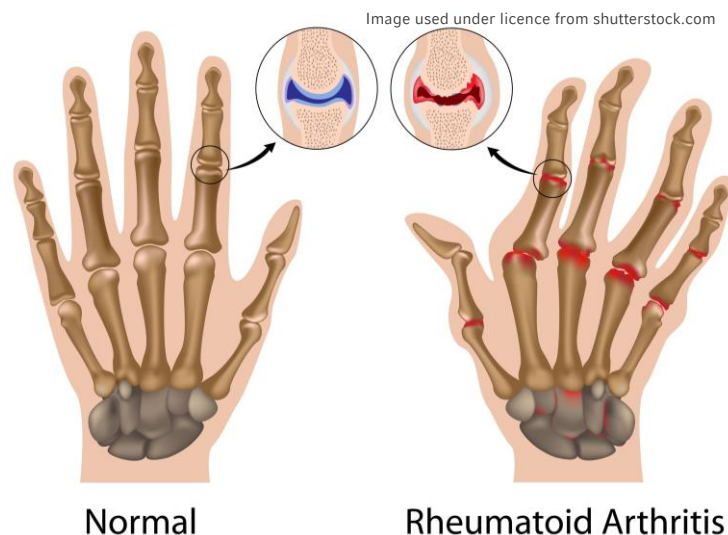


Figure 1: Difference between a healthy hand and a hand with joint damage and deformity due to rheumatoid arthritis

¹ See Rheumatoid Arthritis, Arthritis Foundation, www.arthritis.org

In general, RA occurs in a ‘symmetrical’ mirror pattern. That means, for instance, that if one hand is affected the other hand is typically affected, too. Often, symptoms are worse following a longer period of inactivity, e.g. after awakening in the morning; this ‘morning stiffness’, which can last for more than an hour, is a typical feature in RA patients.



Figure 2: RA patient with hand deformities

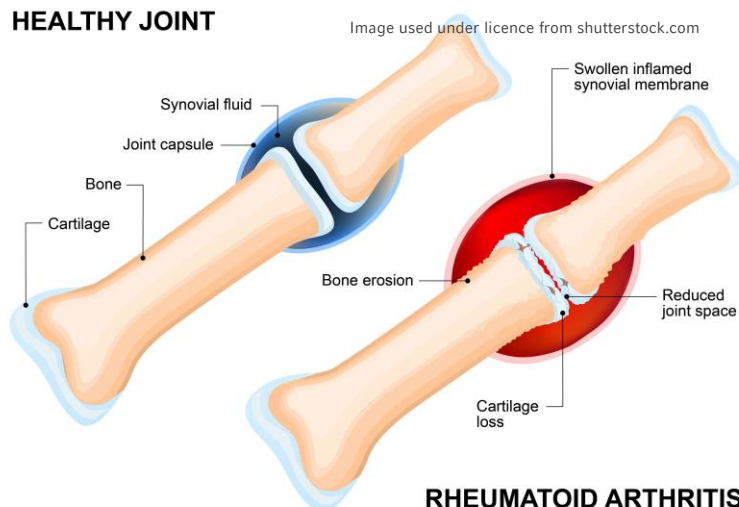
Since RA is regarded as a ‘systemic’ autoimmune disease it may affect not only joints. Other important organ systems can be damaged, too. These so-called extra-articular manifestations may, for instance, include heart and blood vessels, lungs, nerves, kidneys, eyes or skin^{2, 3}. In addition, having RA can influence mood and mental well-being, thus putting RA patients at a higher risk for anxiety and depression⁴.

What happens in rheumatoid arthritis?

Interestingly, in RA the joint function impairment and subsequent damage does not result from the ‘direct’ damage to the cartilage/bone that is seen, for instance, in classical wear and tear osteoarthritis. It is rather an indirect effect due to an attack of the immune system on the inner lining of the joint capsule – the so-called synovium (figure 3). The subsequent inflammation of the synovial cells (called synovitis) leads to a thickening of the synovium and the overall joint capsule, hence causing the typical RA inflammation signs: swelling, pain, redness, warmth and functional decrease. Over time the inflamed synovium will affect the joint cartilage and bone structures, leading to

more permanent damage with joint instability and pain. Nowadays, there is good evidence that such permanent (and often irreversible) damage starts relatively early in the RA disease process.

HEALTHY JOINT



RHEUMATOID ARTHRITIS

Figure 3: RA joint damage versus healthy joint

Epidemiology

RA typically hits people at the most productive time in their lives and the ability to do normal occupational activities may decrease substantially over time. The World Health Organization, for instance, states that in developed countries at least half of RA patients are not able to hold down a full-time job within 10 years of disease onset⁵. Since in many societies the prevalence of RA is in the range of 0.5–1.0%⁶ it has a considerable effect on the overall disease burden in numerous countries. Mortality in RA patients is also increased, mainly due to a higher risk of cardiovascular, respiratory or infectious disease^{7, 8, 9}. For instance, patients with a persistently high disease activity are >2.4 times more likely to die compared to patients with persistently low disease activity¹⁰.

⁵ See Chronic rheumatic conditions, WHO, www.who.int

⁶ See Scott DL, et al., Rheumatoid arthritis. *Lancet*. 376: 1094-108.

⁷ See Smolen JS, et al., Rheumatoid arthritis. *Lancet*. 388: 2023-2038

⁸ See Footnote 6

⁹ See Naz SM, et al., Mortality in established rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 21(5):871-83

¹⁰ See Listing J, et al., Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNF α inhibitors and rituximab. *Ann Rheum Dis*. 74(2):415-21.

² See Rheumatoid Arthritis, Arthritis Foundation, www.arthritis.org

³ See Smolen JS, et al., 2016, Rheumatoid arthritis. *Lancet*. 388: 2023-2038

⁴ See footnote 2

Risk factors

A number of studies have shown a genetic role in RA; the HLA-DRB1 genotype, for example, plays an important role in RA pathogenesis. In addition, a family history of RA can more than triple the risk for RA. Gender is also a significant factor: women are affected around three times more often than men¹¹.

Did you know that smoking is an important RA risk factor?

Smoking is an important avoidable risk factor. Smokers not only show a higher incidence of RA, but the disease severity seems to be increased, too. Certain infectious agents (e.g. the Epstein-Barr virus) have been implicated in the development of RA, but their overall relevance is still inconclusive.

There seems to be an association between periodontal disease and RA, but it is unclear whether this relation is causal. To what extent the body's overall bacterial flora (the so-called microbiome) could influence the pathogenesis of RA is currently a subject of debate. The pace of microbiome research is steadily increasing and new insights are likely to be seen in the future that probably may one day even hint at completely new therapeutic approaches for RA and other diseases.

Diagnosis

RA is often challenging to diagnose since symptoms may only progress gradually and may mimic other joint problems and diseases. Also, there is no single test which can easily confirm a RA diagnosis. Rather, a combination of symptoms and signs, together with medical imaging plus certain laboratory tests, would eventually lead to a diagnostic conclusion. Doctors use internationally standardised classification criteria for diagnosis¹² and then start treatment to delay or avoid long-term damage.

Some of the laboratory markers in use have been well-known in medicine for a long time, including for example erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), but they are quite unspecific for RA. Moreover, even the so-called 'rheumatoid factor' (RF) is not regularly seen in RA patients and can sometimes show up with other chronic problems, too; to complicate things still further, RF is sometimes even detected in completely healthy people.

However, newer laboratory tests have been developed in recent decades that look for so-called ACPAs (anti-citrullinated peptide/protein antibodies). If doctors find such ACPAs the diagnostic RA accuracy increases substantially. Different ACPA laboratory assays are available and nowadays ACPA testing is a standard diagnostic procedure and also has some value in treatment control.

Treatment

Modern RA treatment typically starts very early in order to achieve remission or at least a low disease activity. The main aim is to increase the quality of life by reducing pain and inflammation and to slow down or stop the development of permanent damage at an early stage. Scoring systems help to evaluate RA severity. For instance, the Disease Activity Score 28 (DAS28) takes 28 joint counts and other factors into account – a DAS28 of <2.6 indicates remission; 2.6–3.2 indicates mild, >3.2–5.1 moderate and >5.1 high disease activity¹³.

There are a number of interventional options such as physiotherapy, orthopedic therapy, surgery, occupational therapy, socio-medical measures and many others. However, the most important therapeutic pillar is medication therapy.

So-called non-steroidal anti-inflammatory drugs (NSAIDs) are mainly able to reduce stiffness and pain but do not target underlying joint damage and hence NSAIDs are not considered to be disease-modifying. On the other hand, the so-called disease-modifying anti-rheumatic drugs (DMARDs) can influence the inflammation process and at the same time have the potential to reduce structural tissue damage. Nowadays, there are basically two major classes of DMARDs – synthetic and biological.

¹¹ See Scott DL, et al.; Rheumatoid arthritis. *Lancet*. 376: 1094-108

¹² See Aletaha D, et al., Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 62(9):2569-81

¹³ See Smolen JS, et al., Rheumatoid arthritis. *Lancet*. 388: 2023-2038

Some 'conventional' DMARDs have been known and used for a long time and are still important in first-line intervention approaches (e.g. methotrexate in combination with a low-dose glucocorticoid). More 'modern' DMARDs that have been developed over the last few decades are the 'targeted synthetic' DMARDs and the 'biological' DMARDs. These DMARDs can have a considerable impact since they often still work in cases where conventional DMARD treatment is not sufficiently effective or – for some reason – is not tolerated by the patient. However, since nothing comes without a price, many of these modern DMARD therapeutics can sometimes have unintended side-effects such as increased risk of infections, although overall they appear to reduce disease severity and associated mortality¹⁴. Last but not least, it is important to note that many of these modern drugs can be very if not extremely expensive when compared to DMARD therapies of the past.

Summary

Since RA is not uncommon it will always play an important role for insurers on various levels such as pricing, product wording, underwriting or claims handling. Basically, all morbidity product lines can be affected (e.g. health, disability, critical illness, long-term care) and, depending on disease severity, mortality can also be increased. As in many other areas of medicine, new diagnostic approaches and treatment options have a considerable effect on morbidity and mortality. Of special note for RA are the introduction of diagnostic ACPAs, the implementation of early therapy and the use of new and usually expensive 'targeted synthetic' and 'biological' drugs. Beyond this day-to-day disease-specific relevance, RA is also an example of the significant advances currently being made in so many other areas in medicine that are shaping our industry's present and future.

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¹⁴ See Rheumatoid Arthritis, Arthritis Foundation, www.arthritis.org