Rheumatoid arthritis

Rheumatoid arthritis (RA) is a long-term

autoimmune disorder that primarily affects joints.[1] It Rheumatoid arthritis

typically results in warm, swollen, and painful

joints.[1] Pain and stiffness often worsen following

rest.[1] Most commonly, the wrist and hands are

involved, with the same joints typically involved on

both sides of the body.[1] The disease may also affect

other parts of the body, including skin, eyes, lungs,

heart, nerves, and blood.[1] This may result in a low

red blood cell count, inflammation around the lungs,

and inflammation around the heart.[1] Fever and low A hand severely affected by rheumatoid

energy may also be present.[1] Often, symptoms come arthritis. This degree of swelling and

on gradually over weeks to months.[2] deformation does not typically occur with

current treatment.

While the cause of rheumatoid arthritis is not clear, it Specialty Rheumatology, Immunology

is believed to involve a combination of genetic and Symptoms Warm, swollen, painful

environmental factors.[1] The underlying mechanism joints[1]

involves the body's immune system attacking the

Complications Low red blood cells,

joints.[1] This results in inflammation and thickening of

inflammation around the

the joint capsule.[1] It also affects the underlying bone

lungs, inflammation around

and cartilage.[1] The diagnosis is made mostly on the

the heart[1]

basis of a person's signs and symptoms.[2] X-rays and

laboratory testing may support a diagnosis or exclude Usual onset Middle age[1]

other diseases with similar symptoms.[1] Other Duration Lifelong[1]

diseases that may present similarly include systemic Causes Unknown[1]

lupus erythematosus, psoriatic arthritis, and Diagnostic Based on symptoms, medical

fibromyalgia among others.[2]

method imaging, blood tests[1][2]

The goals of treatment are to reduce pain, decrease Differential Systemic lupus

inflammation, and improve a person's overall diagnosis erythematosus, psoriatic

functioning.[5] This may be helped by balancing rest arthritis, fibromyalgia[2]

and exercise, the use of splints and braces, or the use of Medication Pain medications, steroids,

assistive devices.[1][6][7] Pain medications, steroids, Nonsteroidal anti-

and NSAIDs are frequently used to help with inflammatory drugs, disease-

symptoms.[1] Disease-modifying antirheumatic drugs modifying antirheumatic

(DMARDs), such as hydroxychloroquine and drugs[1]

methotrexate, may be used to try to slow the Frequency 0.5–1% (adults in developed

progression of disease.[1] Biological DMARDs may be world)[3]

used when the disease does not respond to other Deaths 30,000 (2015)[4]

treatments.[8] However, they may have a greater rate of adverse effects.[9] Surgery to repair, replace, or

fuse joints may help in certain situations.[1]

RA affects about 24.5 million people as of 2015.[10] This is 0.5–1% of adults in the developed world with

between 5 and 50 per 100,000 people newly developing the condition each year.[3] Onset is most frequent

during middle age and women are affected 2.5 times as frequently as men.[1] It resulted in 38,000 deaths

in 2013, up from 28,000 deaths in 1990.[11] The first recognized description of RA was made in 1800 by

Dr. Augustin Jacob Landré-Beauvais (1772–1840) of Paris.[12] The term rheumatoid arthritis is based on

the Greek for watery and inflamed joints.[13]

Signs and symptoms

RA primarily affects joints, but it also affects other organs in more than 15–25% of cases.[14] Associated

problems include cardiovascular disease, osteoporosis, interstitial lung disease, infection, cancer, feeling

tired, depression, mental difficulties, and trouble working.[15]

Joints

Arthritis of joints involves inflammation of the synovial

membrane. Joints become swollen, tender and warm, and

stiffness limits their movement. With time, multiple joints

are affected (polyarthritis). Most commonly involved are the

small joints of the hands, feet and cervical spine, but larger

joints like the shoulder and knee can also be

involved.[16]: 1098 Synovitis can lead to tethering of tissue

with loss of movement and erosion of the joint surface

causing deformity and loss of function.[2] The fibroblast-

like synoviocytes (FLS), highly specialized mesenchymal

cells found in the synovial membrane, have an active and

prominent role in these pathogenic processes of the

rheumatic joints.[17]

RA typically manifests with signs of inflammation, with the

affected joints being swollen, warm, painful and stiff,

particularly early in the morning on waking or following

prolonged inactivity. Increased stiffness early in the

morning is often a prominent feature of the disease and

typically lasts for more than an hour. Gentle movements

may relieve symptoms in early stages of the disease. These

signs help distinguish rheumatoid from non-inflammatory

problems of the joints, such as osteoarthritis. In arthritis of

non-inflammatory causes, signs of inflammation and early

morning stiffness are less prominent.[18] The pain associated A diagram showing how rheumatoid

with RA is induced at the site of inflammation and classified arthritis affects a joint

as nociceptive as opposed to neuropathic.[19] The joints are often

affected in a fairly symmetrical fashion, although this is not

specific, and the initial presentation may be asymmetrical.[16]: 1098

As the pathology progresses the inflammatory activity leads to

tendon tethering and erosion and destruction of the joint surface,

which impairs range of movement and leads to deformity. The

fingers may develop almost any deformity depending on which

Hand deformity, sometimes called a

joints are most involved. Specific deformities, which also occur in

swan deformity, in an elderly person

osteoarthritis, include ulnar deviation, boutonniere deformity (also

with rheumatoid arthritis

"buttonhole deformity", flexion of proximal interphalangeal joint

and extension of distal interphalangeal joint of the hand), swan

neck deformity (hyperextension at proximal interphalangeal joint and flexion at distal interphalangeal

joint) and "Z-thumb." "Z-thumb" or "Z-deformity" consists of hyperextension of the interphalangeal

joint, fixed flexion and subluxation of the metacarpophalangeal joint and gives a "Z" appearance to the

thumb.[16]: 1098 The hammer toe deformity may be seen. In the worst case, joints are known as arthritis

mutilans due to the mutilating nature of the deformities.[20]

Skin

The rheumatoid nodule, which is sometimes in the skin, is the most common non-joint feature and occurs

in 30% of people who have RA.[21] It is a type of inflammatory reaction known to pathologists as a

"necrotizing granuloma". The initial pathologic process in nodule formation is unknown but may be

essentially the same as the synovitis, since similar structural features occur in both. The nodule has a

central area of fibrinoid necrosis that may be fissured and which corresponds to the fibrin-rich necrotic

material found in and around an affected synovial space. Surrounding the necrosis is a layer of palisading

macrophages and fibroblasts, corresponding to the intimal layer in synovium and a cuff of connective

tissue containing clusters of lymphocytes and plasma cells, corresponding to the subintimal zone in

synovitis. The typical rheumatoid nodule may be a few millimetres to a few centimetres in diameter and

is usually found over bony prominences, such as the elbow, the heel, the knuckles, or other areas that

sustain repeated mechanical stress. Nodules are associated with a positive RF (rheumatoid factor) titer,

ACPA, and severe erosive arthritis. Rarely, these can occur in internal organs or at diverse sites on the

body.[22]

Several forms of vasculitis occur in RA, but are mostly seen with long-standing and untreated disease.

The most common presentation is due to involvement of small- and medium-sized vessels. Rheumatoid

vasculitis can thus commonly present with skin ulceration and vasculitic nerve infarction known as

mononeuritis multiplex.[23]

Other, rather rare, skin associated symptoms include pyoderma gangrenosum, Sweet's syndrome, drug

reactions, erythema nodosum, lobe panniculitis, atrophy of finger skin, palmar erythema, and skin

fragility (often worsened by corticosteroid use).[24]

Diffuse alopecia areata (Diffuse AA) occurs more commonly in people with rheumatoid arthritis.[25] RA

is also seen more often in those with relatives who have AA.[25]

Lungs

Lung fibrosis is a recognized complication of rheumatoid arthritis. It is also a rare but well-recognized

consequence of therapy (for example with methotrexate and leflunomide). Caplan's syndrome describes

lung nodules in individuals with RA and additional exposure to coal dust. Exudative pleural effusions are

also associated with RA.[26][27]

Heart and blood vessels

People with RA are more prone to atherosclerosis, and risk of myocardial infarction (heart attack) and

stroke is markedly increased.[28][29][30] Other possible complications that may arise include: pericarditis,

endocarditis, left ventricular failure, valvulitis and fibrosis.[31] Many people with RA do not experience

the same chest pain that others feel when they have angina or myocardial infarction. To reduce

cardiovascular risk, it is crucial to maintain optimal control of the inflammation caused by RA (which

may be involved in causing the cardiovascular risk), and to use exercise and medications appropriately to

reduce other cardiovascular risk factors such as blood lipids and blood pressure. Doctors who treat people

with RA should be sensitive to cardiovascular risk when prescribing anti-inflammatory medications, and

may want to consider prescribing routine use of low doses of aspirin if the gastrointestinal effects are

tolerable.[31]

Blood

Anemia is by far the most common abnormality of the blood cells which can be caused by a variety of

mechanisms. The chronic inflammation caused by RA leads to raised hepcidin levels, leading to anemia

of chronic disease where iron is poorly absorbed and also sequestered into macrophages. The red cells are

of normal size and color (normocytic and Normochromic).[32]

A low white blood cell count usually only occurs in people with Felty's syndrome with an enlarged liver

and spleen. The mechanism of neutropenia is complex. An increased platelet count occurs when

inflammation is uncontrolled.[33]

Other

The role of the circadian clock in rheumatoid arthritis suggests a correlation between an early morning

rise in circulating levels of pro-inflammatory cytokines, such as interleukin-6 and painful morning joint

stiffness.[34]

Kidneys

Renal amyloidosis can occur as a consequence of untreated chronic inflammation.[35] Treatment with

penicillamine or gold salts such as sodium aurothiomalate are recognized causes of membranous

nephropathy.[36]

Eyes

The eye can be directly affected in the form of episcleritis[37] or scleritis, which when severe can very

rarely progress to perforating scleromalacia. Rather more common is the indirect effect of

keratoconjunctivitis sicca, which is a dryness of eyes and mouth caused by lymphocyte infiltration of

lacrimal and salivary glands. When severe, dryness of the cornea can lead to keratitis and loss of vision as

well as being painful. Preventive treatment of severe dryness with measures such as nasolacrimal duct

blockage is important.[38]

Liver

Liver problems in people with rheumatoid arthritis may be due to the underlying disease process or as a

result of the medications used to treat the disease.[39] A coexisting autoimmune liver disease, such as

primary biliary cirrhosis or autoimmune hepatitis may also cause problems.[39]

Neurological

Peripheral neuropathy and mononeuritis multiplex may occur. The most common problem is carpal

tunnel syndrome caused by compression of the median nerve by swelling around the wrist. Rheumatoid

disease of the spine can lead to myelopathy. Atlanto-axial subluxation can occur, owing to erosion of the

odontoid process and/or transverse ligaments in the cervical spine's connection to the skull. Such an

erosion (>3mm) can give rise to vertebrae slipping over one another and compressing the spinal cord.

Clumsiness is initially experienced, but without due care, this can progress to quadriplegia or even

death.[40]

Constitutional symptoms

Constitutional symptoms including fatigue, low grade fever, malaise, morning stiffness, loss of appetite

and loss of weight are common systemic manifestations seen in people with active RA.

Bones

Local osteoporosis occurs in RA around inflamed joints. It is postulated to be partially caused by

inflammatory cytokines. More general osteoporosis is probably contributed to by immobility, systemic

cytokine effects, local cytokine release in bone marrow and corticosteroid therapy.[41][42]

Cancer

The incidence of lymphoma is increased, although it is uncommon and associated with the chronic

inflammation, not the treatment of RA.[43][44] The risk of non-melanoma skin cancer is increased in

people with RA compared to the general population, an association possibly due to the use of

immunosuppression agents for treating RA.[45]

Teeth

Periodontitis and tooth loss are common in people with rheumatoid arthritis.[46]

Risk factors

RA is a systemic (whole body) autoimmune disease. Some genetic and environmental factors affect the

risk for RA.

Genetic

Worldwide, RA affects approximately 1% of the adult population and occurs one in 1,000 children.

Studies show RA primarily affects individuals between the ages of 40–60 years and is seen more

commonly in females.[47][48] A family history of RA increases the risk around three to five times; as of

2016, it was estimated that genetics may account for 40–65% of cases of seropositive RA, but only

around 20% for seronegative RA.[3] RA is strongly associated with genes of the inherited tissue type

major histocompatibility complex (MHC) antigen. HLA-DR4 is the major genetic factor implicated – the

relative importance varies across ethnic groups.[49]

Genome-wide association studies examining single-nucleotide polymorphisms have found around one

hundred alleles associated with RA risk.[50] Risk alleles within the HLA (particularly HLA-DRB1) genes

harbor more risk than other loci.[51] The HLA encodes proteins that control recognition of self- versus

non-self molecules. Other risk loci include genes affecting co-stimulatory immune pathways—for

example CD28 and CD40, cytokine signaling, lymphocyte receptor activation threshold (e.g., PTPN22),

and innate immune activation—appear to have less influence than HLA mutations.[3][52]

Environmental

There are established epigenetic and environmental risk factors for RA.[53][3] Smoking is an established

risk factor for RA in Caucasian populations, increasing the risk three times compared to non-smokers,

particularly in men, heavy smokers, and those who are rheumatoid factor positive.[54] Modest alcohol

consumption may be protective.[55]

Silica exposure has been linked to RA.[56]

Negative findings

No infectious agent has been consistently linked with RA and there is no evidence of disease clustering to

indicate its infectious cause,[49] but periodontal disease has been consistently associated with RA.[3]

The many negative findings suggest that either the trigger varies, or that it might, in fact, be a chance

event inherent with the immune response.[57]

Pathophysiology

RA primarily starts as a state of persistent cellular activation leading to autoimmunity and immune

complexes in joints and other organs where it manifests.[58]

The clinical manifestations of disease are primarily inflammation of the synovial membrane and joint

damage, and the fibroblast-like synoviocytes play a key role in these pathogenic processes.[17] Three

phases of progression of RA are an initiation phase (due to non-specific inflammation), an amplification

phase (due to T cell activation), and chronic inflammatory phase, with tissue injury resulting from the

cytokines, IL–1, TNF-alpha, and IL–6.[20]

Non-specific inflammation

Factors allowing an abnormal immune response, once initiated, become permanent and chronic. These

factors are genetic disorders which change regulation of the adaptive immune response.[3] Genetic factors

interact with environmental risk factors for RA, with cigarette smoking as the most clearly defined risk

factor.[54][59]

Other environmental and hormonal factors may explain higher risks for women, including onset after

childbirth and hormonal medications. A possibility for increased susceptibility is that negative feedback

mechanisms – which normally maintain tolerance – are overtaken by positive feedback mechanisms for

certain antigens, such as IgG Fc bound by rheumatoid factor and citrullinated fibrinogen bound by

antibodies to citrullinated peptides (ACPA – Anti–citrullinated protein antibody). A debate on the relative

roles of B-cell produced immune complexes and T cell products in inflammation in RA has continued for

30 years, but neither cell is necessary at the site of inflammation, only autoantibodies to IgGFc, known as

rheumatoid factors and ACPA, with ACPA having an 80% specificity for diagnosing RA.[60] As with

other autoimmune diseases, people with RA have abnormally glycosylated antibodies, which are believed

to promote joint inflammation.[61]: 10

Amplification in the synovium

Once the generalized abnormal immune response has become established – which may take several years

before any symptoms occur – plasma cells derived from B lymphocytes produce rheumatoid factors and

ACPA of the IgG and IgM classes in large quantities. These activate macrophages through Fc receptor

and complement binding, which is part of the intense inflammation in RA.[62] Binding of an autoreactive

antibody to the Fc receptors is mediated through the antibody's N-glycans, which are altered to promote

inflammation in people with RA.[61]: 8

This contributes to local inflammation in a joint, specifically the synovium with edema, vasodilation and

entry of activated T-cells, mainly CD4 in microscopically nodular aggregates and CD8 in microscopically

diffuse infiltrates.[63]

Synovial macrophages and dendritic cells function as antigen-presenting cells by expressing MHC class

II molecules, which establishes the immune reaction in the tissue.[63]

Chronic inflammation

The disease progresses by forming granulation tissue at the edges of the synovial lining, pannus with

extensive angiogenesis and enzymes causing tissue damage.[64] The fibroblast-like synoviocytes have a

prominent role in these pathogenic processes.[17] The synovium thickens, cartilage and underlying bone

disintegrate, and the joint deteriorates, with raised calprotectin levels serving as a biomarker of these

events.[65] Importantly inflammatory events are not limited to synovium but it appear to be systemic,

X-ray of the wrist of a woman with rheumatoid arthritis, showing unaffected carpal bones in the left image,

and ankylosing fusion of the carpal bones eight years later in the right image

evidence suggest that alterations in T helper profile favoring inflammation such as inflammatory IL-17A

producing T helper cells and pathogenic Th17 cells are come from both memory and effector

compartment in RA patients peripheral blood.[66]

Cytokines and chemokines attract and accumulate immune cells, i.e. activated T- and B cells, monocytes

and macrophages from activated fibroblast-like synoviocytes, in the joint space. By signalling through

RANKL and RANK, they eventually trigger osteoclast production, which degrades bone tissue.[3][67] The

fibroblast-like synoviocytes that are present in the synovium during rheumatoid arthritis display altered

phenotype compared to the cells present in normal tissues. The aggressive phenotype of fibroblast-like

synoviocytes in rheumatoid arthritis and the effect these cells have on the microenvironment of the joint

can be summarized into hallmarks that distinguish them from healthy fibroblast-like synoviocytes. These

hallmark features of fibroblast-like synoviocytes in rheumatoid arthritis are divided into seven cell-

intrinsic hallmarks and four cell-extrinsic hallmarks.[17] The cell-intrinsic hallmarks are: reduced

apoptosis, impaired contact inhibition, increased migratory invasive potential, changed epigenetic

landscape, temporal and spatial heterogeneity, genomic instability and mutations, and reprogrammed

cellular metabolism. The cell-extrinsic hallmarks of FLS in RA are: promotes osteoclastogenesis and

bone erosion, contributes to cartilage degradation, induces synovial angiogenesis, and recruits and

stimulates immune cells.[17]

Diagnosis

Imaging

X-rays of the hands and feet are generally performed when many joints affected. In RA, there may be no

changes in the early stages of the disease or the x-ray may show osteopenia near the joint, soft tissue

swelling, and a smaller than normal joint space. As the disease advances, there may be bony erosions and

subluxation. Other medical imaging techniques such as magnetic resonance imaging (MRI) and

ultrasound are also used in RA.[20][69]

Technical advances in ultrasonography like high-frequency

transducers (10 MHz or higher) have improved the spatial

resolution of ultrasound images depicting 20% more erosions than

conventional radiography. Color Doppler and power Doppler

ultrasound are useful in assessing the degree of synovial

inflammation as they can show vascular signals of active

synovitis. This is important, since in the early stages of RA, the

synovium is primarily affected, and synovitis seems to be the best

predictive marker of future joint damage.[70]

Blood tests

When RA is clinically suspected, a physician may test for

rheumatoid factor (RF) and anti-citrullinated protein antibodies

(ACPAs measured as anti-CCP antibodies).[71]: 382 The test is

positive approximately two-thirds of the time, but a negative RF

or CCP antibody does not rule out RA; rather, the arthritis is called

seronegative, which occurs in approximately a third of people with

X-ray of the hand in rheumatoid

RA.[72] During the first year of illness, rheumatoid factor is more

arthritis

likely to be negative with some individuals becoming seropositive

over time. RF is a non-specific antibody and seen in about 10% of

healthy people, in many other chronic infections like hepatitis C,

and chronic autoimmune diseases such as Sjögren's syndrome and

systemic lupus erythematosus. Therefore, the test is not specific

for RA.[20]

Hence, new serological tests check for anti-citrullinated protein

antibodies ACPAs. These tests are again positive in 61–75% of all

RA cases, but with a specificity of around 95%.[73] As with RF,

ACPAs are many times present before symptoms have started.[20]

The by far most common clinical test for ACPAs is the anti-cyclic

citrullinated peptide (anti CCP) ELISA. In 2008 a serological

point-of-care test for the early detection of RA combined the

detection of RF and anti-MCV with a sensitivity of 72% and

specificity of 99.7%.[74][75]

Appearance of synovial fluid from a

joint with inflammatory arthritis

To improve the diagnostic capture rate in the early detection of

patients with RA and to risk stratify these individuals, the

rheumatology field continues to seek complementary markers to both RF and anti-CCP. 14-3-3η

(YWHAH) is one such marker that complements RF and anti-CCP, along with other serological measures

like C-reactive protein. In a systematic review, 14-3-3η has been described as a welcome addition to the

rheumatology field. The authors indicate that the serum based 14-3-η marker is additive to the

armamentarium of existing tools available to clinicians, and that there is adequate clinical evidence to

support its clinical benefits.[76]

Other blood tests are usually done to differentiate from other

causes of arthritis, like the erythrocyte sedimentation rate (ESR),

C-reactive protein, full blood count, kidney function, liver

enzymes and other immunological tests (e.g., antinuclear

antibody/ANA) are all performed at this stage. Elevated ferritin

levels can reveal hemochromatosis, a mimic of RA, or be a sign of

Still's disease, a seronegative, usually juvenile, variant of

rheumatoid Arthritis.[77]

Classification criteria

In 2010, the 2010 ACR / EULAR Rheumatoid Arthritis

Classification Criteria were introduced.[78]

Closeup of bone erosions in

The new criteria are not diagnostic criteria, but are classification rheumatoid arthritis[68]

criteria to identify disease with a high likelihood of developing a

chronic form.[20] However a score of 6 or greater unequivocally

classifies a person with a diagnosis of rheumatoid arthritis.[79]

These new classification criteria overruled the "old" ACR criteria of 1987 and are adapted for early RA

diagnosis. The "new" classification criteria, jointly published by the American College of Rheumatology

(ACR) and the European League Against Rheumatism (EULAR) establish a point value between 0 and

10. Four areas are covered in the diagnosis:[78]

joint involvement, designating the metacarpophalangeal joints, proximal interphalangeal

joints, the interphalangeal joint of the thumb, second through fifth metatarsophalangeal joint

and wrist as small joints, and shoulders, elbows, hip joints, knees, and ankles as large

joints:

Involvement of 1 large joint gives 0 points

Involvement of 2–10 large joints gives 1 point

Involvement of 1–3 small joints (with or without involvement of large joints) gives 2

points

Involvement of 4–10 small joints (with or without involvement of large joints) gives 3

points

Involvement of more than 10 joints (with involvement of at least 1 small joint) gives 5

points

serological parameters – including the rheumatoid factor as well as ACPA – "ACPA" stands

for "anti-citrullinated protein antibody":

Negative RF and negative ACPA gives 0 points

Low-positive RF or low-positive ACPA gives 2 points

High-positive RF or high-positive ACPA gives 3 points

acute phase reactants: 1 point for elevated erythrocyte sedimentation rate, ESR, or elevated

CRP value (c-reactive protein)

duration of arthritis: 1 point for symptoms lasting six weeks or longer

The new criteria accommodate to the growing understanding of RA and the improvements in diagnosing

RA and disease treatment. In the "new" criteria, serology and autoimmune diagnostics carries major

weight, as ACPA detection is appropriate to diagnose the disease in an early state, before joints

destructions occur. Destruction of the joints viewed in radiological images was a significant point of the

ACR criteria from 1987.[80] This criterion no longer is regarded to be relevant, as this is just the type of

damage that treatment is meant to avoid.

Differential diagnoses

Several other medical

Synovial fluid examination[81][82]

conditions can resemble

RA, and need to be Type WBC (per mm3) % neutrophils Viscosity Appearance

distinguished from it at Normal <200 0 High Transparent

the time of diagnosis:[83]

Osteoarthritis <5000 <25 High Clear yellow

Crystal induced Trauma <10,000 <50 Variable Bloody

arthritis (gout, and Inflammatory 2,000–50,000 50–80 Low Cloudy yellow

pseudogout) –

usually involves Septic arthritis >50,000 >75 Low Cloudy yellow

particular joints Gonorrhea ~10,000 60 Low Cloudy yellow

(knee, MTP1,

heels) and can be Tuberculosis ~20,000 70 Low Cloudy yellow

distinguished with Inflammatory: Arthritis, gout, rheumatoid arthritis, rheumatic fever

an aspiration of

joint fluid if in

doubt. Redness, asymmetric distribution of affected joints, pain occurs at night and the

starting pain is less than an hour with gout.

Osteoarthritis – distinguished with X-rays of the affected joints and blood tests, older age,

starting pain less than an hour, asymmetric distribution of affected joints and pain worsens

when using joint for longer periods.

Systemic lupus erythematosus (SLE) – distinguished by specific clinical symptoms and

blood tests (antibodies against double-stranded DNA)

One of the several types of psoriatic arthritis resembles RA – nail changes and skin

symptoms distinguish between them

Lyme disease causes erosive arthritis and may closely resemble RA – it may be

distinguished by blood test in endemic areas

Reactive arthritis – asymmetrically involves heel, sacroiliac joints and large joints of the leg.

It is usually associated with urethritis, conjunctivitis, iritis, painless buccal ulcers, and

keratoderma blennorrhagica.

Axial spondyloarthritis (including ankylosing spondylitis) – this involves the spine, although

an RA-like symmetrical small-joint polyarthritis may occur in the context of this condition.

Hepatitis C – RA-like symmetrical small-joint polyarthritis may occur in the context of this

condition. Hepatitis C may also induce rheumatoid factor auto-antibodies.

Rarer causes which usually behave differently but may cause joint pains:[83]

Sarcoidosis, amyloidosis, and Whipple's disease can also resemble RA.

Hemochromatosis may cause hand joint arthritis.

Acute rheumatic fever can be differentiated by a migratory pattern of joint involvement and

evidence of antecedent streptococcal infection.

Bacterial arthritis (such as by Streptococcus) is usually asymmetric, while RA usually

involves both sides of the body symmetrically.

Gonococcal arthritis (a bacterial arthritis) is also initially migratory and can involve tendons

around the wrists and ankles.

Sometimes arthritis is in an undifferentiated stage (i.e. none of the above criteria is positive), even if

synovitis is witnessed and assessed with ultrasound imaging.

Difficult-to-treat

Rheumatoid arthritis (D2T RA) is a specific classification RA by the European League against

Rheumatism (EULAR).[84]

Signs of illness:

1. Persistence of signs and symptoms

2. Drug resistance

3. Does not respond on two or more biological treatments

4. Does not respond on anti-rheumatic drugs with different mechanism of action

Factors contributing to difficult-to-treat disease:

1. Genetic risk factors

2. Environmental factors (diet, smoking, physical activity)

3. Overweight and obese

Genetic factors

Genetic factors such as HLA-DR1B1,[85] TRAF1, PSORS1C1 and microRNA 146a[86] are associated

with difficult to treat rheumatoid arthritis, other gene polymorphisms seem to be correlated with response

to biologic modifying anti-rheumatic drugs (bDMARDs). Next one is FOXO3A gene region been

reported as associated with worst disorder. The minor allele at FOXO3A summon a differential response

of monocytes in RA patients. FOXO3A can provide an increase of pro-inflammatory cytokines, including

TNFα. Possible gene polymorphism: STAT4, PTPN2, PSORS1C1 and TRAF3IP2 genes had been

correlated with response to TNF inhibitors.[87]

HLA-DR1 and HLA-DRB1 gene

The HLA-DRB1 gene is part of a family of genes called the human leukocyte antigen (HLA) complex.

The HLA complex is the human version of the major histocompatibility complex (MHC). Currently, have

been identified at least 2479 different versions of the HLA-DRB1 gene.[88] The presence of HLA-DRB1

alleles seems to predict radiographic damage, which may be partially mediated by ACPA development,

and also elevated sera inflammatory levels and high swollen joint count. HLA-DR1 is encoded by the

most risk allele HLA-DRB1 which share a conserved 5-aminoacid sequence that is correlated with the

development of anti-citrullinated protein antibodies.[89] HLA-DRB1 gene have more strong correlation

with disease development. Susceptibility to and outcome for rheumatoid arthritis (RA) may associate

with particular HLA-DR alleles, but these alleles vary among ethnic groups and geographic areas.[90]

MicroRNAs

MicroRNAs are a factor in the development of that type of disease. MicroRNAs usually operate as a

negative regulator of the expression of target proteins and their increased concentration after biologic

treatment (bDMARDs) or after anti-rheumatic drugs. Level of miRNA before and after anti-

TNFa/DMRADs combination therapy are potential novel biomarkers for predicting and monitoring

outcome. For instance, some of them were found significantly upregulated by anti-TNFa/DMRADs

combination therapy. For example, miRNA-16-5p, miRNA-23-3p, miRNA125b-5p, miRNA-126-3p,

miRNA-146a-5p, miRNA-223-3p. Curious fact is that only responder patients showed an increase in

those miRNAs after therapy, and paralleled the reduction of TNFα, interleukin (IL)-6, IL-17, rheumatoid

factor (RF), and C-reactive protein (CRP).[91]

Monitoring progression

Many tools can be used to monitor remission in rheumatoid arthritis.

DAS28: Disease Activity Score of 28 joints (DAS28) is widely used as an indicator of RA

disease activity and response to treatment. Joints included are (bilaterally): proximal

interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2),

shoulders (2) and knees (2). When looking at these joints, both the number of joints with

tenderness upon touching (TEN28) and swelling (SW28) are counted. The erythrocyte

sedimentation rate (ESR) is measured and the affected person makes a subjective

assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and

100, where 0 is "no activity" and 100 is "highest activity possible". With these parameters,

DAS28 is calculated as:[92]

From this, the disease activity of the affected person can be classified as follows:[92]

Current DAS28 decrease from initial value

DAS28 > 1.2 > 0.6 but ≤ 1.2 ≤ 0.6

≤ 3.2 Inactive Good improvement Moderate improvement No improvement

> 3.2 but ≤ 5.1 Moderate Moderate improvement Moderate improvement No improvement

> 5.1 Very active Moderate improvement No improvement No improvement

It is not always a reliable indicator of treatment effect.[93] One major limitation is that low-grade

synovitis may be missed.[94]

Other: Other tools to monitor remission in rheumatoid arthritis are: ACR-EULAR Provisional

Definition of Remission of Rheumatoid arthritis, Simplified Disease Activity Index and

Clinical Disease Activity Index.[95] Some scores do not require input from a healthcare

professional and allow self-monitoring by the person, like HAQ-DI.[96]

Management

There is no cure for RA, but treatments can improve symptoms and slow the progress of the disease.

Disease-modifying treatment has the best results when it is started early and aggressively.[97][48] The

results of a recent systematic review found that combination therapy with tumor necrosis factor (TNF)

and non-TNF biologics plus methotrexate (MTX) resulted in improved disease control, Disease Activity

Score (DAS)-defined remission, and functional capacity compared with a single treatment of either

methotrexate or a biologic alone.[98]

The goals of treatment are to minimize symptoms such as pain and swelling, to prevent bone deformity

(for example, bone erosions visible in X-rays), and to maintain day-to-day functioning.[99] This is

primarily addressed with disease-modifying antirheumatic drugs (DMARDs); dosed physical activity;

analgesics and physical therapy may be used to help manage pain.[7][5][6] RA should generally be treated

with at least one specific anti-rheumatic medication[8] while combination therapies and corticosteroids

are common in treatment.[100] The use of benzodiazepines (such as diazepam) to treat the pain is not

recommended as it does not appear to help and is associated with risks.[101]

Lifestyle

Regular exercise is recommended as both safe and useful to maintain muscle strength and overall

physical function.[102][103] Physical activity is beneficial for people with rheumatoid arthritis who

experience fatigue,[104] although there was little to no evidence to suggest that exercise may have an

impact on physical function in the long term, a study found that carefully dosed exercise has shown

significant improvements in patients with RA.[6][105] Physical activity increases the production of

synovial fluid, which lubricates the joints and reduces friction.[106] Moderate effects have been found for

aerobic exercises and resistance training on cardiovascular fitness and muscle strength in RA.

Furthermore, physical activity had no detrimental side effects like increased disease activity in any

exercise dimension.[107] It is uncertain if eating or avoiding specific foods or other specific dietary

measures help improve symptoms,[108] but several studies have shown that high-vegetable diets improve

RA symptoms whereas high-meat diets make symptoms worse. [1] (https://www.ncbi.nlm.nih.gov/pmc/ar

ticles/PMC6746966/) Occupational therapy has a positive role to play in improving functional ability in

people with rheumatoid arthritis.[109] Weak evidence supports the use of wax baths (thermotherapy) to

treat arthritis in the hands.[110]

Educational approaches that inform people about tools and strategies available to help them cope with

rheumatoid arthritis may improve a person's psychological status and level of depression in the shorter-

term.[111] The use of extra-depth shoes and molded insoles may reduce pain during weight-bearing

activities such as walking.[112] Insoles may also prevent the progression of bunions.[112]

Disease-modifying agents

Disease-modifying antirheumatic drugs (DMARDs) are the primary treatment for RA.[8] They are a

diverse collection of drugs, grouped by use and convention. They have been found to improve symptoms,

decrease joint damage, and improve overall functional abilities.[8] DMARDs should be started early in

the disease as they result in disease remission in approximately half of people and improved outcomes

overall.[8]

The following drugs are considered DMARDs: methotrexate, sulfasalazine, leflunomide,

hydroxychloroquine, TNF inhibitors (certolizumab, adalimumab, infliximab and etanercept), abatacept,

anakinra, and auranofin. Additionally, rituximab and tocilizumab are monoclonal antibodies and are also

DMARDs.[8] Use of tocilizumab is associated with a risk of increased cholesterol levels.[113]

The most commonly used agent is methotrexate with other frequently used agents including sulfasalazine

and leflunomide.[8] Leflunomide is effective when used from 6–12 months, with similar effectiveness to

methotrexate when used for 2 years.[114] Sulfasalazine also appears to be most effective in the short-term

treatment of rheumatoid arthritis.[115]

Hydroxychloroquine, in addition to its low toxicity profile, is considered effective for treatment of

moderate RA symptoms.[116]

Agents may be used in combination, however, people may experience greater side effects.[8][117]

Methotrexate is the most important and useful DMARD and is usually the first treatment.[8][5][118] A

combined approach with methotrexate and biologics improves ACR50, HAQ scores and RA remission

rates.[119][48] This benefit from the combination of methotrexate with biologics occurs both when this

combination is the initial treatment and when drugs are prescribed in a sequential or step-up manner.[48]

Triple therapy consisting of methotrexate, sulfasalazine and hydroxychloroquine may also effectively

control disease activity.[120] Adverse effects should be monitored regularly with toxicity including

gastrointestinal, hematologic, pulmonary, and hepatic.[118] Side effects such as nausea, vomiting or

abdominal pain can be reduced by taking folic acid.[121]

Rituximab combined with methotrexate appears to be more effective in improving symptoms compared

to methotrexate alone.[122] Rituximab works by decreasing levels of B-cells (immune cell that is involved

in inflammation). People taking rituximab had improved pain, function, reduced disease activity and

reduced joint damage based on x-ray images. After 6 months, 21% more people had improvement in their

symptoms using rituximab and methotrexate.[122]

Biological agents should generally be used only if methotrexate and other conventional agents are not

effective after a trial of three months.[8] They are associated with a higher rate of serious infections as

compared to other DMARDs.[123] Biological DMARD agents used to treat rheumatoid arthritis include:

tumor necrosis factor alpha inhibitors (TNF inhibitors) such as infliximab; interleukin 1 blockers such as

anakinra, monoclonal antibodies against B cells such as rituximab, interleukin 6 blockers such as

tocilizumab, and T cell co-stimulation blockers such as abatacept. They are often used in combination

with either methotrexate or leflunomide.[8][3] Biologic monotherapy or tofacitinib with methotrexate may

improve ACR50, RA remission rates and function.[124][125] Abatacept should not be used at the same time

as other biologics.[126] In those who are well controlled (low disease activity) on TNF inhibitors,

decreasing the dose does not appear to affect overall function.[127] Discontinuation of TNF inhibitors (as

opposed to gradually lowering the dose) by people with low disease activity may lead to increased

disease activity and may affect remission, damage that is visible on an x-ray, and a person's function.[127]

People should be screened for latent tuberculosis before starting any TNF inhibitor therapy to avoid

reactivation of tuberculosis.[20]

TNF inhibitors and methotrexate appear to have similar effectiveness when used alone and better results

are obtained when used together.[128] Golimumab is effective when used with methotraxate.[129] TNF

inhibitors may have equivalent effectiveness with etanercept appearing to be the safest.[130] Injecting

etanercept, in addition to methotrexate twice a week may improve ACR50 and decrease radiographic

progression for up to 3 years.[131] Abatacept appears effective for RA with 20% more people improving

with treatment than without but long term safety studies are yet unavailable.[132] Adalimumab slows the

time for the radiographic progression when used for 52 weeks.[133] However, there is a lack of evidence

to distinguish between the biologics available for RA.[134] Issues with the biologics include their high

cost and association with infections including tuberculosis.[3] Use of biological agents may reduce

fatigue.[135] The mechanism of how biologics reduce fatigue is unclear.[135]

Gold and cyclosporin

Sodium aurothiomalate, auranofin, and cyclosporin are less commonly used due to more common

adverse effects.[8] However, cyclosporin was found to be effective in the progressive RA when used up to

one year.[136]

Anti-inflammatory and analgesic agents

Glucocorticoids can be used in the short term and at the lowest dose possible for flare-ups and while

waiting for slow-onset drugs to take effect.[8][3][137] Combination of glucocorticoids and conventional

therapy has shown a decrease in rate of erosion of bones.[138] Steroids may be injected into affected joints

during the initial period of RA, prior to the use of DMARDs or oral steroids.[139]

Non-NSAID drugs to relieve pain, like paracetamol may be used to help relieve the pain symptoms; they

do not change the underlying disease.[5] The use of paracetamol may be associated with the risk of

developing ulcers.[140]

NSAIDs reduce both pain and stiffness in those with RA but do not affect the underlying disease and

appear to have no effect on people's long term disease course and thus are no longer first line

agents.[3][141] NSAIDs should be used with caution in those with gastrointestinal, cardiovascular, or

kidney problems.[142][143][144][140] Rofecoxib was withdrawn from the global market as its long-term use

was associated to an increased risk of heart attacks and strokes.[145] Use of methotrexate together with

NSAIDs is safe, if adequate monitoring is done.[146] COX-2 inhibitors, such as celecoxib, and NSAIDs

are equally effective.[147][148] A 2004 Cochrane review found that people preferred NSAIDs over

paracetamol.[149] However, it is yet to be clinically determined whether NSAIDs are more effective than

paracetamol.[149]

The neuromodulator agents topical capsaicin may be reasonable to use in an attempt to reduce pain.[150]

Nefopam by mouth and cannabis are not recommended as of 2012 as the risks of use appear to be greater

than the benefits.[150]

Limited evidence suggests the use of weak oral opioids but the adverse effects may outweigh the

benefits.[151]

Alternatively, physical therapy has been tested and shown as an effective aid in reducing pain in patients

with RA. As most RA is detected early and treated aggressively, physical therapy plays more of a

preventative and compensatory role, aiding in pain management alongside regular rheumatic therapy.[7]

Surgery

Especially for affected fingers, hands, and wrists, synovectomy may be needed to prevent pain or tendon

rupture when drug treatment has failed. Severely affected joints may require joint replacement surgery,

such as knee replacement. Postoperatively, physiotherapy is always necessary.[16]: 1080, 1103 There is

insufficient evidence to support surgical treatment on arthritic shoulders.[152]

Physiotherapy

For people with RA, physiotherapy may be used together with medical management.[153] This may

include cold and heat application, electronic stimulation, and hydrotherapy.[153] Although medications

improve symptoms of RA, muscle function is not regained when disease activity is controlled.[154]

Physiotherapy promotes physical activity. In RA, physical activity like exercise in the appropriate dosage

(frequency, intensity, time, type, volume, progression) and physical activity promotion is effective in

improving cardiovascular fitness, muscle strength, and maintaining a long term active lifestyle. In the

short term, resistance exercises, with or without range of motion exercises, improve self-reported hand

functions.[154] Physical activity promotion according to the public health recommendations should be an

integral part of standard care for people with RA and other arthritic diseases.[6] Additionally, the

combination of physical activities and cryotherapy show its efficacy on the disease activity and pain

relief.[155] The combination of aerobic activity and cryotherapy may be an innovative therapeutic strategy

to improve the aerobic capacity in arthritis patients and consequently reduce their cardiovascular risk

while minimizing pain and disease activity.[155]

Compression gloves

Compression gloves are handwear designed to help prevent the occurrence of various medical disorders

relating to blood circulation in the wrists and hands. They can be used to treat the symptoms of

arthritis,[156] though the medical benefits may be limited.[157]

Alternative medicine

In general, there is not enough evidence to support any complementary health approaches for RA, with

safety concerns for some of them. Some mind and body practices and dietary supplements may help

people with symptoms and therefore may be beneficial additions to conventional treatments, but there is

not enough evidence to draw conclusions.[158] A systematic review of CAM modalities (excluding fish

oil) found that " The available evidence does not support their current use in the management of RA."[159]

Studies showing beneficial effects in RA on a wide variety of CAM modalities are often affected by

publication bias and are generally not high quality evidence such as randomized controlled trials

(RCTs).[160]

A 2005 Cochrane review states that low level laser therapy can be tried to improve pain and morning

stiffness due to rheumatoid arthritis as there are few side-effects.[161]

There is limited evidence that tai chi might improve the range of motion of a joint in persons with

rheumatoid arthritis.[162][163] The evidence for acupuncture is inconclusive[164] with it appearing to be

equivalent to sham acupuncture.[165]

A Cochrane review in 2002 showed some benefits of the electrical stimulation as a rehabilitation

intervention to improve the power of the hand grip and help to resist fatigue.[166] D‐penicillamine may

provide similar benefits as DMARDs but it is also highly toxic.[167] Low-quality evidence suggests the

use of therapeutic ultrasound on arthritic hands.[168] Potential benefits include increased grip strength,

reduced morning stiffness and number of swollen joints.[168] There is tentative evidence of benefit of

transcutaneous electrical nerve stimulation (TENS) in RA.[169] Acupuncture‐like TENS (AL-TENS) may

decrease pain intensity and improve muscle power scores.[169]

Low-quality evidence suggests people with active RA may benefit from assistive technology.[170] This

may include less discomfort and difficulty such as when using an eye drop device.[170] Balance training is

of unclear benefits.[171]

Dietary supplements

Fatty acids

There has been a growing interest in the role of long-chain omega-3 polyunsaturated fatty acids to reduce

inflammation and alleviate the symptoms of RA. Metabolism of omega-3 polyunsaturated fatty acids

produces docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which inhibits pro-

inflammatory eicosanoids and cytokines (TNF-a, IL-1b and IL-6), decreasing both lymphocyte

proliferation and reactive oxygen species.[172][173] These studies showed evidence for significant clinical

improvements on RA in inflammatory status and articular index. Gamma-linolenic acid, an omega-6 fatty

acid, may reduce pain, tender joint count and stiffness, and is generally safe.[174] For omega-3

polyunsaturated fatty acids (found in fish oil, flax oil and hemp oil), a meta-analysis reported a favorable

effect on pain, although confidence in the effect was considered moderate. The same review reported less

inflammation but no difference in joint function.[175] A review examined the effect of marine oil omega-3

fatty acids on pro-inflammatory eicosanoid concentrations; leukotriene4 (LTB4) was lowered in people

with rheumatoid arthritis but not in those with non-autoimmune chronic diseases.[176] Fish consumption

has no association with RA.[177] A fourth review limited inclusion to trials in which people eat ≥2.7 g/day

for more than three months. Use of pain relief medication was decreased, but improvements in tender or

swollen joints, morning stiffness and physical function were not changed.[178] Collectively, the current

evidence is not strong enough to determine that supplementation with omega-3 fatty acids or regular

consumption of fish are effective treatments for rheumatoid arthritis.[175][176][177][178]

Herbal

The American College of Rheumatology states that no herbal medicines have health claims supported by

high-quality evidence and thus they do not recommend their use.[179] There is no scientific basis to

suggest that herbal supplements advertised as "natural" are safer for use than conventional medications as

both are chemicals. Herbal medications, although labelled "natural", may be toxic or fatal if

consumed.[179] Due to the false belief that herbal supplements are always safe, there is sometimes a

hesitancy to report their use which may increase the risk of adverse reactions.[160]

Pregnancy

More than 75% of women with rheumatoid arthritis have symptoms improve during pregnancy but might

have symptoms worsen after delivery.[20] Methotrexate and leflunomide are teratogenic (harmful to

foetus) and not used in pregnancy. It is recommended women of childbearing age should use

contraceptives to avoid pregnancy and to discontinue its use if pregnancy is planned.[99][118] Low dose of

prednisolone, hydroxychloroquine and sulfasalazine are considered safe in pregnant women with

rheumatoid arthritis. Prednisolone should be used with caution as the side effects include infections and

fractures.[180]

Vaccinations

People with RA have an increased risk of infections and mortality and recommended vaccinations can

reduce these risks.[181] The inactivated influenza vaccine should be received annually.[182] The

pneumococcal vaccine should be administered twice for people under the age 65 and once for those over

65.[183] Lastly, the live-attenuated zoster vaccine should be administered once after the age 60, but is not

recommended in people on a tumor necrosis factor alpha blocker.[184]

Prognosis

The course of the disease varies greatly.[186] Some

people have mild short-term symptoms, but in most the

disease is progressive for life. Around 25% will have

subcutaneous nodules (known as rheumatoid

nodules);[187] this is associated with a poor

prognosis.[188]

Disability-adjusted life year for RA per

Prognostic factors 100,000 inhabitants in 2004.[185]

Poor prognostic factors include, no data

<40

Persistent synovitis 40–50

Early erosive disease 50–60

Extra-articular findings (including 60–70

subcutaneous rheumatoid nodules) 70–80

Positive serum RF findings 80–90

Positive serum anti-CCP autoantibodies 90–100

Positive serum 14-3-3η (YWHAH) levels above 100–110

0.5 ng/ml [189][190] 110–120

120–130

Carriership of HLA-DR4 "Shared Epitope"

alleles 130–140

Family history of RA >140

Poor functional status

Socioeconomic factors[48]

Elevated acute phase response (erythrocyte sedimentation rate [ESR], C-reactive protein

[CRP])

Increased clinical severity.

Distance from primary care and specialist care in rural communities[48]

Mortality

RA reduces lifespan on average from three to twelve years.[99] Young age at onset, long disease duration,

the presence of other health problems, and characteristics of severe RA – such as poor functional ability

or overall health status, a lot of joint damage on x-rays, the need for hospitalisation or involvement of

organs other than the joints – have been shown to associate with higher mortality.[191] Positive responses

to treatment may indicate a better prognosis. A 2005 study by the Mayo Clinic noted that individuals with

RA have a doubled risk of heart disease,[192] independent of other risk factors such as diabetes, excessive

alcohol use, and elevated cholesterol, blood pressure and body mass index. The mechanism by which RA

causes this increased risk remains unknown; the presence of chronic inflammation has been proposed as a

contributing factor.[193] It is possible that the use of new biologic drug therapies extend the lifespan of

people with RA and reduce the risk and progression of atherosclerosis.[194] This is based on cohort and

registry studies, and still remains hypothetical. It is still uncertain whether biologics improve vascular

function in RA or not. There was an increase in total cholesterol and HDLc levels and no improvement of

the atherogenic index.[195]

Epidemiology

RA affects 0.5–1% of adults in the developed world

with between 5 and 50 per 100,000 people newly

developing the condition each year.[3] In 2010 it

resulted in about 49,000 deaths globally.[196]

Onset is uncommon under the age of 15 and from then

on the incidence rises with age until the age of 80.

Women are affected three to five times as often as Deaths from rheumatoid arthritis per million

men.[20] persons in 2012

0–0 7–8

The age at which the disease most commonly starts is 1–1 9–9

in women between 40 and 50 years of age, and for men 2–3 10–12

[197] [198] 4–5 13–20

somewhat later. RA is a chronic disease, and

6–6 21–55

although rarely, a spontaneous remission may

occur,[199] the common course of progression consists

of persistent symptoms that wax and wane in intensity, along with continued deterioration of joint

structures, leading to deformation and disability.[200][201]

There is an association between periodontitis and rheumatoid arthritis (RA), hypothesised to lead to

enhanced generation of RA-related autoantibodies. Oral bacteria that invade the blood may also

contribute to chronic inflammatory responses and generation of autoantibodies.[202]

History

The first recognized description of RA in modern medicine was in 1800 by the French physician Augustin

Jacob Landré-Beauvais (1772–1840) who was based in the famed Salpêtrière Hospital in Paris.[12] The

name "rheumatoid arthritis" itself was coined in 1859 by British rheumatologist Alfred Baring

Garrod.[203]

The art of Peter Paul Rubens may possibly depict the effects of RA. In his later paintings, his rendered

hands show, in the opinion of some physicians, increasing deformity consistent with the symptoms of the

disease.[204][205] RA appears to some to have been depicted in 16th-century paintings.[206] However, it is

generally recognized in art historical circles that the painting of hands in the 16th and 17th century

followed certain stylized conventions, most clearly seen in the Mannerist movement. It was conventional,

for instance, to show the upheld right hand of Christ in what now appears a deformed posture. These

conventions are easily misinterpreted as portrayals of disease.

Historic (though not necessarily effective) treatments for RA have also included: rest, ice, compression

and elevation, apple diet, nutmeg, some light exercise every now and then, nettles, bee venom, copper

bracelets, rhubarb diet, extractions of teeth, fasting, honey, vitamins, insulin, magnets, and

electroconvulsive therapy (ECT).[207]

Etymology

Rheumatoid arthritis is derived from the Greek word ῥεύμα-rheuma (nom.), ῥεύματος-rheumatos (gen.)

("flow, current"). The suffix -oid ("resembling") gives the translation as joint inflammation that resembles

rheumatic fever. Rhuma which means watery discharge might refer to the fact that the joints are swollen

or that the disease may be made worse by wet weather.[13]

Research

Meta-analysis found an association between periodontal disease and RA, but the mechanism of this

association remains unclear.[208] Two bacterial species associated with periodontitis are implicated as

mediators of protein citrullination in the gums of people with RA.[3]

Vitamin D deficiency is more common in people with rheumatoid arthritis than in the general

population.[209][210] However, whether vitamin D deficiency is a cause or a consequence of the disease

remains unclear.[211] One meta-analysis found that vitamin D levels are low in people with rheumatoid

arthritis and that vitamin D status correlates inversely with prevalence of rheumatoid arthritis, suggesting

that vitamin D deficiency is associated with susceptibility to rheumatoid arthritis.[212]

The fibroblast-like synoviocytes have a prominent role in the pathogenic processes of the rheumatic

joints, and therapies that target these cells are emerging as promising therapeutic tools, raising hope for

future applications in rheumatoid arthritis.[17]

Possible links with intestinal barrier dysfunction are investigated.[213]

See also

Osteoarthritis

Psoriatic arthritis