**Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation and hyperplasia, autoantibody production, underlie the cardinal manifestations of this disease, which include pain, swelling and tenderness followed by cartilage destruction, bone erosion, and subsequent joint deformities ***(Faddaa et al., 2016).***

The availability of effective therapies makes it imperative to identify patients early so that control of inflammation can prevent joint destruction and disability ***(Mody and Cardiel, 2008).***

RA has a significant impact on health-related quality of life, it is associated with increased health-care costs and an increased mortality when affected patients are compared with the general population ***(Sihvonen et al., 2004).***

***Epidemiology***

RA affects between 0.5 and 1% of adults in the [developed world](https://en.wikipedia.org/wiki/Developed_world) with between 5 and 50/ 100,000 people newly developing the condition each year ***(Scott et al.,2010)*.**

One study in the united-kingdom (UK) found the population minimum prevalence of RA to be 1.16% in women and 0.44% in men .The incidence of the condition is low, with around 1.5 men and 3.6 women developing RA per 10,000 people per year. The overall occurrence of RA is two to four times greater in women than in men. The peak age of incidence in the UK for both genders is the 40s, but people of all ages can develop the disease **(*Charles et al., 2013).***

In recent study , the new American College of Rheumatology/ European League Against Rheumatism classification criteria for rheumatoid arthritis **(** ACR/ EULAR classification criteria ***(Aletaha et al., 2010)***, it had shown that the incidence of RA, as estimated by the 2010 classification criteria at baseline, is very similar to the estimates using the 1987 criteria cumulatively over 5 years**.**

These result indicated that the 2010 criteria may identify RA patients earlier in the disease course and will be important in order to plan timely, cost effective and efficacious management of patients presenting with inflammatory arthritis **(*Humphreys et al., 2013).***

***Etiology***

RA results from an interaction between genetic susceptibility and environmental factors, including high birth weight, smoking, silica exposure, alcohol abstention, obesity, diabetes mellitus, rheumatoid factor (RF), and anti-citrullinated protein (AntiCCP) antibodies ***(korczowska et al., 2014****)*

**Genetic factors:**

Half of the risk for RA is believed to be genetic***.*** It is strongly associated with the inherited tissue type [major histocompatibility complex](https://en.wikipedia.org/wiki/Major_histocompatibility_complex) (MHC) antigen [HLA](https://en.wikipedia.org/wiki/Human_leukocyte_antigen)-DRB1 (most specifically the shared epitope alleles, including \*0401 and born 0404), and the protein tyrosine phosphatase , non receptor type 22 genes (PTPN22) and peptidyle arginine deaminase4 (PADI4) hence family history is an important risk factor ***(Goeldner et al., 2010).***

The only genetic region that has emerged in linkage and in genome-wide association studies in all ethnic groups is the major histocompatibility complex (MHC) region ***(Fernando et al., 2008).***

Human leukocyte antigen (HLA) alleles appear to be more closely associated with the presence of antibodies to IgG Fc or to citrullinated peptides than with RF itself, suggesting that the polymorphisms primarily predispose to autoantibody production and that seronegative RA is fundamentally different from seropositive RA **(*Van der Helm-van Mil***

***et al., 2006).***

A polymorphism within the (PTPN22) genes has been unequivocally associated with RA in several studies in Canada, Europe, and USA. The polymorphism is responsible for an amino acid exchange from an arginine to tryptophan within the coding region of the gene. This polymorphism represents a minor allele that is infrequent in healthy control individuals as well as in the RA population (8.7% versus 14.4%) **(*Wesoly et al., 2005).***

***●***[**Smoking**](https://en.wikipedia.org/wiki/Tobacco_smoking)**:**

[Smoking](https://en.wikipedia.org/wiki/Tobacco_smoking) is the most significant non-genetic risk with RA being up to three times more common in smokers than non-smokers, particularly in men, heavy smokers, and those who are RF positive, as it leads to apoptosis and antigen protein citrullination ***(Chang et al., 2014)*.**

**Infection:**

Epidemiological studies have confirmed a potential association between RA and two [herpes virus](https://en.wikipedia.org/wiki/Herpesvirus) infections: [Epstein-Barr virus](https://en.wikipedia.org/wiki/Epstein-Barr_virus) (EBV) and [Human Herpes Virus 6](https://en.wikipedia.org/wiki/Human_Herpesvirus_Six) (HHV-6) ***(Alvarez-Lafuente et al., 2005).***

One possibility is that these microorganisms trigger the development of RA in individuals who carry genetic susceptibility factors to the disease. However, the role for microorganisms as initiating factors of RA remains controversial. Clearly, no single microorganism is responsible for the development of RA ***(Meron et al., 2010).***

**Hormonal**

The predominance of RA in females suggests a role for hormonal factors. In addition, estrogens stimulate the immune system. Low testosterone levels have been reported in men with RA. A history of child-bearing may protect against RA. In patients with RA, pregnancy often leads to a remission, followed by a flare-up after delivery ***(Cutolo et al., 2002).***

**Others:**

Some evidence supports foods rich with omega-3 fatty acids and [gamma-linolenic acid](https://en.wikipedia.org/wiki/Gamma-linolenic_acid) in RA .The benefit from omega-3 appears modest but consistent. Though the current evidence is not strong enough to determine that supplementation with [omega-3 polyunsaturated fatty acids](https://en.wikipedia.org/wiki/Omega-3_fatty_acid) (found in fish oil) is an effective treatment for RA ***(Miles et al., 2012)*.**

[Vitamin D deficiency](https://en.wikipedia.org/wiki/Vitamin_D_deficiency) is more common in people with RA than in the general population. However, whether vitamin D deficiency is a cause or a consequence of the disease remains unclear. Some trials have found a decreased risk for RA with vitamin D supplementation while others have not ***(Gatenby et al., 2013)****.*

***Pathogenesis of Rheumatoid Arthritis:***

Understanding of the chronic inflammatory disease, RA has evolved considerably during the past decade. Introduction of novel therapeutic strategies has had a major impact not only on how we treat affected patients but also on how we conceptualize the disease process ***(Smolen and Aletaha 2009)***. RA is an immune-mediated disease for which an autoimmune pathogenesis is postulated ***(Panayi et al., 2001).***

All components of the immune system are involved in mediating tissue damage and systemic inflammation. T cells, B cells, and macrophages infiltrate into the synovium and form highly sophisticated lymphoid structures ***(Goodson et al., 2008).***

***\*Antigen presentation by major histocompatability complex (MHC)***

***class-II:***

Autoimmunity is characterized by spontaneous inflammatory tissue damage and by impaired physiological function resulting from loss of tolerance to self-antigen. It is associated with a partially over active immune system, which is characterized by an excess of T helper (Th) cells. The engagement of an antigen-specific T-cell receptor (TCR) with complexes of (MHC) and peptide displayed on antigen-presenting cells (APCs) provide the first essential signal for T cell activation ***(Lee et al., 2011).***

Accumulating data from the past few years have indicated that the HLA, DRB1 shared epitope is associated only with a subset of rheumatoid arthritis that is defined by presence of (ACPA) antibodies or RF, or both ***(Arend et al., 2012).***

One implication of these findings is that the genetic hypothesis for involvement of adaptive, B-cell, and T-cell-mediated immunity in pathogenesis is valid only for the ACPA positive or RF positive disease subset. Another implication is that all further causal studies that include genetics need to judge these subsets of RA as separate entities ***(Willemze et al., 2012*).**

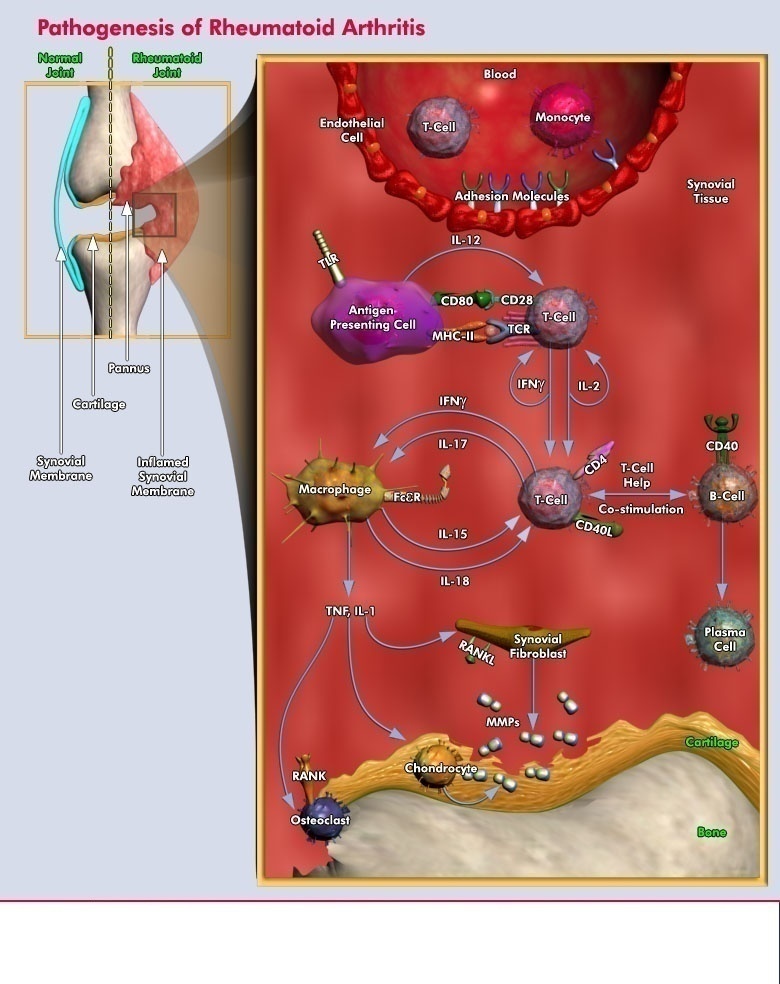
Moreover, the demonstration of (ACPA) predates the clinical onset of arthritis by several years in some patients. It predicts a more severe, erosive natural history ***(Meyer et al., 2012).***

***\*T lymphocytes proliferation:***

Multiple subsets of T cells have been implicated in the pathogenesis of RA, ***Figure (1)****.*Suppressor T cells were found to express CD8 more often than CD4. However, the existence of suppressor T cells, as described at the time, failed to explain many functional data***.*** Thus, the word ''suppressor'', which reflected the functional definition of these cells, has been replaced by regulatory (Treg cells) ***(Vignali et al., 2008).***

Treg-cell deficiency or absence correlates with the development or exacerbation of autoimmune diseases, emphasizing the crucial role for Treg cells in maintaining immunological self-tolerance ***(Smolen and Günter, 2003).*** Treg cells release transforming growth factor-β (TGF-ß). In addition, suppressor T cells (Tr1 cells) release large amounts of the immune- modulating cytokine IL-10 ***(Vignali et al., 2008).***

The IL-12 family (IL-12, IL-23, IL-27, and IL-35) is closely involved in immune regulation. IL-35 is an identified cytokine that maybe crucial to optimal Treg function ***(Collison et al., 2007).***

**

**Figure (1):** Pathogenesis of Rheumatoid Arthritis **(*Smolen and Günter, 2003)***

***\*The role of B cells and autoantibodies in Rheumatoid Arthritis:***

B lymphocytes play a key role in RA through their contributions to immune complex formation, antigen presentation, and causing direct injurious effects through production of autoantibodies, cytokines, vaso- active substances, and other mediators ***(Browning et al., 2005).***

B lymphocyte cells, including those bearing (RF), are highly competent (APCs). B cells capture and concentrate antigens through antigen-specific surface immunoglobulin receptors, whereas conventional APC, such as macrophages, display no binding specificity for antigen. For this reason, specific B cells are able to present antigens to CD4+ T cells with very high capacity and efficacy. After antigens are internalized and processed by specific B cells, they are presented to CD4+T cells in an MHC-restricted manner indistinguishable from that characteristic of conventional APC ***(Silverman et al., 2003).***

Presence of autoantibodies to IgGFc, known as (RF), and to (ACPA) is an integral part of RA disease process. As is the case with many other autoimmune diseases, people with RA have abnormally glycosylated antibodies, It is believed that these glycan (oligosaccharide) alterations promote joint inflammation **(*Maverakis et al., 2015).***

Once the abnormal immune response has become established (which may take several years before any symptoms occur), plasma cells derived from B lymphocytes produce RF and ACPA of the IgG and IgM classes in large quantities. These are not deposited in the way that they are in systemic lupus. Rather, they activate macrophages through Fc receptor and complement binding, which seems to play an important role in the intense inflammatory response present in RA ***(Boldt et al., 2012)***. 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 **(*Maverakis et al., 2015).***

B cells when present, are virtually restricted to follicular structures with wide variation in size and density distribution. These structures are the preferential environment in which interactions between B cells and T cells, macrophages, mesenchymal stromal cells , and dendritic cells are favoured, which makes them the elective intra synovial site for potential intercellular (cell-contact dependent or paracrine) immunological interactions to take place ***(Manzo et al., 2010***).

B cells accumulating in reactive lymph nodes can indeed translocate from the follicular area to the sinusoidal lymphatic sinuses, impairing afferent lymphatic drainage and leading to lymph node collapse, a process associated with increased inflammation and erosions in the drained joint ***( Li et al., 2011)***.

These events have been shown to be reversible by B-cell depleting agents, explaining a potential alternative mechanism of action of B cell-targeted therapies in RA ***(Li et al., 2013).***

The chemokine CXC ligand 13 protein (CXCL13), also known as B-cell-attracting chemokine-1 or B-lymphocyte chemoattractant (BLC), is a CXC subtype member of the chemokine superfamily. Chemokines have been shown to orchestrate migration and preferential sequestration of B and T cells in inflammatory lesions ***(Kulkarni et al., 2008).***

BLC (CXCL13), is a homeostatic chemokine, is the only chemokine which is known to specifically chemoattract B cells, belonging to both B-1 and B-2 subsets through the interaction with its receptor CXCR5. The gene for CXCL13 is located on human chromosome 4 in a cluster of other CXC chemokines. CXCL13 and CXCR5 together control the organization of B cells within follicles of lymphoid tissues and are expressed highly in the liver, spleen, lymph nodes, and gut of humans ***(Ansel et al., 2000).***

C-X-C motif chemokine ligand 13 (CXCL13) is a critical agent for B-cell homing to inflammatory foci that is implicated in the pathogenesis of several immunologic disorders (***Rupprecht et al., 2009).***The B-cell ligand for CXCL13 that mediates lymphocyte chemotaxis is C-X-C chemokine receptor 5(CXCR5) ***(Nelson et al., 2006).***

The CXCL13-CXCR5 axis is critical to the generation of immunological memory based on long-lived plasma cells because the interaction between TFH and B cells is necessary for the formation of plasma cells, autoantibody production and maintenance of epithelial cell angiostatic activity ***( Romagnani et al., 2004*)** and ***(Manzo et al., 2008*).**

However, expressin of CXCR5 is crucial for the localization of T cells in the germinal cells (GCs) of secondary lymphoid organs. Recently, CXCR5follicular regulatory T (Tfr) cells were shown to localize in the GC of secondary lymphoid organs and to inhibit humoral immunity more effectively than do conventional CXCR5–Treg cells, therefore, it is likely that iTh13 cells, which are negative for CXCR5, localize and exert B cell helper activity in secondary lymphoid organs less effectively than do CXCR5+ Tfh cell ***(Chevalier et al., 2011*).**

Within the RA synovium CXCL13 is expressed in areas of B cell accumulation characteristic of ectopic lymphoid follicles where subtypes of CXCL13-expressing T cells (CD3+ and CD4+) and monocytes /macrophages colocalize ***(Kobayashi et al., 2013).***

Proinflammatory cytokines play a role upstream of CXCL13 expression and lymphoid tissue organization, as demonstrated in animal models of lymphoid tissue ontogenesis and neogenesis, Proinflammatory cytokines alone were unable to induce significant expression of CXCL13 ***(Rangel-Moreno et al., 2011)***.

***\*New blood vessels formation:***

Angiogenesis within the hypertrophic synovial sub lining is an important early event in RA, driven by the increased metabolic demands and hypoxia of the expanding inflammatory tissue. New vessels in the RA pannus are of a characteristic branching morphology. This is thought to result from the unfavorable co-expression by intimal fibroblast-like synoviocytes (FLSs) and vascular endothelial cells (ECs) of the angiogenic factor VEGF (vascular endothelial angiogenic factor VEGF (vascular endothelial growth factor ***(Paleolog, 2002)***.

VEGF and angiopoietin-2together promote the invasive proliferation of ECs, and inhibition of this process may be one mechanism of anti-TNFα drug activity. It is hoped that the complex paracrine pathways that promote angiogenesis may yield additional therapeutic targets **(*Markham et al., 2006).***

***\* Cytokine networks in RA:***

Based on the cytokine profile of RA, paracrine and autocrine networks likely participate in disease perpetuation. Macrophages and FLSs in the intimal lining produce factors that activate adjacent cells and

enhance synovial inflammation **(*Sweeney and Firestein, 2004)*.**

IL-1 and TNF-α , both produced by the synovial macrophages can stimulate fibroblast proliferation and increase production of IL-6, granulocyte -macrophage colony-stimulating factor (GM-CSF) , IL-8, other chemokines , as well as enzymes that result in joint destruction, these cytokines, in turn, can activate macrophages in the environment and lead to continued cytokine production .This creates a positive feedback mechanism between the FLS and macrophages that perpetuates synovial inflammation ***(Gracie et al., 2002).***

IL-17 is a discovered cytokine that is secreted by a restricted set of cells, whereas its receptor is ubiquitously expressed on many cell types.

IL-17 production has been demonstrated in RA synovial tissue and it enhances IL-1 mediated IL-6 production in vitro. The CD4+CD45 are the major source of IL-17. It is not clear whether IL-17 operates downstream of IL-15 and whether IL-17 has a direct role in T cell activation. The contribution of IL-17 in destructive arthritis was suggested by the fact that the cellular responses induced by IL-17 look similar to that of IL-1 **(*Chabaud et al., 2001).***

IL-18 which resembles IL-1 enhances IFN γ production by T cells and TNFα production by macrophages ***(Liew and Mcïnnes, 2002).***

***\* Destruction of cartilage and bone:***

Destruction of the extracellular matrix leads to significant joint destruction in patients with RA. Current concepts of joint destruction suggest that distinct mechanisms contribute to bone and cartilage damage.

Cartilage destruction is mediated in large part through the elaboration of proteases by synoviocytes and cellular invasion into the matrix metallo proteinases and aggrecanases, induced by IL-1, TNF-α, and IL-17, play a key role in this process. In addition, RA- FLSs can be permanently altered in the inflammatory synovial environment. Oxidative stress and altered DNA repair potentially cause mutations in certain key genes, such as the p53 tumor suppressor, and can increase synoviocyte proliferation and cartilage invasion ***(Rannou et al., 2006).***

Osteoclast differentiation is in part driven by the receptor activator of nuclear factor-kappa B ligand (RANKL) , which is expressed on tissue residingCD4+ T cells and on synovial fibroblasts and is upregulated by a number of proinflammatory cytokines . By engaging RANK, RANKL induce the differentiation of monocytic cells into osteoclasts. Osteoclast differentiation can be inhibited by osteoprotegerin (OPG), which does not ameliorate the inflammatory signs of disease but can prevent structural damage to the joint ***(Schett and Gravallese, 2012).***

***Signs and symptoms***

RA primarily affects joints, however it also affects other organs in15–25% of individuals ***(Turesson et al., 2003).***

***\*Clinical presentations:***

Typical "classic" RA- The disease onset is usually insidious, with the predominant symptoms being pain, stiffness, and swelling of many joints ***(Lee and Weinblatt, 2001).***

***Joints:***

[Arthritis](https://en.wikipedia.org/wiki/Arthritis) of joints involves [inflammation](https://en.wikipedia.org/wiki/Inflammation) of the [synovial membrane](https://en.wikipedia.org/wiki/Synovial_membrane). Joints become swollen, tender and warm, and stiffness limits their movement. With time, multiple joints are affected (it is a [polyarthritis](https://en.wikipedia.org/wiki/Polyarthritis)), most commonly involved joints are the small joints of the [hands](https://en.wikipedia.org/wiki/Hand) , [feet](https://en.wikipedia.org/wiki/Foot) and [cervical spine](https://en.wikipedia.org/wiki/Cervical_spine), but larger joints like the shoulder and knee can also be involved the joints are often affected in a fairly symmetrical fashion , although this is not specific, and the initial presentation may be asymmetrical ***(Nicki et al., 2010).***

As the pathology progresses the inflammatory activity leads to tendon tethering, erosion and destruction of the joint surface, which impairs range of movement and leads to deformity. The fingers may suffer from almost any deformity depending on which joints are most involved. Specific deformities, which also occur in [osteoarthritis](https://en.wikipedia.org/wiki/Osteoarthritis), include [ulnar deviation](https://en.wikipedia.org/wiki/Ulnar_deviation), [boutonniere deformity](https://en.wikipedia.org/wiki/Boutonniere_deformity), [swan neck deformity](https://en.wikipedia.org/wiki/Swan_neck_deformity) and "Z-thumb." "Z-thumb" or "Z-deformity" consists of [hyperextension](https://en.wikipedia.org/wiki/Hyperextension) of the [inter- phalangeal joint](https://en.wikipedia.org/wiki/Interphalangeal_articulations_of_hand) , fixed [flexion](https://en.wikipedia.org/wiki/Flexion) and [subluxation](https://en.wikipedia.org/wiki/Subluxation) of the [metacarpo- phalangeal joint](https://en.wikipedia.org/wiki/Metacarpophalangeal_joint) and gives a "Z" appearance to the thumb ***(Nicki et al., 2010).***

* **Mono arthritis**:

Persistent single joint arthritis (monoarthritis) frequently of a large joint such as the knee, shoulder, hip, wrist, or ankle, may be the sole manifestation or may herald the onset of polyarticular disease. There may be a history of joint trauma as an apparent initiating event. The interval between mono arthritis and polyarthritis may extend from days to several weeks in patients whose disease progresses ***(Maksymowych et al., 2002).***

* **Palindromic rheumatism**:

The onset of RA is episodic in a few patients, with one to several joint areas being affected sequentially for hours to days, with symptom free periods that may last from days to months, associated with swelling and erythema ***(Boldt et al., 2012).***

***Extraarticular involvement:***

***\*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 patients with active RA ***(Turesson et al., 2003).***

***\*Skin***

The [rheumatoid nodule](https://en.wikipedia.org/wiki/Rheumatoid_nodule), which is sometimes in the [skin](https://en.wikipedia.org/wiki/Cutaneous), is the most common non joint feature. They occur in 30% of people. It is a type of inflammatory reaction known as a "[necrotizing](https://en.wikipedia.org/wiki/Necrotizing) [granuloma](https://en.wikipedia.org/wiki/Granuloma)". The [initial](https://en.wikipedia.org/wiki/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](https://en.wikipedia.org/wiki/Fibrinoid_necrosis) that May be [fissured](https://en.wikipedia.org/wiki/Fissure) and which corresponds to the [fibrin](https://en.wikipedia.org/wiki/Fibrin)-rich necrotic material found in and around an affected synovial space. Surrounding the necrosis is a layer of [palisading](https://en.wikipedia.org/w/index.php?title=Palisading&action=edit&redlink=1) [macrophages](https://en.wikipedia.org/wiki/Macrophages) and [fibroblasts](https://en.wikipedia.org/wiki/Fibroblasts), corresponding to the [intimal layer](https://en.wikipedia.org/w/index.php?title=Intimal_layer&action=edit&redlink=1) in synovium and a cuff of [connective tissue](https://en.wikipedia.org/wiki/Connective_tissue) containing clusters of [lymphocytes](https://en.wikipedia.org/wiki/Lymphocyte) and [plasma cells](https://en.wikipedia.org/wiki/Plasma_cell), corresponding to the [subintimal zone](https://en.wikipedia.org/w/index.php?title=Subintimal_zone&action=edit&redlink=1) in synovitis ***(Turesson, 2013)***.

The typical rheumatoid nodule may be a few millimeters to a few centimetres in diameter and is usually found over bony prominences , such as the [elbow](https://en.wikipedia.org/wiki/Olecranon), the [heel](https://en.wikipedia.org/wiki/Calcaneal_tuberosity) , the [knuckles](https://en.wikipedia.org/wiki/Metacarpophalangeal_joints) , or other areas that sustain repeated mechanical stress . Nodules are associated with a positive RF [titer](https://en.wikipedia.org/wiki/Titer) and severe erosive arthritis. Rarely, these can occur in internal organs or at diverse sites on the body ***(Turesson*, *2013)***.

***\*Lungs***

Pleural disease is common in patients with RA, but it is usually subclinical. When symptoms or signs occur , chest pain and /or fever are most common. Patients with significant pleural effusions may report dyspnea. Physical examination may reveal a pleural rub, and there maybe unilateral or bilateral effusions ***(Balbir-Gurman et al., 2006).***

Fibrosis of the lungs is a recognized response to rheumatoid disease. It is also a rare but well recognized consequence of therapy (for example with methotrexate MTX and leflunomide) . Caplan's syndrome describes lung nodules in individuals with RA and additional exposure to coal dust. Pleural effusions are also associated with RA ***(Clair et al., 2004).***

***\*Heart and blood vessels***

Clinically apparent pericarditis and myocarditis are uncommon disorders in patients with RA. There is an increased risk of coronary artery disease in patients with RA, and there may be an increased risk of heart failure and atrial fibrillation ***(Gabriel et al., 2010).***

Myocarditis, which can be either granulomatous or interstitial, is rare in RA and is usually associated with active articular disease and with other nonarticular manifestations ***(Lindhardsen et al., 2012).***

The prevalence of atherosclerotic coronary artery disease (CAD) is increased in patients with chronic inflammatory diseases affecting connective tissue, particularly those with RA ***(Rho et al., 2010).***

It is postulated that, in patients with RA, chronic inflammation may accelerate the progression of atherosclerosis, perhaps via the effects of cytokines; abnormal effector functions of T lymphocytes, macrophages, and dendritic cells; immune complexes; coagulation abnormalities; oxidative stress; or a combination of these factors ***(Rho et al., 2010).***

To reduce cardiovascular risk, it is crucial to maintain optimal control of the inflammation caused by RA and to use exercise and medications appropriately to reduce other cardiovascular risk factors such as blood lipids and blood pressure. Physicians who treat RA patients 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 ***(Gupta and Fomberstein, 2009).***

***\*Ocular***

The eye is directly affected in the form of episcleritis which when severe can very rarely progress to perforating scleromalacia. Rather more common is the indirect effect of keratoconjunctivitissicca, 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. Preventive treatment of severe dryness with measures such as nasolacrimal duct blockage is important ***(Turesson et al., 2003).***

***\*Hematological***

Anemia is by far the most common abnormality of the blood cell 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. RA may also cause a warm autoimmune hemolytic anemia. The red cells are of normal size and color (normocytic and normochromic). A low white blood cell count (neutropenia) usually only occurs in patients 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 ***(Rehman, 2008).***

***\*Kidneys***

Chronic inflammation in RA may be associated with increased production of the acute phase reactant serum amyloid A results in secondary amyloidosis ***(Karstila et al., 2007).***

RA may affect the kidney glomerulus directly through avasculopathy or a mesangial infiltrate but this is less well documented ***(Robbins et al., 2010).***

***\*Hepatic***

Liver problems in people with RA may be due to the underlying disease process or as a result of the medications used to treat the disease. A coexisting autoimmune liver disease, such as [primary biliary cirrhosis](https://en.wikipedia.org/wiki/Primary_biliary_cirrhosis) or [autoimmune hepatitis](https://en.wikipedia.org/wiki/Autoimmune_hepatitis) may also cause problems **(*Selmi et al., 2011).***

***\*Osteopenia***

Osteopenia in RA may be generalized, resulting from immobility, the inflammatory process, and treatment effects with glucocorticoids; it also includes periarticular demineralization typical of RA. It is due to the combined actions of prostaglandins and cytokines in association with normal amounts of parathyroid hormone. In the absence of anti resorptive therapy, all patients with RA can be expected to lose bone mineral ***(Rossouw et al., 2002).***

***\*Lymphoma***

The incidence of lymphoma is increased in RA, although it is still uncommon ***(Baecklund et al., 2006).***

***Diagnosis***

***\*Imaging***

Features seen on plain X-ray are periarticular swelling, erosions, osteopenia, cysts, subluxation, periosteal reaction, and joint space narrowing (loss of cartilage, ankylosis. Distribution of damage in RA is in order of frequency; hands, feet, knees, hip, cervical spine, shoulders and elbows ***(Ory, 2003).***

There have been technical advances in ultrasonography. High frequency transducers (10 MHz or higher) have improved the spatial resolution of ultrasound images; these images can depict 20% more erosions than conventional radiography. Also, color doppler and power doppler ultrasound, which show vascular signals of active synovitis depending on the degree of inflammation, are useful in assessing synovial inflammation. 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 ***(Schueller et al., 2010).***

***\*Blood tests***

When RA is clinically suspected, immunological studies are required, such as testing for the presence of RF, anon specific antibody ***(Westwood et al., 2006).***

During the first year of illness, RF is more likely to be negative with some individuals converting to seropositive status overtime. RF is also seen in other illnesses, for example Sjögren's syndrome, hepatitis C, systemic lupus erythematosus, chronic infections and in approximately 10% of the healthy population, therefore the test is not very specific. Because of this low specificity, new serological tests have been developed, which test for the presence of the (ACPAs). Like RF, these tests are positive in only a proportion (67%) of all RA cases, but are rarely positive if RA is not present, giving it a specificity of around 95% ***(Westwood et al., 2006).***

As with RF, there is evidence for ACPAs being present in many cases even before onset of clinical disease. The most common tests for ACPAs are the anti-CCP (cyclic citrullinated peptide) test and the Anti-MCV assay (antibodies against mutated citrullinated vimentin). Recently a serological point-of-care test (POCT) for the early detection of RA has been developed. This assay combines the detection of RF and anti-MCV for diagnosis of RA and shows a sensitivity of 72% and specificity of 99.7 ***(Nishimura et al., 2007).***

**Table (1):** The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria (ACR / EULAR classification criteria) for rheumatoid arthritis Score **(*Aletaha et al., 2010).***

|  |  |
| --- | --- |
| **Score** | **Criteria** |
| 0  1  2  3  5 | **A-Joint involvement :(Swollen or tender)**  1 large joint  2-10 large joints  1-3 small joints (with or without involvement of large j.)  4-10 small joints (with or without involvement of large j.)  >10 joints(at least 1 small joint) |
| 0  2  3 | **B-Serology:**(at least 1 test is needed for classification)  Negative RF and negative ACPA  Low positive RF or low positive ACPA  High positive RF or high positive ACPA |
| 0  1 | **C-Acute-phase reactants:** (at least 1 test is needed ):  Normal CRP and normal ESR  Abnormal CRP or abnormal ESR |
| 0  1 | **D- Duration of symptoms:**  < 6 weeks  ≥ 6 weeks |

1. ***Joint involvement:***

Refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis, distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment.

“*Large joints*” refers to shoulders, elbows, hips, knees, and ankles.

“*Small joints*” refers to the metacarpophalangeal joints , proximal inter-phalangeal joints, second through fifth metatarsophalangeal joints ,thumb interphalangeal joints and wrists.

In the category of ">10 joints", at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g. temporomandibular, acromioclavicular, sternoclavicular, etc.).

1- large joint 0.

2-10 large joints 1.

1-3 small joints (with or without involvement of large joints) 2.

4-10 small joints (with or without involvement of large joints) 3.

5-> 10joints (at least 1 small joint) 5.

***B. Serology (at least 1 test result is needed for classification):***

Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are > 3 times the ULN for the laboratory and assay.

Where (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF.

Negative RF and negative ACPA 0

Low-positive RF or low-positive ACPA 2

High-positive RF or high-positive ACPA 3

C. ***Acute phase reactants:***

At least 1 test result is needed for classification.

Normal CRP and normal ESR 0

Abnormal CRP or abnormal ESR 1

***D. Duration of symptoms:***

Refers to patient self-report of the duration of signs or symptoms of synovitis (e.g. pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status:

< 6 weeks 0

≥ 6 weeks 1

Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA**.**

***Management***

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 ***(Amy, 2011).***

**I. Patient education:**

Patients should be educated about the disease and referred to these an cillary specialists to maintain joint function and delay disability. Patient education and counseling help to reduce pain, disability, and frequency of physician visits. These may represent the most cost-effective intervention ***(Amy, 2011).***

**II-Non pharmacological therapy:**

A range of interventions are available and these include exercise, heat therapy, laser treatment, magnetic fields, electrotherapy, complementary and alternative medicine therapies. The major goals of treatment are to relieve pain, reduce inflammation, slow down or stop joint damage, prevent disability, and preserve or improve the patient's sense of wellbeing and ability to function ***(Shaw et al., 2007).***

***-* Splinting:**

The patients with acutely and severely inflamed joints may need application of resting splints to immobilize the joint until anti-inflammatory medication takes effects. Even the most painful joints when splinted must be moved passively through a full range of motion each day to prevent flexion contractures ***(Silva et al., 2008).***

**-Exercises**:

Physical activity is beneficial for persons with Rheumatoid arthritis complaining of fatigue (***Cramp and Fiona, 2013).***

**III. Pharmacological therapy*:***

[Disease-modifying antirheumatic drugs](https://en.wikipedia.org/wiki/Disease-modifying_antirheumatic_drugs) (DMARDs) are the primary treatment for RA. 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 ***(Scott et al., 2010).***

It is based on identification of patients with early RA, early use of available therapies in suspected cases to control inflammation as completely as possible, tight control according to quantitative monitoring in order to prevent long-term damage and using as the anchor MTX drug ***(Combe et al., 2007).***

**A-Analgesics:**

Acetaminophen is a very useful drug and can prove a useful adjunct in the treatment of arthritis. Combination of acetaminophen with codeine or other narcotic derivatives produces a powerful but potentially addictive combination ***(Genovese and Harris, 2005).***

**B - Non steroidal anti -inflammatory drugs (NSAIDs):**

[NSAIDs](https://en.wikipedia.org/wiki/NSAIDs) reduce both pain and stiffness in those with RA ***(Scott et al., 2010)***, generally they appear to have no effect on people's long term disease course and thus are no longer first line agents ***(Tarp et al., 2012)***. NSAIDs should be used with caution in those with [gastrointestinal](https://en.wikipedia.org/wiki/Gastrointestinal_problem), [cardiovascular](https://en.wikipedia.org/wiki/Cardiovascular) , or kidney problems (***Radner et al., 2012).***

**C - Glucocorticoids**:

Corticosteroids are potent anti-inflammatory drugs that are commonly used in patients with RA to bridge the time until treatment with DMARDs is effective. These agents are effective adjuncts to DMARD or NSAID therapy. Timely dose reductions and cessation are important because of the adverse effects associated with long-term steroid use. Corticosteroids can be administered by oral, IV, or intraarticular routes ***(Hoes et al., 2010).***

**D - Disease modifying antirheumatic drug (DMARDs) and immunosuppressive drugs:**

[Disease-modifying antirheumatic drugs](https://en.wikipedia.org/wiki/Disease-modifying_antirheumatic_drugs) (DMARDs) are the primary treatment for RA. 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 ***(scott et al., 2010)***, DMARDs should be started early in the disease as they result in disease remission in approximately half of people and improved outcomes overall ***(Gramling et al., 2012).***

**These drugs include:**

**\* Antimalarials**:

The anti-malarial drug hydroxychloroquine (HCQ) is widely used in treating RA patients. It has a very acceptable toxicity profile and can be safely combined with other DMARDs. Maculopathy occur almost exclusively at higher than recommended doses (6mg/kg/day), although eye examination is recommended every 6 months during therapy ***(Klippel et al., 1997).***

**\* Sulphasalazine (SSZ):**

Sulphasalazine decreases the inflammatory response and systemically inhibits Prostaglandin (PG) synthesis, dose is 0.5–1gm/day increased to maintenance dose of 2gm/d increased to 3gm/day if response is not satisfactory after 12 weeks of treatment ***(O Dell, 2004).***

**\*Methotrexate (MTX):**

Considered by many rheumatologists to be the most important and useful DMARD and is often part of the initial line of treatment ,recommended doses started with 7.5mg/w then increased by 2.5-5mg every 4-8w if poor response, till reach maximum dose of 15-20mg/ of 15-20mg PO/IM/SC /w  ***(Wasserman, 2011)***.

**\* Leflunomide**:

Leflunomide is a competitive inhibitor of an intracellular enzyme needed for de novo pyrimidine synthesis by activated lymphocytes ***(Olsen and Stein, 2004).***

Leflunomide slows progression of joint damage as measured radiographically, and it was found to prevent new joint erosions in 80% of patients over a two-year period.It's extended plasma half – life which is 15 to 18 days led to the recommendation that it can be given as a loading dose (100 mg /day) for 3 days followed by 20 mg/day ***(Cohen et al., 2001).***

**\* Azathioprine (AZA):**

Azathioprine is effective in the treatment of RA with a slow clinical response over several months but is not as effective as MTX. The combination of AZA and MTX is no more effective than MTX alone in RA The dose of AZA in RA is (1.25 – 1.5 mg/kg/day) ***(Blom and Riel, 2007).***

**\* Cyclophosphamide**:

Cyclophosphamide is an alkylating agent that causes alkylation of DNA. It shows efficacy in doses less than 1.5 mg/kg/day. It reaches its peak of effectiveness after approximately 16 weeks. Remission may be maintained for several years after withdrawal of cyclophosphamide, but most patients will have recurrence of RA symptoms. Oral cyclophosphamide is effective in treatment of RA. In rheumatoid vasculitis patients, I.V. cyclophosphamide improves the vasculitis but does not improve the arthritis ***(Gaffney and Scott, 1998).***

**\* Cyclosporine A:**

Cyclosporine inhibits the activation of CD4+ helper / inducer T lymphocytes by blocking IL-2 and other T helper type 1 (Th1) cytokine production,adding lower doses (2.5 – 5 mg/kg/day) to a stable dose of MTX and decreasing the cyclosporine if the patient’s creatinine level rises to more than 30% of initial values ***(Blom and Riel et al., 2007).***

[Cyclosporin](https://en.wikipedia.org/wiki/Cyclosporin) are less commonly used due to more common adverse effects. Agents may be used in combinations ***(Scott et al., 2010).***

**E- Biological:**

Biological agents should generally only be used if MTX and other conventional agents are not effective after a trial of three months. They are associated with a higher rate of serious infections as compared to other DMARDs ***(Singh et al., 2015).***

**\* Tumour necrosis factor** **(TNF-****) inhibitors:**

They are biologic medications that intercept a messenger protein in the joints (tumor necrosis factor or TNF) that promotes inflammation of the joints in RA ***(Aaltonen et al., 2012).***

- **Etanercept:**

Is a soluble TNF-receptor fusion protein. Its long-term effects are comparable with MTX in some studies, but it elicits improvement in symptoms much more rapidly, it is given by subcutaneous injection of 25 mg twice weekly ***(Bathon et al., 2000).***

- **Infliximab:**

Another TNF antagonist is a chimeric IgG1 anti-TNF alpha antibody, patients that had a poor response to MTX had a greater response with infliximab than placebo, the initial recommended dose is 3 mg/kg given as an intravenous infusion, followed by doses at 2 and 6 weeks after the first infusion, then every 8 weeks ***(Lipsky et al., 2000).***

- **Adalimumab**:

Also is a recombinant human IgG1 antibody and has an additive effect, when taken with MTX the initial recommended dose is 40 mg every other week administered subcutaneously ***(Weinblatt et al., 2003)***.

**\*Interluekin-1 receptor antagonist (IL-1 Ra) Anakinra**:

Is a recombinant interleukin-1 receptor antagonist, several randomized controlled trials have found it to be more effective than placebo when administered alone or in combination with MTX adverse effects include skin irritation at the site of injection, increased risk of infection, and leucopenia a recommended dose is 100 mg/day administered by subcutaneous injection ***(Olsen and Stein et al., 2004).***

**\* Interluekin-6 receptor inhibitor:Tocilizumab (Actemra):**

Tocilizumab has recently been approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Tocilizumab is the first approved biologic medication that blocks interleukin-6 (IL-6), which is a chemical messenger of the inflammation of rheumatoid arthritis. Significant efficacy has been seen with both the 4 mg/kg and 8 mg/kg doses intravenous infusion given monthly ***(Patel and Moreland, 2010).***

**\* B cell modulating agents:**

***- Rituximab:***

Rituximab is an antibody that can be effective in treating autoimmune diseases like RA, because it depletes B-cells which are important cells of inflammation and in the production of abnormal antibodies that are common in these conditions ***(Gerlag and Tak, 2008) .***

Rituximab in combination with MTX is indicated for the treatment of adult patients with moderately-to-severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies, the usual regimen consists of 2 intravenous (IV) infusions of 1000 mg , separated by 2weeks ***(Cohen et al., 2010).***

**\* T cell modulating agents:**

**-*Abatacept (Orencia)*:**

Abatacept is a biologic medication that blocks T-cell activation . Abatacept is used to treat adult patients who have failed treatment with a traditional DMARD medication. Abatacept is dosed according to body weight ;<60 kg: 500 mg, 60-100 kg: 750 mg, >100 kg: 1 g IV infusion after the initial IV infusion, it is repeated at week 2 and week 4 and then every 4 weeks. Maintenance doses may be administered as a monthly IV infusion or by the patient as a weekly SC injection ***(Maxwell and Singh, 2009).***

**\*\*Future treatments:**

Despite significant advances over the past decades, RA continues to be a chronic disease. It remains active in many patients whose conditions partially or completely fail to respond to DMARDs. Therefore, the vigorous search for new therapeutic agents continues. Several newCD20 B-cell−targeted biologic agents are under investigation, including atacicept, belimumab, epratuzumab, ofatumumab, ocrelizumab . Small molecules directed at enzymes involved in signal transduction of TNF and other proinflammatory cytokines are effective in treating RA ***(Weinblatt et al., 2010)***.

Aphase II study reported that in comparison with placebo, fostamatinib, an inhibitor of spleen tyrosine kinase (Syk), reduced disease activity in RA patients who did not have a response to MTX therapy. Further investigation is required to determine the safety and (MMPs), though initially unsuccessful could prove to be efficacious, as could inhibition of osteoclast activation. Apheresis procedures are also being investigated. High-dose immune suppression combined with autologous stem cell transplantation has been used in study protocols for patients whose conditions are resistant to other therapies ***(Weinblatt et al., 2010)***.

**2014 EULAR Recommendations for Use of DMARDS and Biologic –**

**Agents *(Smolen et al., 2014):***

This section summarizes the 2014 updates of EULAR recommendations for the use of non biologic and biologic DMARDs in the treatment of RA. It is recommended that low disease activity or remission should be targeted for all patients with early or established disease who are receiving a DMARD or a biologic agent.

* Consider glucocorticoids.
* Low-dose glucocorticoids should be considered as part of initial treatment plan (in combination with 1 or more csDMARDs) for up to 6 months; they should be tapered as soon as clinically appropriate.
* "Low-dose" generally refers to ≤ 7.5 mg prednisone or its equivalent per day.
* Glucocorticoid monotherapy is not recommended, except in some cases in which all DMARDs have contraindications.

- **When the Treatment Target Is Not Achieved**

* If the treatment target is not reached with the initial DMARD
* Approach, in the absence of poor prognostic factors, considering switching to another csDMARD approach.
* When poor prognostic factors exist, consider addition of a bDMARD.
* Risk factors for a poor clinical outcome include high disease activity, autoantibody positivity for RF or (ACPA) antibodies, and the early presence of joint damage.

In patients with low risk for poor outcomes, another csDMARD strategy (with glucocorticoids) is preferred; in those at high risk, consider adding a bDMARD.

- **Introducing Biologics**

* If response to MTX or other csDMARD strategies, with or without glucocorticoids, fails to achieve the treatment goal by 6 months or results in no improvement at 3 months, bDMARDs should be initiated with MTX.
* bDMARDs include TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and approved biosimilars); abatacept or tocilizumab; and, under certain circumstances, rituximab.
* Rituximab (currently the least expensive biologic) is approved in patients who have responded insufficiently to TNF inhibitors, and maybe considered a first-line bDMARD in the setting of the following contraindications for other agents: recent lymphoma history, latent tuberculosis with contraindications to chemoprophylaxis, living in atuberculosis-endemic region, or a history of demyelinating disease.
* No preferential order of biologic selection is provided in the new recommendations, although the Task Force acknowledges that there is more experience with TNF inhibitors than with other bDMARDs.

- **When the First Biologic Fails**

* If the initial bDMARD fails, patients should be treated with a subsequent bDMARD. If the first TNF inhibitor fails, patients can receive either another TNF-blocking agent or another biologic with a different mechanism of action.
* Current evidence does not support any particular biologic over switching to another TNF inhibitor when the initial anti-TNF agent fails.
* With multiple biologic biosimilar medications around the corner, the Task Force emphasizes that, for example, an infliximab biosimilar should not be regarded as "another" TNF inhibitor in patients who do not respond adequately to infliximab.

- **When to Taper**

* If a patient is in persistent remission after glucocorticoids are tapered, consider tapering bDMARDs, especially when combined with DMARDs**.**

- **Strategies in Long-term Remission**

* In cases of sustained remission, consider careful reduction of the csDMARD dose; this should be a collaborative decision between physician and patient**.**
* Recognize that stopping csDMARD therapy altogether in a patient with remitted RA results in disease flares in up to 70% of patients -twice as frequently as in those maintained on a regimen of any kind.

- **Therapy Adjustment: Factors to Consider**

* If therapy needs adjustment, the following factors beyond just disease activity should be considered: Progression of structural damage, safety issues, and co-morbidities.
* Reaching the outcome of low disease activity or remission is not always a prerequisite if the above considerations are a factor; some patients with low disease activity may still develop progressive radiographic joint damage and may require intensification of therapy.

**2015 ACR Recommendations for Use of DMARDS and Biologic –**

**Agents *(Singh et al., 2016):***

This section summarizes the 2015 updates of ACR recommendations for the use of non biologic and biologic DMARDs in the treatment of RA. It is recommended that low disease activity or remission should be targeted for all patients with early or established disease who are receiving a DMARD or a biologic agent**.**

**In early Rheumatoid Arthritis:**

* Regardless of disease activity use a treat -to- target strategy rather than non targeted strategy.
* If disease activity is low in patients who never taken drugs use:
* Monotherapy (MTX preferred)more than double therapy
* Monotherapy (MTX preferred)more than triple therapy
* If disease activity is moderate or high in patients who never taken DMARDs use :
* Mono therapy DMARD more than double therapy.
* Mono therapy DMARD more than triple therapy.
* If disease activity is moderate or high despite monotherapy DMARD (with or without glucocorticoids) use:
* Combination therapy or TNFI or non TNF biologic (with or without MTX), no particular preference better than DMARD monotherapy alone.
* If disease activity is moderate or high despite DMARD (with or without glucocorticoids) use:
* TNFI over tofacitnib
* TNFI with MTX over tofacitnib with MTX
* If disease activity is moderate or high despite biologic DMARD add low dose glucocorticoids.
* If disease flares add glucocorticoid use lowest possible dose glucocorticoids and for shortest duration. .

**In established Rheumatoid Arthritis:**

* Regardless of disease activity use a treat -to- target strategy rather than non targeted strategy
* If disease activity is low in patients who never taken drugs use
* Monotherapy (MTX preferred)more than double therapy
* Monotherapy (MTX preferred)more than triple therapy
* If disease activity is moderate or high in patients who never taken DMARDs use :
* Mono therapy DMARD (MTX preferred) more than tofacitnib.
* Mono therapy DMARD (MTX preferred) more than combination therapy.
* If disease activity is moderate or high despite monotherapy DMARD (with or without glucocorticoids) use:

Combination traditional DMARD therapy or TNFI or non TNF biologic (with or without MTX), no particular preference better than DMARD monotherapy alone.

* If disease activity remains moderate or high despite TNFI therapy in patients who are not on DMARDs use: TNFI with one or two DMARDs over TNFI.
* If disease activity remains moderate or high despite single TNFI therapy use:
* Non TNF biologic (with or without MTX) over another TNFI with or without MTX.
* Non TNF biologic (with or without MTX) over another tofacitinib with or without MTX.
* If disease activity is moderate or high despite single non TNF biologic DMARD use:

Another non TNF biologic (with or without MTX) over tofacitinib with or without MTX.

* If disease activity is moderate or high multiple despite sequetional TNFI therapies use:

Another non TNF biologic (with or without MTX) over another TNFI therapies or tofacitinib .

* If disease activity is moderate or high despite multiple sequetional TNFI therapies use:

Tofacitinib (with or without MTX) over another TNFI therapies (with or without MTX). If non TNF biologic is not option.

* If disease activity is moderate or high despite at least one TNFI and at least non TNF biologic use:

Non TNFI therapies (with or without MTX) over tofacitinib (with or without MTX) or tofacitinib (with or without MTX) over another TNFI.

* If disease activity is moderate or high despite use DMARD, TNFI, non TNF biologic add low dose steroid.
* If disease flares despite use DMARD, TNFI, non TNF biologic add glucocorticoid use lowest possible dose and for shortest possible duration.
* If disease is in remission: Taper DMARD, TNFI, non TNF biologic or tofacitinib.
* If disease is low: Continue DMARD, TNFI, non TNF biologic or tofacitinib rather than discontinuing respective medication.
* If disease is in remission: Do not discontinue all RA therapies.

**ACR and EULAR update of 1981 criteria for RA Remission:**

Definition specifies that scores be less than or equal to 1 for tender joint count, swollen joint count (both using the 28-joint count), C-reactive protein (in mg/dL), and patient global assessment (0–10 scale**) (*Felson et al., 2011).***

**IV -Surgery:**

In early phases of the disease, an arthroscopic or open [synovectomy](https://en.wikipedia.org/wiki/Synovectomy) may be performed. It consists of the removal of the inflamed [synovia](https://en.wikipedia.org/wiki/Synovia)l and prevents a quick destruction of the affected joints. Severely affected joints may require [joint replacement](https://en.wikipedia.org/wiki/Joint_replacement) surgery, such as knee replacement[,](https://en.wikipedia.org/wiki/Rheumatoid_arthritis#cite_note-Lancet2010-3) Post operatively [physiotherapy](https://en.wikipedia.org/wiki/Physiotherapy) is always necessary ***(Scott et al., 2010).***

***Prognosis:***

Predictors of poor outcomes in the early stages of rheumatoid arthritis include a relatively bad functional score early in the disease progression, lower socioeconomic status, and lower education level, strong family history of the disease and early involvement of many joints.

Prognosis is worse in patients who have a persistent high ESR or CRP level, positive RF, or early radiologic changes ***(Boers et al., 2001).***

***Mortality:***

RA is known to reduce the lifespan of patients by anywhere from three to 12 years ***(Wasserman et al., 2011).*** However, the use of new biologic drug therapies extends the Life span of patients with RA and reduces the risk and progression of atherosclerosis ***(Atzeni et al., 2010).***

# \*\*B Lymphocyte Attracting Chemokine 1(CXCL13)\*\*

Introduction:

Chemokines are a family of small [cytokines](http://en.wikipedia.org/wiki/Cytokine) or [proteins](http://en.wikipedia.org/wiki/Protein) secreted by [cells](http://en.wikipedia.org/wiki/Cell_(biology)). Their name is derived from their ability to induce directed [chemotaxis](http://en.wikipedia.org/wiki/Chemotaxis) in nearby responsive cells; they are chemotactic cytokine, they have emerged as crucial orchestrators for lymphocyte trafficking and activation ***(Mackay, 2001).***

These secreted polypeptides exert their function by binding to specific cell surface receptors called [chemokine receptors](http://en.wikipedia.org/wiki/Chemokine_receptor), that are selectively found on the surfaces of their target cells ***(Zlotnik and Yoshie, 2000)***.

The major role of chemokines is to act as a chemoattractant to guide the migration of cells. Cells that are attracted by chemokines follow a signal of increasing chemokine concentration towards the source of the chemokine. Some chemokines control cells of the [immune system](http://en.wikipedia.org/wiki/Immune_system) during processes of immune surveillance, such as directing [lymphocytes](http://en.wikipedia.org/wiki/Lymphocyte) to the [lymph nodes](http://en.wikipedia.org/wiki/Lymph_node) so they can screen for invasion of pathogens by interacting with [antigen-presenting cells](http://en.wikipedia.org/wiki/Antigen-presenting_cell) residing in these tissues. These are known as [homeostatic](http://en.wikipedia.org/wiki/Homeostatic) chemokines and are produced, secreted without any need to stimulate their source cells. Some chemokines have roles in development, they promote [angiogenesis](http://en.wikipedia.org/wiki/Angiogenesis) (the growth of new [blood vessels](http://en.wikipedia.org/wiki/Blood_vessel)) or guide cells to tissues that provide specific signals critical for cellular maturation. Other chemokines are [inflammatory](http://en.wikipedia.org/wiki/Inflammation) and are released from a wide variety of cells in response to infection ***(Fernandez and Lolis, 2002).***

Disappointingly, however, none of the cytokines that drive the acute systemic response and that can be produced at least in part at the synovial tissue level, such as IL-1, IL-6 and TNF-α, has been convincingly shown to be associated with progression of joint damage, thus making the crude assessment of classical inflammatory biomarkers hardly advisable. Additional value could be provided by serological markers which reflect more specific aspects of synovial pathology, differently regulated in different patients, such as angiogenesis (and vascular biology in general) and mononuclear cell infiltration ***(Rooney et al., 2010)***.

Identification of new variables derived from understanding pathogenic mechanisms that correlate more specifically with synovitis, at both the clinical and the sub-clinical level, might refine our ability to build early prognostic algorithms ***(Jones et al., 2014).***

CXCL13 has been considered a putative diagnostic marker for some acute or chronic infectious and inflammatory diseases ***(Rupprecht et al., 2014).***

CXC chemokine ligand 13 protein (CXCL13) is homeostatic chemokine characterized as the sole B cell chemoattractant signal, originally named B-cell-attracting chemokine-1(BCA-1) or B-lymphocyte chemoattractant (BLC), is a CXC subtype member of the chemokine superfamily ***(Hui et al., 2015***)**.**

C-X-C motif chemokine 13 ( CXCL13)is critical agent for B-cell homing to inflammatory foci by redistributing B lymphocytes into injured tissues, organizing their microanatomical positioning and possibly enhancing their B cell receptor (BCR)-mediated activation that is implicated in the pathogenesis of several immunologic disorder ***(Corsiero et al.,2012).***

Circulating CXCL13 is increased in many classical autoimmune syndromes including multiple sclerosis, RA, systemic lupus erythematosus, systemic sjӧgren and levels of this chemokine are often correlated with the clinical activity of these diseases ***(Lee et al., 2010).*** Increased CXCL13 production by osteoblasts from osteoarthritis patients in response to stimulation with IL-1β has been reported ***(Lisignoli et al., 2004).***

Interestingly, renal CXCL13mRNA and protein were over expressed starting at the onset of systemic lupus erythematosus disease, even prior to the appearance of renal manifestations. Also there are enhanced plasma levels of CXCL13 in patients suffering from type IV lupus nephritis as well as in lupus-prone mice. Expression of CXCL13 in the kidneys of the murine model of lupus progressively increased during the course of LN. Furthermore, elevated levels of CXCL13 correlated with enhanced numbers of B cells in the kidney, glomerular and tubule interstitial damage, albuminuria, and loss of renal function ***(Moreth et al., 2010).***

CXCL13 expression was recognized in the liver of mixed cryoglobuliemia patients with morphologic pictures of follicle-like structures, suggesting its major role in the organization and maintenance of ectopic lymphoid tissue ***(Magliozzi et al., 2004).***

Using a computer model representing the biology of the rheumatic joint, the B cell attracting chemokine CXC (CXCL13) has been recently identified as a new potential serologic marker for severity in RA ***(Meeuwisse et al., 2011).***

Recently, CXCL13 has risen to be a possible new marker of disease and inflammation in RA. CXCL13 is reported up-regulated in RA patients, and is suggested to be connected with both disease activity and CXCL13 is expressed in ectopic lymphoid structures, including islets in mice, the aorta in apolipoprotein E–deficient mice, and synovial tissue in patients with RA ***(***[***Henry et al., 2010***](http://onlinelibrary.wiley.com/doi/10.1002/art.38173/full#art38173-bib-0023)***)***, and participates in ectopic germinal center (GC) formation **.** These ectopic (GC) provide an optimal microenvironment for B-cell activation, differentiation, maturation, and autoantibody generation, resulting in accelerated disease progression ***(Carlsen et al., 2004)***, as well as for local affinity maturation of the immunoglobulin genes ***(Scheel et al., 2011).***

In mice , CXCL13 is produced mainly by stromal cells , such as follicular dendritic cells , in the secondary lymphoid organs(spleen, lymph nodes and Peyer’s patches) but not by T cells, such as antigen-experienced T cells, follicular helper T (Tfh) cells in the GC, and a subset of memory CD+4 cells ***(***[***Crotty et al., 2011)***](http://onlinelibrary.wiley.com/doi/10.1002/art.38173/full#art38173-bib-0021) and ***(Corsiero et al., 2012).***

Showed that CD4+ T cells subsets in RA synovium appear to produce CXCL13 spontaneously ,also human CD14+/CD68+monocytes/ macrophages are potent inducible sources of CXCL13 ***(Kobayashi et al., 2013).***

CXCL13 is essential in establishing an adaptive immune response, as involved in the positioning, cooperation and activation of B and T cells within lymphoid and extralymphoid sites, including RA synovium which facilitates the generation of antibodies, local inflammation and subsequent tissue damage noted in serial autoimmune diseases ***(Manzo et al ., 2010) .***

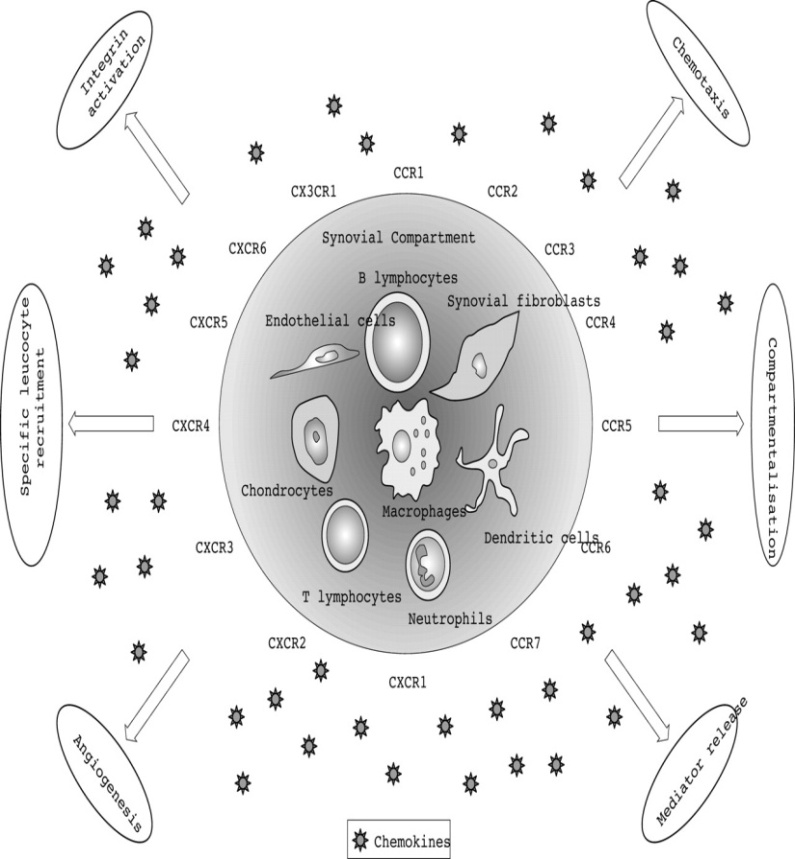
***CXCL13 Receptors:***

The B-cell ligand for CXCL13 that mediates lymphocyte chemotaxis is C-X-C chemokine receptor type 5 (CXCR5), ***Figure (2) (Nelson et al., 2006).*** CXCR5, the only known receptor for CXCL13, is expressed by naïve B cells and subset of CD4+ and CD8+ TFH cells, T helper (Th 17), regulatory T (Treg) cells in secondary lymphoid tissue follicles, immature dendritic cells (DCs), and macrophages and it controls the migration of these cells to the follicle ***(Chan et al., 2009)*.**

The CXCL13-CXCR5 axis is critical to the generation of immunological memory based on long-lived plasma cells because the interaction between TFH and B cells is necessary for the formation of plasma cells, autoantibody production and maintenance of epithelial cell angiostatic activity ***(Manzo et al., 2008*)** and ***( Romagnani et al., 2004*).**

Human CXCL13 is also reported to be an agonist of human CXCR3 receptor, which plays an important role in recruitment of activated T cells into secondary lymphoid tissues ***(Jenh et al., 2001).***

Characteristically of all chemokine receptors, binding of a chemokine leads to an internalization of the ligand-receptor complex with subsequent activation of the associated intracellular signaling cascade ***(Klimatcheva et al., 2015).***



**Figure (2):** Overview of homoeostatic and inflammatory functional interactions of chemokines and their receptors in inflammatory joint disease ***(Nelson et al., 2006).***

***Role of CXCLI3 in Rheumatoid Arthritis:***

Within the RA synovium CXCL13 is expressed in areas of B cell accumulation characteristic of ectopic lymphoid follicles where subtypes of CXCL13-expressing T cells (CD3+ and CD4+) and monocytes /macrophages colocalize ***(Kobayashi et al., 2013).***

In RA synovium, ectopic expression of CXCL13 associates with the local organization of infiltrating lymphocytes and with the expression of activation-induced cytidinedeaminase, an enzyme sufficient and required for somatic hyper mutation and class-switch recombination of immunoglobulin genes ***(Manoz et al., 2010)*.**

Proinflammatory cytokines play a role in upstream of CXCL13 expression and lymphoid tissue organization, as demonstrated in animal models of lymphoid tissue ontogenesis and neogenesis, Proinflammatory cytokines alone were unable to induce significant expression of CXCL13 ***(Rangel-Moreno et al., 2011)*.**

When present, B cells are virtually restricted to follicular structures with wide variation in size and density distribution, these structures are the preferential environment in which topographic interactions between B cells and T cells, macrophages, mesenchymal stromal cells, and dendritic cells are favoured, which makes them the elective intra-synovial site for potential intercellular (cell-contact dependent or paracrine) immunological interactions to take place **(*Manzo et al., 2010*).**

In animal models, inflammatory stimuli promote the local migration and retention of B lymphocytes within non lymphoid tissues through the induction of chemoattracting factors, such as CXCL13, but they are no further required for their maintenance ***(Rangel-Moreno et al., 2011)***, furthers CXCL13 expression is up regulated by tumor necrosis factor alpha (TNFα) and by T cell receptor stimulation***(Kobayashi et al., 2013)*.**

Memory B cells express the chemokine receptors CXCR5, CXCR4, and CCR7 ***(Nanki et al., 2009*)** that account for their migration across different anatomic compartments under homeostatic and inflammatory conditions. Serum levels of their ligands CXCL13, CXCL12 , and CCL19 (which may well reflect the degree of expression of these factors in peripheral tissues) have been actually shown to be inversely correlated with the frequency of blood memory B in RA (***Sellam et al., 2013).***

B1 cells are a specialized cell population that is distinguished from conventional B cells (B2 cells) by their origin, antigen specificity, so the aberrant high expression of BLC/CXCL13 in the target organs, ***Figure (3****)*, and decreased number of BLC producing peritoneal macrophages result in defective B1 cell homing to the peritoneal cavity and preferential B1 cell trafficking to the target organs ***(Ito et al., 2004).***



**Figure (3):** High expression of BLC/CXCL13 in the target organs *(****Ito et al., 2004).***

CXCL13enhances BCR-mediated B cell activation , guides migration of CXCR5+CD4+ follicular helper T cells and possibly impacts on other CXCR5-bearing cells , including dendritic cells and bone cells ***(León et al., 2012).***

B cells were recently identified as major producers of receptor activator nuclear factor kappa B ligand (RANKL) in the synovial fluid of RA patients ***(van der PouwKraan et al., 2003)***, and rituximab treatment strongly affects the RANKL/ osteoprotegerin (OPG) system as well as the genes involved in healing processes in the synovium **(*Boumans et al., 2012*).**

Furthermore, and perhaps more relevant, autoantibodies produced locally may directly influence bone loss by promoting osteoclast o genesis ***(Gutierrez-Roelens et al., 2011) .***

Continuous synovial expression of CXCL13may mark ongoing immune cell activation and the establishment of a local milieu favouring tissue remodeling, as suggested by increased levels of interferon (IFγ), and IL-2 expression and a higher RANKL / OPG ratio in tissues expressing increasing levels of the chemokine **(*Bugatti et al., 2014).***

CXCL13 plays a role in the development of both IgG ACPAs and IgA-RF prior to the development of clinical signs and symptoms. In addition to the development of autoantibodies in the preclinical phase, CXCL13 has been associated with synovial inflammation in RA **(*Manzo et al., 2008).*** Accordingly, synovial levels of CXCL13 expression and lymphocyte infiltration appear associated with features of local disease activity in early RA ***(Bugatti et al., 2014).***

T cells are present in elevated numbers in the synovial joints in RA where they form cellular infiltrates that resemble ectopic lymphoid aggregates with germinal center formation ***(Manzo et al., 2005).***

This suggests the presence of an ongoing antigen presentation and follicle formation in the synovium. The follicle is a well-organized structure, generated by follicular dendritic cells (FDCs), B cells, and follicular helper CD4 T (TFH) cells. Within the follicle, B cells are activated and matured into long-lived plasma cells, which secrete high-affinity antibodies ***(Humby et al., 2009).***

CXCL13-producing CD4+ T cells may modify the local chemokine environment coordinately with stromal cells to recruit CXCR5+ naive B cells and CXCR5+ blood CD4+ T cells containing circulating Tfh cells ***(Morita et al., 2011)****,* which contribute to the generation of ectopic tertiary lymphoid organs in RA ST; this leads to the production of autoantibodies in tertiary lymphoid organs and persistent proliferating synovium. It is found that production of CXCL13 by synovial CD4+ T cells was lower in RA patients who were negative for (RF) ***(Corsiero et al., 2012).***

In RA Synovial tissue, existing proinflammatory cytokines could support persistent CXCL13 production and ectopic lymphoid structures. Because both Tfh and iTh13 cells exhibit similar expression of CXCL13, IL-21, and PD-1, their differentiation and function need to be further determined. Tfh and iTh13 cells might share their function or development process to some extent (as Th1 and Tfh cells share the process of differentiation in the early phase) ***(Nakayamada et al., 2011).***

The expression pattern of CXCR5 and CXCL13 also differed between CD4+ T cells from the tonsil and from RA synovium**.** Although IL-21+ cells were more frequent in RA synovial CXCL13+CD4+ T cells than in tonsil CXCR5+ Tfh cells, RA synovial CXCL13+CD4+ T cells produced as much IL-21 as did synovial Th1 cells, indicating that CXCL13+CD4+ T cells exert a significant amount of B helper activity but have no specialized commitment to this activity compared to Th1 cells in the same environment ***(Morita et al., 2011).***

However, expression of CXCR5 is crucial for the localization of T cells in the GCs of secondary lymphoid organs**.** Recently, CXCR5+ FoxP3+ follicular regulatory T (Tfr) cells were shown to localize in the GC of secondary lymphoid organs and to inhibit humoral immunity more effectively than do conventional CXCR5– Treg cell, therefore, it is likely that iTh13 cells, which are negative for CXCR5, localize and exert B cell helper activity in secondary lymphoid organs less effectively than do CXCR5+ Tfh cells ***(Sage et al., 2013).***

High levels of CXCL13 were measured in synovial fluids from RA patients, with RA synovial T helper cells contributing to CXCL13 secretion ***(Corsiero et al., 2012).***

Supporting a role for CXCL13 as an important mediator of autoimmune arthritis, neutralization of CXCL13 or CXCR5 gene deletion significantly reduced disease severity in animal models of arthritis ***(Finch et al., 2013)*.**

**Musculoskeletal Ultrasonography**

***Introduction***

In general, MSUS has gained an important position in rheumatologists’ clinical practice. This is due to its intrinsic characteristics, such as low costs, rapidity and lack of radiation ***(Janow et al., 2011).***

Ultrasound images are analyzed in real time, and the information that is acquired can be used directly to adjust the clinical assessment, which can be particularly useful if there are few verbal complaints , e.g., in infants ***(Moore and Copel, 2011).***

Ultrasonography is a safe, well-tolerated, and has few technical limitations. High-frequency ultrasound has better spatial resolution than magnetic resonance imaging (MRI), and ultrasonography really excels in its ability to perform real-time dynamic studies and interventions. Sonography also allows easy comparison with the contralateral side, which can help in identifying subtle abnormalities ***(Ahmed and Nazarian, 2010).***

MSUS technology offers several inherent advantages. There are several advantages from the clinician’s point of view. As it does not pose limitations due to metal artifacts, which can be problematic in magnetic resonance imaging (MRI). The ability to visualize needles and target structures in real time makes it an ideal tool for the guidance procedures used in diagnosis and management ***(***[***Del Cura et al., 2008***](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3458614/#bibr14-1759720X12442112)***)*.**

**Basic Physics:**

Ultrasonography (U/S) is an imaging modality that uses sound waves in the higher frequency range of 20,000 Hz, which normally cannot be heard by human beings. Ultrasound travels as a longitudinal wave, and images are generated when pulses of ultrasound from the transducer produce echoes at tissue or organ interfaces ***(Shapiro et al., 2000).***

* **Wavelength:**

It is the distance between two identical adjacent points in consecutive waves. Wave lengths are most accurately measured in sinusoidal waves, which have a smooth and repetitive oscillation ***(Smith and Finnoff, 2009).***

* **Frequency:**

Is the number of waves per second. It is measured in hertz (Hz),with 1 Hz being one complete cycle per second, the frequencies used in diagnostic ultrasound typically ranges from2 to 20 MHz (1 MHz = 1million Hz). The frequency is inversely proportional to the wave length; the higher the frequency, the shorter the wave length, higher frequency leads to a better resolution, while lower frequency provides better penetration. To examine the musculoskeletal system, electronic high-frequency linear transducers are used, which provide uniform anatomical information on all images, have good resolution in both near and distance fields, and are easy to apply and maintain**.** For overview and guidance, transducers with frequencies between 7.5 and 10 MHz are recommended, while for deeper-located structures, such as hip or shoulder joints, transducers with lower frequencies (2–6 MHz) are recommended. Detailed study of musculoskeletal structures requires the use of high-frequency transducers, 15–18 or 20 MHz ***(Smith and Finnoff, 2009)*.**

* **Resolution:**

Some of the waves are absorbed by the tissues, and the extent to which the ultrasound is absorbed or reflected gives information about the structures scanned. Resolution is defined as the smallest distance that can be discriminated in the image. Better resolutions are attained with higher frequencies. But, in doing so, signals are attenuated, decreasing the depth of the field ***(Van Holsbeeck and Introcaso, 1992).***

**Ultrasound Equipment** :

An ultrasound device consists of a console, comprising a computer, a monitor, a keyboard, and transducers***, Figure (4****)****.***

****

**a**

**b**

**Figure (4):** Musculoskeletal ultrasond equipment with its probes **(a)** Hocky stick probe **(b)** Linear probe.

**The transducer or probe:**

Is the centerpiece of the equipment, with built-in piezo electric crystals that emit and receive ultrasound ***Figure (5a, b, c)****,*It contains a linear array of very thin crystals, characterized by a piezoelectric property. This property can be described as: the appearance of a difference in the electric potential between two surfaces of a piezoelectric crystal, when it is subjected to mechanical deformation. The phenomenon occurs inversely as well: A piezoelectric crystal subjected to a potential difference suffers a mechanical deformation, which generates ultrasound ***(Borg et al., 2008).***

Depending on the ultrasound transducers’ emission and sequencing beam, they are classified into: linear, sectorial, and combined, with functions and/ or multiple frequencies ***(Smith and Finnoff, 2009).***

***Linear transducers*** ***Figure (4b, 5b):*** Are able to cover almost all musculoskeletal ultrasound examinations. On this type of transducers, the ultrasound beam emerges parallel to each other and perpendicular to the surface of the transducer and the image produce is a rectangular one. These may have a contact surface length, with the skin, between 2 and 6 cm. Larger transducers provide a better overview and are used particularly for large joints, such as the hip joint, or for knee or shoulder joint stability tests. Smaller transducers, also known as “**the hockey stick**” or **“fingerprint” *Figure (4a,5c)***, because of their shape, were originally developed for intra-operative use, but are excellent for small and superficial structures and for the valuation of inaccessible areas such as metacarpophalangeal (MCP), metatarsophalangeal (MTP), proximal interphalangeal (PIP), or distal interphalangeal (DIP) joints ***(Bajaj et al., 2007).***

* ***Convex transducers***: Have a curved, convex ultrasound emission, with electronic activation of the piezoelectric crystals and obtain a trapezoidal image. They are mainly used for abdominal ultrasound, whereas in musculoskeletal-ultrasonography they are used to explore the hip joint, especially in overweight patients**.**
* ***Combined transducers*:** Combine the several possibilities presented before. These include multi-frequency transducers known as “broadband” (wide-band transducer), which include in a one-piece the necessary elements for an examination with a wide range of frequencies. Another type of combined transducers is transducers with multiple functions, which allow examination in several ways: bi-dimensional (2D) mode, M-mode, doppler (continuous and pulsed), harmonic, three-dimensional elastography ***(ElMiedany et al., 2011).***

****

cؤccؤc

bللbلا

b

a

**Figure (5):** Musculoskeletal ultrasound Probes **(a)** Convex probe **(b)** Linear probe **(c)** Hocky stick probe **(*ElMiedany et al., 2011)***

**Probe Markers:**

Every probe has a mark on one of its sides, it could be a raised marker or indentation or some other identifier that is correlated to a dot or the manufacturer’s logo on the display screen. Structures on the same side of the probe marker will appear on the side of the screen mark on the display screen while structures on the opposite side of the probe marker will appear on the other side of the screen marker. Most machines have a button that lets you flip the screen marker from right to left ***(Smith et al., 2009).***

***Probe handling when scanning****:*

To scan a structure in the longitudinal or sagittal view, the transducer is oriented along the long access of the body with the probe marker directed towards the patient head , so the cephalad structures will appear on the side of the display screen with the marker, the transverse or axial is obtained by rotating the probe 90 ° from the long axis of the patient; the probe marker should be directed to the right side of the patient so that the right-side structures of the body will appear on the side of the display screen with the marker.

***Scanning Technique and Image Optimization:***

Following transducer selection, ultrasound gel is placed on the transducer and the transducer is applied to the skin of the region of interest. Next step is to adjust the image depth (depth control on the console), so that the displayed image includes the region of interest without losing information and with no unused space ***(Smith and Finnoff, 2009).***

The examiner must change the position and number of focuses so that the focal zone is located at the same position and depth as the targeted structure, in order to obtain an optimal lateral resolution ***(Smith and Finnoff, 2009).***

All ultrasound machines are equipped with microprocessors that allow various facilities: measurement of distances, perimeters, areas, angles, and volumes; marking areas of interest; schematic display of the transducer position; enrolment of general information (date and time of the examination, transducer frequency and other data on the operating mode of the device, the institution where the examination is performed, and simultaneous display of multiple images in 2D ultrasound or in other different modes. Images are stored on sensitive papers or on devices with large capacity of digital memory. The technical features of the devices depend on the manufacturing company and are different from one machine to another ***(Cimmino et al., 2008).***

***Color Doppler (Color Flow Imaging (CFI):***

Is the ability to show blood flow in a selected area within B-mode image. It represents both direction and velocity of blood flow in this area. The color in the image represents color coding of doppler frequency shift detected within each pixel of the returning echoes, and the detected color is super imposed on the corresponding B-mode image. The flow towards the transducer is usually coded in red while the flow away from the transducer is usually coded blue. Color doppler has disadvantage of aliasing affected by the steering angle and it slow sensitivity to slow flow.

***Power Doppler Imaging*** *(****PDI****)***:**

Is based on the integrated power (or amplitude) of the doppler signal, instead of the mean doppler frequency shift as in color doppler-sonography. The color map in power doppler (PD) sonography displays the integrated power of the doppler signal, which is related to the number of red blood cells that produce the doppler shift ***(Backhaus et al., 2009).*** PDI has three times the sensitivity of conventional color doppler for the detection of flow and is particularly useful for small vessels and those with low-velocity flow **(*Arida et al., 2010).***

***Image Control :***

* **Gain**:

Gain correction is crucial to obtain an interpretable image as it affects the gray scale of the whole image. Decreased gain will give a black image, and details will be masked. Increased gain will give a white image, and details will be saturated ***(Ahmed and Nazarian, 2010).***

* **Color Gain**:

The doppler gain is different from the B-mode gain. Setting the color gain is crucial for accurate diagnosis of tissue hypervascularity which indicates the degree of disease activity. Increased gain causes noise and over estimation of the tissue vascularity. On the other hand, lowering the color gain decreases the color sensitivity resulting in underestimation of the activity. To adjust the color gain, first the gain must be increased until noise appears in the image then gradually decreased until noise disappears. The predictive value of PDUS was higher than that of GSUS. This is in line with the findings that GSUS signs of inflammation also occur in non-arthritic individuals ***(Balsa et al., 2010).***

* **Focus :**

The focus of the image is usually marked on the side of the screen by a small arrow head. The ultrasound beam is narrowed at that depth revealing the best lateral resolution which improves the image quality and ensures high definition of tissue at that depth. The focus is usually adjusted by means of a knobor an up/down button on the control panel; the focus pointer should move to region of interest**.**

* **Depth adjustment**:

Increases or decreases the depth of the examined region on the image. It is best to have the structure that is being examined in the center of the screen.

**Terminology:**

Ultrasound, like other imaging methods, uses specific terminology due to ultrasound propagation and behavior in human body

**Table (2):** Musculoskeletal ultrasonographic terminology.***(Smith and Finnoff, 2009):***

|  |  |
| --- | --- |
| **Term** | **Definition** |
| **Anechoic or transonic** | Is the term used for any structure that is entirely crossed by the ultrasound beam without any reflection on their route, resulting in a “lack of echoes,” displayed as a black image on the monitor. This shows the fluid content of a structure, in most cases. |
| **Echoic or echogenic** | Is the term used for the appearance of a structure that strongly reflects ultrasound, appearing white on the image. This can be produced in musculoskeletal ultrasound by connective structures (bone, calcifications) as well as other high-density structures (air, metal crystals). |
| **Hyper-, iso- , or hypoechoic** | Are terms used when making comparisons between the intensities of echoes produced by the examined structure and the reference structure (hyperechoic—appears whiter, brighter than the reference structure; isoechoic—appears with the same echogenicity compared with the reference structure; hypoechoic—appears darker than the reference structure). |
| **Impure liquid** | Defines the aspect of a structure almost anechoic, containing inside scattered, fine echoes, often mobile under the pressure of the ultrasound beam. |

***Musculoskeletal Ultrasonogrphy in RA:***

(RA) is traditionally considered as the prototype of destructive arthritis. Chronic inflammation of the synovial membrane in RA indeed results in bone and cartilage resorption through the production of inflammatory mediators that support the differentiation and activation of osteoclasts as well as enzymes which degrade articular cartilage and bone ***(Hitchon et al., 2011).***

The central importance of joint remodeling processes in RA pathology is highlighted by the fact that the assessment of structural damage using imaging techniques is a major diagnostic, monitoring, and outcome parameter in both clinical trials and routine clinical practice ***(Lillegraven et al., 2012).***

This requires prompt referral and recognition of RA. New classification criteria ***(Aletaha et al., 2010)***, and new remission criteria *(****Felson et al., 2011)*** have been published. In the new classification criteria, it is suggested that imaging techniques such as ultrasonography (MSUS) may be used for in making the diagnosis of RA ***(Nakagomi et al., 2013).***

Regarding remission criteria, a considerable number of patients in clinical remission according to several clinical criteria shows signs of inflammation on MSUS*.* Also, the variables that have been shown to be predictors of the diagnosis of RA or of remission, such as radiographic joint data and anti-citrullinated protein antibodies (ACPA) test results, have not all been taken into account. This might have inflated the added value of MSUS (***Saleem et al., 2011)***.

The importance of MSUS in RA has recently been recognized by the European League against Rheumatism (EULAR), including this tool in its recommendations on the use of imaging in RA ***(Colebatch et al., 2013).***

***Clinical Applications:***

MSUS has also been shown to be more sensitive than clinical assessment in detecting joint inflammation in RA patients. Irrespective of the number of joints studied, disease activity, or duration, MSUS has detected inflammation in significantly more joints than clinical assessment ***(Naredo et al., 2013).***

Currently, the main role of MSUS assessment in RA includes diagnosis especially in seronegative patients, monitoring disease activity and treatment response as well as guiding intra-articular procedures ***(Freeston et al., 2010).***

Early US-detected abnormalities at this level were mostly synovitis and tenosynovitis, although erosion detection was not uncommon. Results of these studies paved the way for EULAR recommendations regarding the use of MSUS when diagnostic doubts arise, as this would improve the certainty of RA diagnosis above clinical criteria alone ***(Colebatch et al., 2013).***

1. ***Value in diagnosis***

This technique is more sensitive and reproducible than clinical evaluation in assessing joint inﬂammation ***(Scheel et al., 2006)*.** Also, it is more sensitive than conventional radiology as 6.5-fold more erosions were seen by MSUS versus radiography in an early RA cohort (disease duration under 12 months), while 3.4-fold more erosions were visualized by MSUS in a late RA cohort (disease duration over 12 months), with MRI as the gold standard in this study ***(Wakefield et al., 2000).***

The main advantage of MSUS over MRI is that all peripheral joints can be examined as many times as required at the time of consultation, which improves the accuracy of clinical evaluation. Both color doppler and power doppler US (PDUS) techniques detect synovial ﬂow, which is a sign of increased synovial vascularization. The presence of intra articular color doppler/ power doppler signal aids in distinguishing active synovitis from inactive intra -articular thickening *(****Walther et al., 2002****).*

MSUS can aid in the prediction of future radiographic (and potentially clinical outcomes. showed that MCPs in RA patients displaying an increased power doppler signal at baseline assessment were 12 times more likely to develop radiographic damage at one year than those without such hyperemia ***(Brown et al., 2008).***

It also help in differentiation between RA and psoriatic arthritis (PsA) in seronegative patients without a clear diagnosis. A more recent study evaluating MCP involvement in patients with RA versus PsA found that a high percentage of PsA patients had an MSKUS pattern characterized by hypoechoic swelling of the soft tissue surrounding the extensor digitorum tendon, which was not seen in any of the RA patients ***(Gutierrez et al., 2011)***.

Carpal tunnel syndrome is a common extra-articular manifestation of RA . Ultrasonography is a sensitive and specific imaging modality for diagnosis of carpal tunnel syndrome and is therefore, often applied in daily clinical practice in the assessment of patients with symptoms of this syndrome***.***

The prevalence of carpal tunnel syndrome in individuals with RA and whether this syndrome is correlated with disease activity in these patients has been ultrasonographically measured. Consequently, the median nerve of patients with RA and typical carpal tunnel symptoms should be examined by ultrasonography, as the identification of carpal tunnel syndrome in these patients might prompt an escalation of treatment ***(El Miedany et al., 2015)***.

In early, untreated RA patients, finger flexor tenosynovitis was observed more frequently than peri-extensor tenosynovitis, and the most frequently involved tendons were the tendons from second and third fingers ***(Wakefield et al., 2007).***

The detection of erosions is also useful in RA diagnosis. Although erosions can be detected in several rheumatic diseases, some areas can be considered as target for RA. MSUS assessment of the styloid process of the ulnar, the radial part of second MCP joint, and the ulnar part of fifth MCP joint can provide important information for RA diagnosis ***(Zayat et al., 2014).***

The strongest independent predictor factor for developing RA in early, undifferentiated arthritis was PD positivity. Moreover, the positivity of PD in more than three joints increased significantly the risk of progression to RA ***(Salaffi et al., 2010).***

Furthermore, the presence of both B-mode and PD synovitis increases the risk for the development of arthritis in patients with arthralgia, without arthritis at clinical examination and positive (ACPA) and/or immunoglobulin M-rheumatoid factor (IgM-RF***) (Van de Stadt et al., 2010).***

MSUS is useful in identifying pathologic changes related to degenerative musculoskeletal disorders **(e.g., OA)** or regional pain syndromes in RA patients, thus helping in differentiating these pathologies from active disease**.** MSUS can be used to detect various manifestations of OA including (effusion, synovitis, erosion and osteophytes). Unlike in RA, synovial hypertrophy is seen in association with osteophytes in OA of the hand with no or minimal doppler signal ***(***[***Hayashi* et al*., 2011***](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3458614/#bibr30-1759720X12442112)***)****.*

***2-Monitoring Disease Activity:***

When compared to MRI, MSUS showed a high sensitivity in detecting both synovitis and tenosynovitis ***(Schmidt et al., 2013)***, MSUS was also reported to be more sensitive than conventional radiology **(CR)** and as sensitive as MRI, in detecting bone erosion ***(Baillet et al., 2011).***

All the evidence coming from the studies points to MSUS as a useful and valuable tool in monitoring RA patients. Taking all of this into consideration, EULAR recommendations for the use of imaging in RA endorsed the use of MSUS for more accurate assessment of inflammation ***(Colebatch et al., 2013).***

MSUS evaluation of second to fourth PIP and MCP joints with a semiquantitative score is sufficient for diagnosis and follow-up in RA patients ***(Scheel et al., 2005).***

However, a reduced 6-joint count, i.e., bilateral wrist, second MCP, and knee, correlated excellently with the 12-joint count and was also shown to be sensitive tochange in RA patients treated with etanercept (ETA) ***(Perricone et al., 2012) .***

Synovitis was considered as active if doppler signal was detected ***(Cheung et al., 2013).*** Other authors considered synovitis active if SH is greater than grade two together with the presence of doppler activity ***(Ramirez et al., 2014).***

Furthermore, the role of MSUS in identifying subclinical inflammation represents a further expansion of this tool’s use in standard clinical practice. Several studies have demonstrated the presence of MSUS-detected synovitis in patients in clinical remission. This subclinical synovitis has been detected in RA patients irrespective of the treatment received, whether synthetic or biologic DMARD ***(Naredo et al., 2013).***

***3-Guided Intra-Articular Procedures:***

Joint puncture for fluid aspiration purposes or intra-articular injection of different drugs represents routine procedures for rheumatologists, MSUS guidance has a number of advantages against blinded injections, ***Figure (6).***

**Firstly,** MSUS allows for better diagnosis and better characterization of the pattern of joint inflammation, whether it be SH or SE.

**Secondly**, MSUS allows direct visualization of the needle within the joint structure facilitating fluid aspiration. Therefore MSUS-guided procedures significantly improve the accuracy of intra-articular injections. Moreover, MSUS-guided punctures significantly reduce patient discomforts and shorten procedure ***(Cunnington et al., 2010).***

MSUS is the best available imaging technique for guiding needle position within inflamed joints and tendon sheaths in local procedures ***(Kawashiri et al., 2014).***



**Figure (6):** Intra-articular corticosteroid injection of the radiocarpal joint **(a)** Patient and transducer position—transverse scanning of the radiocarpal joint. **(b)**Transverse scanning of the radio-carpal joint; R radius, capsular distension (arrow heads), needle (arrow). **(c)** Post procedural longitudinal scanning of the radio-carpal joint; R radius, C carpal bone, corticosteroid drug deposition is identified intra-articular (arrow**) *(Cunnington et al., 2010).***

***Ultrasound Findings****.****:***

* ***Synovitis:***

Is one of the most important features in RA. The term “synovitis” is used to indicate the presence of synovial effusion (SE) and/or synovial hypertrophy (SH), ***Figure (7a, 8a, 9a)****.*

According to the Outcome Measures in Rheumatology **(OMERACT)** definitions published **in 2005**, SE was defined as an abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular material that is displaceable and compressible, but does not exhibit doppler signal**.**

SH was defined as an abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular tissue that is non-displaceable and poorly compressible and which may exhibit doppler signal ***(Wakefield et al., 2005).***

While knee arthroscopy, a frequent procedure in clinical practice, has permitted a relatively easier histopathological assessment of inflamed joints, MSUS, both B-mode and doppler MSUS examination , were reported to be accurate in detecting joint synovitis in comparison to arthroscopy and histology, respectively ***(Karim et al.,2004).***

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**Figure (7)**: Transverse view over the parapatellar recess of the knee joint showing **(a)** B-mode grey scale SH and SE **(b)** SH with doppler signal; f femur, p patella ***(Karim et al., 2004).***

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**Figure (8):** Longitudinal view over the midline dorsal aspect of the wrist joint showing **(a)** B-mode grey scale SH and SE **(b)** SH with doppler signal in radio-carpal (asterix) and midcarpal (star) joints; r radius, c capitat ***(Szkudlarek et al.,2003).***

In RA inflamed joints, there was a similar good correlation between histologic and doppler inflammatory changes in different joints ***(Andersen et al., 2014).*** When comparing histopathology with B-mode MSUS and (PDUS) and MRI, the highest correlation was found for PDUS and histopathology ***(Takase et al., 2012).*** Although false-negative results were found for doppler techniques when compared to histology ***(Andersen et al., 2014)***, the presence of a positive doppler signal in the synovium was an indicator of active synovial inflammation, ***Figure (7b, 8b, 9b).***



**Figure (9):** Longitudinal view of the dorsal aspect of the metacarpophalangeal joint showing (**a**) B-mode grey scale SH and SE (**b**) SH with doppler signal; mc metacarpal head; pp proximal phalanx ***(Szkudlarek et al., 2003).***

* ***Tenosynovitis:***

Is another important feature in RA patients. MSUS-detected tenosynovitis is defined as **(**hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit doppler signal ***(Wakefield et al., 2005).*** Tenosynovitis on doppler mode is defined as the presence of peri-tendinous doppler signal within the synovial sheath, seen in two perpendicular planes, excluding normal nutrient vessels in mesotenon or vinculae, only if the tendon shows peri-tendinous synovial sheath widening on BM ***(Naredo et al., 2006).***

Tenosynovitis is of the Extensor Carpi Ulnaris **(ECU)** commonly seen in early RA, can easily be detected on MSUS, ***Figure (10a, b).*** Recently, involvement of the Extensor Carpi Ulnaris was found to be associated with erosive progression in early RA ***([Lillegraven](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3458614/" \l "bibr41-1759720X12442112)* [et al.,](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3458614/" \l "bibr41-1759720X12442112) *[2011](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3458614/" \l "bibr41-1759720X12442112)).***

****Figure (10): (a)** Longitudinal and **(b)** Transverse view over the extensor carpiulnaris tendon showing B-mode and doppler tenosynovitis ***(Wakefield et al., 2005).***

Compared to MRI, MSUS has shown to be accurate in detection of tenosynovitis. MSUS has also shown a high specificity, but a fair to moderate sensitivity for detecting tenosynovitis **(*Wakefield et al., 2007).***

For tenosynovitis, the most studied tendons have been the hand and ankle tendons. However, in RA not all tendons are affected in the same way. At hand and finger level, the most frequently involved tendons are the ECU and the flexor tendons of the second, third, and fourth fingers ***(Filippucci et al., 2012).***

Recently, the OMERACT MSUS group developed a four-grade semiquantitative scoring system for B-mode and doppler tenosynovitis which showed a good intra and inter observer reliability.

**This score is as follows**:

**Grade 0**—normal.

**Grade1**—minimal.

**Grade 2**—moderate.

**Grade 3**—severe**.**

**Doppler tenosynovitis was scored as following:**

**Grade 0**—no doppler signal.

**Grade 1**—minimal.

**Grade 2**—moderate.

**Grade 3**—severe pathological peri-tendinous doppler signal within the synovial sheath ***(Naredo et al., 2013).***

**In 2013**, the OMERACT MSUS group defined tendon damage on B-mode as internal and/or peripheral focal tendon defect (i.e., absence of fibers) in the region enclosed by tendon sheath, seen in two perpendicular planes.

For tendon damage, a three-grade semiquantitative scoring system has recently been developed.

**Grade 0**—normal.

**Grade 1**—partial.

**Grade 3**—complete rupture. This scoring system resulted in good inter-observer agreement and excellent intra-observer agreement ***(Bruyn et al., 2013).***

* ***Bone erosions:***

Are defined, according to OMERACT, as intra-articular discontinuity of the bone surface that is visible in two perpendicular planes, ***Figure (11).***

**Grade 0**= regular bone surface.

**Grade 1**= irregularity of the bone surface without formation of a defect seen in 2 planes.

**Grade 2**= formation of a defect in the surface of the bone seen in 2 planes.

**Grade 3**= bone defect creating extensive bone destruction.

The most frequent site for MSUS-detected erosions in RA patients at hand level are the second MCP and fifth MCP joints, and at foot level are the first MTP and fifth MTP joints, while the fewest erosions are detected at fourth MCP joint ***(Schmidt et al., 2013).***

Over the past decades, conventional radiology (CR) has been the primary choice in assessing bone erosions. However, early in the disease course, CR cannot always detect bone changes. MSUS was shown to be more sensitive than CR in detecting bone erosions at finger and toe joint level. This was supported by various studies which revealed a high agreement between MSUS and MRI in detecting bone erosion at hand and foot finger joints ***(Szkudlarek et al., 2006).***

Furthermore, using MRI and CT as reference, MSUS has shown a high specificity with a moderate sensitivity in detecting bone erosions ***(Dohn et al., 2013).***

**Figure (11):** **(a)** Longitudinal and **(b)** Transverse view of the dorsal aspect of the metacarpophalangeal joint showing anerosion (arrow); *mc* metacarpal head, *pp* proximal phalanx ***(Szkudlarek et al., 2006).***

* ***Bursitis:***

Inflammation of periarticular soft tissue, including synovial bursae, is a major cause of pain in RA patients. Accurate diagnosis of such pathologies is of outmost importance for adequate management of these patients***.*** An important cause of knee pain is the presence of Baker’s cyst, **Figure *(12, a, b)*** ***(Bowen et al., 2010)*.**

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**Figure (12):** **(a)** Longitudinal **(b)** Transverse view over a Baker’s cyst showing synovial hypertrophy (*asterix*) with doppler signal and synovial effusion (*star)* ***(Bowen et al., 2010).***

* ***Rheumatoid nodules***:

Are more frequently found at pressure sites, usually associated with more severe disease. At MSUS examinations, they appear oval shaped, with well defined hypoechoic formation, generally homogenous, and in the majority of cases they are usually found close to the bone surface. They can present a central very hypoechoic, well-defined area. Compared to gout tophi, rheumatoid nodules show less frequent posterior acoustic shadowing and less erosion at adjacent bone level ***(Nalbant et al., 2003).***

***Artifacts:***

* **Anisotropy**

Anisotropy is an artifact produced by the linear configuration of tendons where by hypoechoic change is seen if the transducer is slightly angulated. This artifact can mimic hypoechoic tendinopathy, but careful minor changes to transducer angulation make anisotropy disappear where as true pathologic findings do not.

Anisotropy can be beneficial for confirming tendon position as the artifact can be produced in the linear tendon while the surrounding nonlinear echogenic fat is not affected; increasing contrast between the two structures ***(Brown et al., 2008).***

* **Acoustic shadow :**

Defines important focal attenuation of ultrasound due to complete reflection. Distal to such structures ultrasound are no longer propagated, the appearance being of anechoic area “non image” that extends deep from Sound attenuation behind the bone surface—longitudinal view Echo structure of the normal muscle. Examples of structures that produce shadowing include interfaces with bone or calcification and some foreign bodies Acoustic enhancement (amplification) Apparent and selective increasing in the intensity of echoes beyond an anechoic structure ***(Iagnocco et al., 2013)****.*

* **Cartilage Interface Sign:**

Also a consequence of multiple reflections at the interface between two distinct tissues with different acoustic impedances, the cartilage interface sign appears always accompanied by intra-articular fluid. Normally, the cartilage has an anechoic appearance without an upper hyperechoic limit. In contact with the fluid, a hyperechoic line can become visible at the interface. The “double contour” line must be differentiated from the urate deposition in gout, also a double contour appearance**.** Interface cartilage sign is useful in differentiating calcifications inside fluid from osteophytes; these can appear like double lines due to the fact that they are covered by cartilage, like the rest of the bone**.**

Tips to overcome: The artifact disappears when fluid is compressed with the probe, while the urate line remains unchanged during all kinds of joint movements. Gout also has other MSUS-specific signs like the presence of tophi inside/outside of joint space ***(Holsbeeck et al., 2001).***