INTRODUCTION

Definition of Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by swelling, tenderness and destruction of the synovial joints. It most commonly affects the peripheral joints of the hands, feet and wrists in a symmetric pattern leading to severe disability and reduction in life expectancy.[1,2]

Prevalence

There is a considerable amount of epidemiologic data on the occurrence of RA worldwide. Incidence differs between populations with regional variation in the prevalence of RA, where there is evidence of a recent decline in the incidence worldwide.[3,4] The overall world prevalence of RA is approximately 0.5% to 1%.[5] The incidence appears to be highest in India (6.8-5.3%) and lowest in China and Japan (0.2-0.3%).[6,7] These observations provide possible clues to the contribution of both genetic and environmental influences on disease etiology.[3] The prevalence of RA in rural Egypt is 0.29%, similar to other oriental rural populations, but lower than Western populations.[8]

Rheumatoid arthritis is more prevalent in females than males with a ratio of 2:1 or 3:1.[5] RA usually occurs in middle age, but there is an age-related increase in arthritis frequency which is more prominent in women, with greatest increase in prevalence between the age of 45 to 54 years.[9-11]

Clinical picture

The course of RA can range from slowly progressive disease to rapidly progressive multisystem inflammation. The spectrum of the clinical course of the disease can range from mild pauciarticular synovitis to severe painful polyarticular synovitis with extensive joint damage and extra-articular or systemic manifestation (EAM).[12]

The initial symptoms may be systemic or articular.[12] Patients predominantly complain of pain, stiffness, and swelling of their peripheral joints.[13] Morning stiffness is a cardinal sign of inflammatory arthritis that may appear even before the arthritis and pain. This may be related to the edema within the inflamed tissue that accumulates overnight.[14,15] RA can also affect non-articular muscular structures such as tendons, ligaments, and fascia.[16]

Seronegative RA

A well recognized subset of RA is the seronegative RA, it represents as many as 15% to 20% of all RA patients. These patients ultimately meet all of the usual criteria for RA; however, they are rheumatoid factor (RF) and anti-cyclic-citrullinated peptide antibodies (ACPA)-negative.[17]

The difference in progression rates between ACPA-positive and ACPA-negative RA, raise the question of whether they are two different disease entities with distinct clinical characteristics. In a study of 228 RA patients with and 226 without ACPA which were extensively compared in regards to clinical characteristics, no differences were observed, while after 4 years of follow-up, patients with ACPA had more swollen joints and more severe radiologic destruction.[18]

In another study, the synovial tissues from the ACPA-positive patients showed higher number of infiltrating lymphocytes, and expressed more cluster of differentiation (CD) 3 and CD8 than the tissues from ACPA-negative patients. These data indicate that the risk factors and histology are different for ACPA-positive and ACPA-negative disease.[19] Several studies have also shown that ACPA and RF are associated with a more destructive disease course.[18,20] In conclusion, the phenotype of RA patients with or without ACPA is similar with respect to clinical presentation but differs with respect to disease course.[18]

Although considered a "joint disease" RA is associated with involvement of EAM,[21] they occur in nearly 40% of patients.[22] They are usually associated with older age, smoking, early disability,[23] high titers of RF or ACPA,[24] more active and severe joint disease, longer duration of the disease and worse function.[21]

Extra articular manifestation include; secondary fibromyalgia (FM), rheumatoid nodules (RN), rheumatoid vasculitis,[23,25,26] pleuropulmonary involvement,[27,28] neurologic, digestive, cardiovascular, cutaneous, hematologic (as anaemia and thrombocytosis), and ocular complications.[23,26]

The prevalence of EAM in RA has declined in recent years; this indicates that disease-modifying RA treatments may be changing the natural history of the disease.[29-31]

There are also important disease-associated comorbidities in RA, including non-Hodgkin's lymphoma, ischaemic heart disease and osteoporosis (OP).[32]

The diagnosis of RA is guided by specific criteria several of which have been proposed over the years as the 1957 proposed diagnostic criteria[33] and the 1987 American Rheumatism Association (ARA) revised criteria;[34] the most recent is the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) RA Classification Criteria which represents an international collaborative effort supported by both a data-driven and a consensus-based approach.[35] (Annex I)

The assessment and follow up of the disease course and progression in RA in both daily clinical practice and in clinical trials can be done through specific indices that have been developed over the years.[35] This includes the disease activity score (DAS),[36] the EULAR response criteria, based on the attained level and change in DAS,[37] as well as the ACR improvement (20, 50 and 70%) criteria, based on the change in the core set variables are the easiest and most commonly used.[38]

Prognosis

Sero-positive patients with early patterns of large proximal joints involvement, as the shoulder, elbow, wrist, and knee joints, or metacarpopharengeal (MCP) I and II joints involvement appear to have more severe and erosive disease with worse prognosis. Patients with ankle, midtarsal or metatarsopharengeal (MTP) II, III, IV, and V joints involvement have greater risk for erosive disease. Older sero-positive patients also tend to have more serious outcomes.[39]

There is a high risk for morbidity and mortality secondary to the earlier development of cardiovascular, lung diseases and malignancy.[40] Recent epidemiologic studies of EAM in RA patients have emphasized their major role as predictors of reduction in life expectancy.[41] A recent study has shown that cigarette smoking also increases the severity and progression of the disease.[42]

Pathogenesis

The exact cause of RA is unknown; it involves a complex interplay among genotype, environmental triggers, and chance.[43] Genome analyses suggest that immune regulatory factors underlie the disease.[44] Human leukocyte antigen (HLA)–DRB1 locus has been confirmed in patients who are positive for RF or ACPA.[45] Exposure to various environmental factors increase the risk for RA, one of the most implicated is smoking. It also increases the risk for development of ACPA positive RA. Infectious agents including bacteria and their poducts as bacterial deoxyribonucleic acid (DNA), peptidoglycans and lipopolysaccharides have been implicated as an initiating factor for RA. Several viruses are also considered etiological factors in RA, epstein barr virus and parvovirius B19 are suggested. These products detected in RA joint participate indirectly to arthritis.[46]

The gene–environment interactions promote loss of tolerance to self-proteins that contain a citrulline residue in a susceptible individual by stimulating innate immunity and amplifying adaptive immunity. (Figure 1) This leads to an inflammatory response in the joint that probably involve microvascular, neurologic, biomechanical, or other tissue-specific pathways.[47]

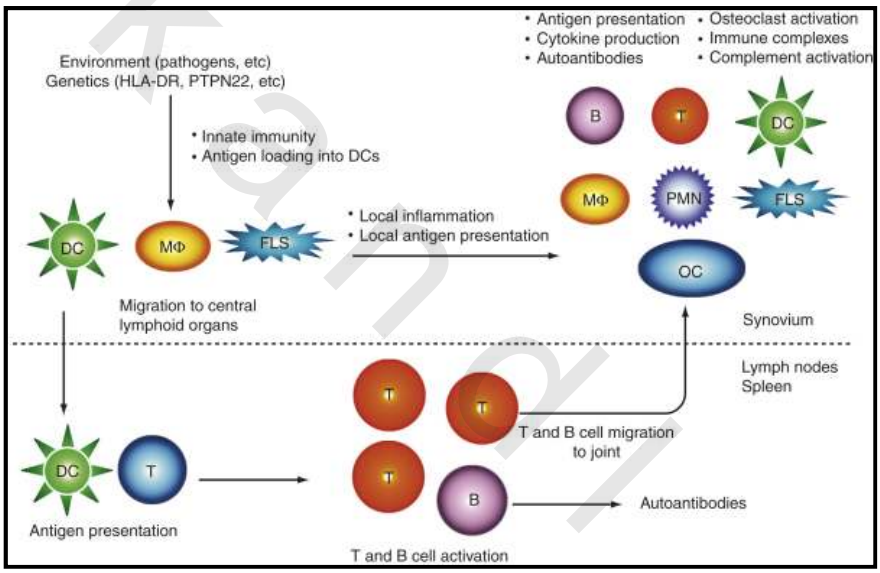

Figure (1): Innate and adaptive immunity in rheumatoid arthritis pathogenesis.

Rheumatoid arthritis is characterized by synovial inflammation and hyperplasia, autoantibody production (RF and ACPA), cartilage and bone destruction, and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders.[48]

The micro-environmental changes with leukocytic infiltration and neoangiogenesis, combined with profound synovial architectural reorganization and local fibroblast activation, permit the buildup of synovial inflammatory tissue in RA, which is the primary site of inflammation in RA.[49,50] (Figure 2) The integration of adaptive and innate immune pathways promotes tissue remodeling and damage. Positive feedback loops mediated by the interactions shown among leukocytes, synovial fibroblasts, chondrocytes, and osteoclasts, together with the molecular products of damage, drive the chronic phase in the pathogenesis of RA as well as the systemic disorders that make up the syndrome of RA. The genetics of RA and the presence of autoantibodies clearly place adaptive immunity at the center of early pathogenesis, and the hyperplastic synovium is the major contributor to cartilage damage in RA.[48]

Cytokine production that arises from numerous synovial cell populations is central to the pathogenesis of RA. Tumor necrosis factor- alpha (TNF-α) plays a fundamental role in the pathogenesis of RA through activation of cytokine and chemokine expression, expression of endothelial- cell adhesion molecules, protection of synovial fibroblasts, promotion of angiogenesis, suppression of regulatory T cells, and induction of pain.[51] Similarly, interleukin (IL) -6 drives local leukocyte activation and autoantibody production.[52]

Loss of the normally protective effects of the synovium, as reduction in lubricin expression alters the protein-binding characteristics of the cartilage surface,[53] promoting fibroblast like synoviocytes (FLS) adhesion and invasion. FLS synthesis of matrix metalloproteinases (MMPs) promotes disassembly of the type II collagen network, a process that alters glycosaminoglycan content and water retention and directly leads to biomechanical dysfunction. Bone erosions occur rapidly, affecting nearly 80% of patients within 1 year after diagnosis,[54] and are associated with prolonged, increased inflammation.[55] Mechanical factors predispose particular sites to erosion. Thus, "mechanically vulnerable" sites such as the second and third metacarpals are prone to erosive changes.[56]

Synovial cytokines, particularly monocyte/macrophage colony- stimulating factor (M-CSF) and receptor activator of nuclear factor–Kappa beta (NF-κB) ligand (RANKL), promote osteoclast differentiation and invasion of the periosteal surface adjacent to articular cartilage.[57] Breach of cortical bone permits synovial access to the bone marrow, which causes edema and inflammation of the bone marrow, osteitis as observed on magnetic resonance imaging (MRI), in which T- and B-cell aggregates gradually replace marrow fat. It is unclear whether these lesions occur in conjunction with synovial induced erosions or whether osteitis independently precedes erosions.

Inflammatory mediators, including cytokines, immune complexes, and altered lipid metabolism, circulate to promote several coexisting conditions in patients with RA.[58,59]

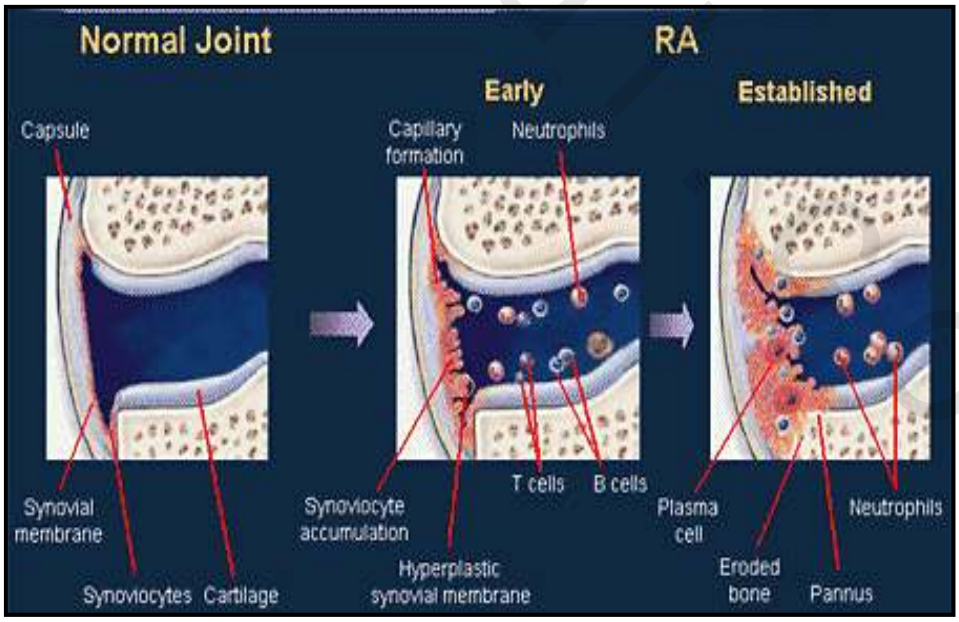

Figure (2): Pathogenesis of Rheumatoid Arthritis.[60]

Bone loss in rheumatoid arthritis

Chronic inflammation disturbs bone homeostasis and precipitates bone loss. (Figure 3) All inflammatory diseases, including rheumatic diseases, connective tissue diseases, inflammatory bowel diseases, and chronic infections lead to premature OP.[61,62] In chronic arthritis, such as RA and psoriatic arthritis, bone loss is a common finding, which is closely linked to disease duration and inflammatory disease activity.[61] Also disease mediated effects as the release of cytokines,[63] corticosteroid (Cs) use,[64] and reduced physical activity,[65,66] have been implicated in its pathogenesis. This tight link between inflammation and bone destruction in inflammatory arthritis can only be explained by an imbalance between bone resorption and bone formation.[67]

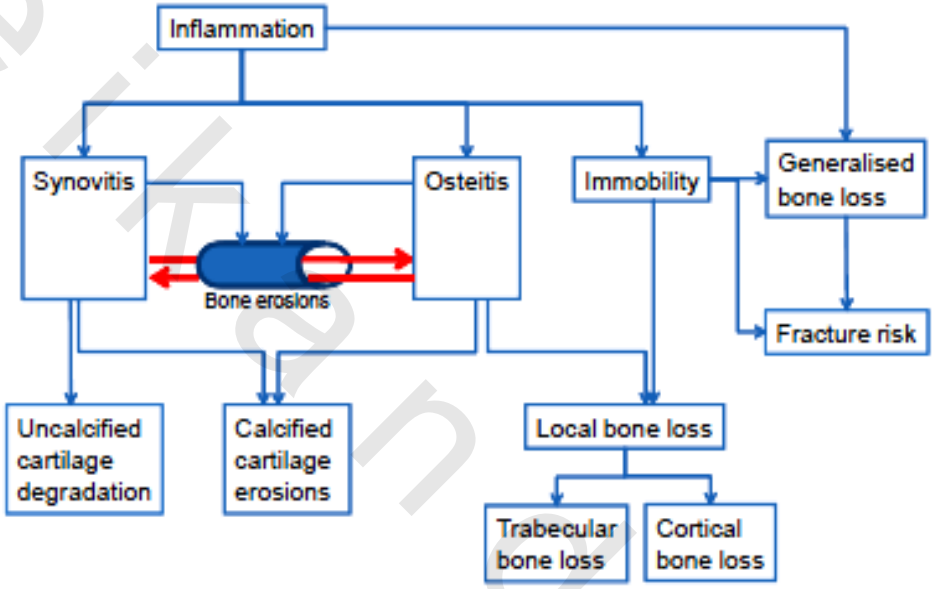

Figure (3): Effect of inflammation on bone.[68]

These bone complications are very characteristic of RA and several distinct patterns of bone loss have been observed in individuals with RA.[69] The immune-mediated inflammatory synovitis, that exhibits the capacity to directly invade and destroy the extracellular matrices of joint cartilage and bone by pannus, leading to the characteristic focal marginal erosions of the subchondral bone and joint margins that is seen radiographically is the localized form of bone loss. The other form of bone loss is the juxtaarticular osteopenia adjacent to the inflamed joints. The inflammatory process in RA, may also lead to systemic effects on bone remodeling that is associated with generalized osteopenia and OP of the axial and appendicular skeleton.[62,70] Recently it was shown that the presence of joint erosions in patients with RA is associated with generalized OP.[64]

The degree of inflammation and autoantibody positivity have both been identified as important indicators of skeletal damage in RA.[20] It has been recently shown that ACPA bind osteoclast precursor cells and directly promote their differentiation into bone-resorbing osteoclasts.[71] It has been also shown that in ACPA-positive RA patients bone loss starts even before the onset of clinical disease; this is indicative of the effect of these antibodies in initiating skeletal damage.[20]

A huge increase in the understanding of immune modulation and disruption of bone homeostasis in rheumatic diseases has occurred over the past two decades through identification of the molecular pathways for increased bone loss. Enzymatic breakdown of extracellular matrix components by MMPs,[72] cathepsins,[70] and mast cell proteinases[73] has been demonstrated to play an important role in cartilage destruction in RA and may contribute to bone loss as well.[74] However, resorption of bone requires the removal of mineralized bone matrix, which in physiologic bone remodeling is accomplished by osteoclasts.[57]

Osteoimmunology in RA

The role of osteoclasts in bone destruction in RA has attracted growing interest. Gravallese et al[57] reported that the multinucleated cells present in the inflamed synovial tissue of RA patients showed the specific marker profile of osteoclasts, as tartrate-resistant acid phosphatase (TRAP), calcitonin receptor (CTR) and CD68 positivity, suggesting that bone-resorbing cells are indeed an integral part of the inflamed synovial membrane. Abundant mature osteoclasts were found at the bone pannus junctions in RA. In addition to the bone marrow stroma, osteoclast precursors are also abundant in the hyperplastic synovial tissue. Mature osteoclasts are formed by differentiation of osteoclast progenitors in the presence of RANKL on osteoblastic cells and M-CSF.

It was proven that RANKL is an essential factor for osteoclast differentiation.[75] Several studies have shown that both RANKL and its receptor activator of NF-kB (RANK) are expressed on cells of the RA synovial membrane, including T cells.[76-78] RANKL expressed on activated T-cells can trigger osteoclast activation and it is possible that RANKL/RANK might play a major role in inflammation-induced bone loss and joint destruction in arthritis.[79] Osteoprotegerin (OPG) is a decoy receptor that binds to RANKL[80] and prevents it from interacting with its receptor RANK,[81] which when lowered induces osteoclastic differentiation.[82] (Figure 4)

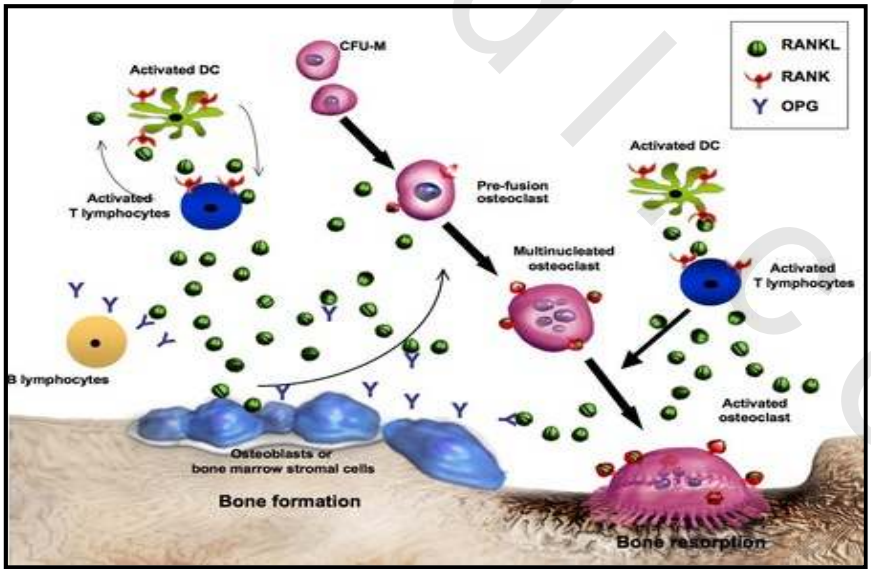

Figure (4): Mechanism of osteoclastic differentiation.[78]

Osteoclast differentiation is stimulated by a wide variety of hormones and cytokines, including 1,25-dihydroxyvitamin D3, parathyroid hormone, TNF-α, IL-1, IL-6, and IL-11.[83] Most of these agents are thought to stimulate osteoclast differentiation indirectly by

inducing bone marrow stromal cells or osteoblasts to increase the production of RANKL, and/or decrease the production of OPG.[75,82] Activated T cells have long been associated with the increased osteoclast formation and the accelerated bone resorption characteristic of inflammatory conditions.[84,85] Over the years, evidence has accumulated suggesting that T cells stimulate osteoclast formation by producing the key osteoclastogenic cytokine, RANKL.[77,79]

The wingless (Wnt) pathway is a regulatory pathway of osteoblast activity. At the molecular level, the activation of the Wnt/B catenin pathway is crucial for osteoblastic differentiation.[86,87] Two blockers of the Wnt-signaling pathway that play an important role in RA are dickkopf-1 (Dkk-1) and sclerostin. TNF-α, for instance, can induce both sclerostin and Dkk-1.[88] In RA patients, OPG was proven to be lower than in healthy controls, while Dkk-1 and sclerostin were proven to be higher.[89] (Figure 5,6)

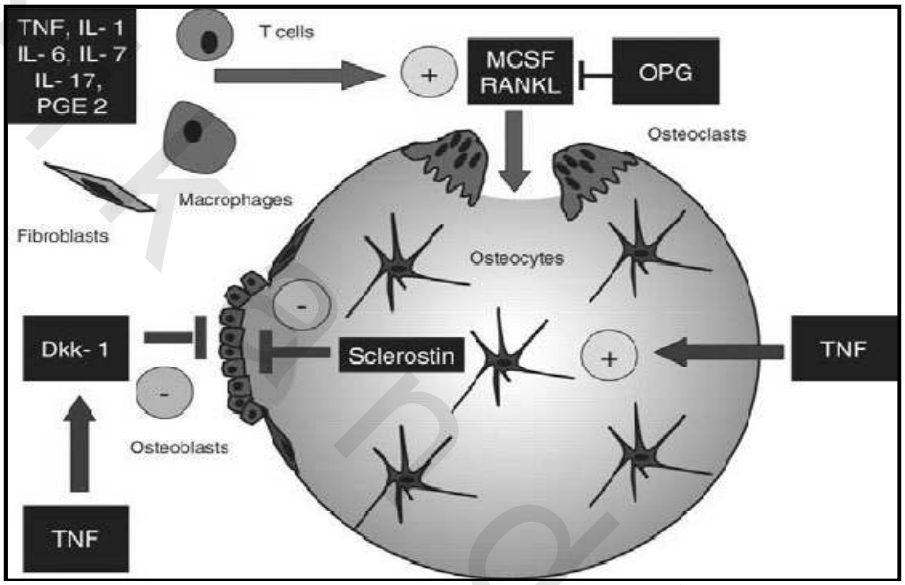

Figure (5): Effect of inflammatory cells in the synovium on bone homeostasis.[90]

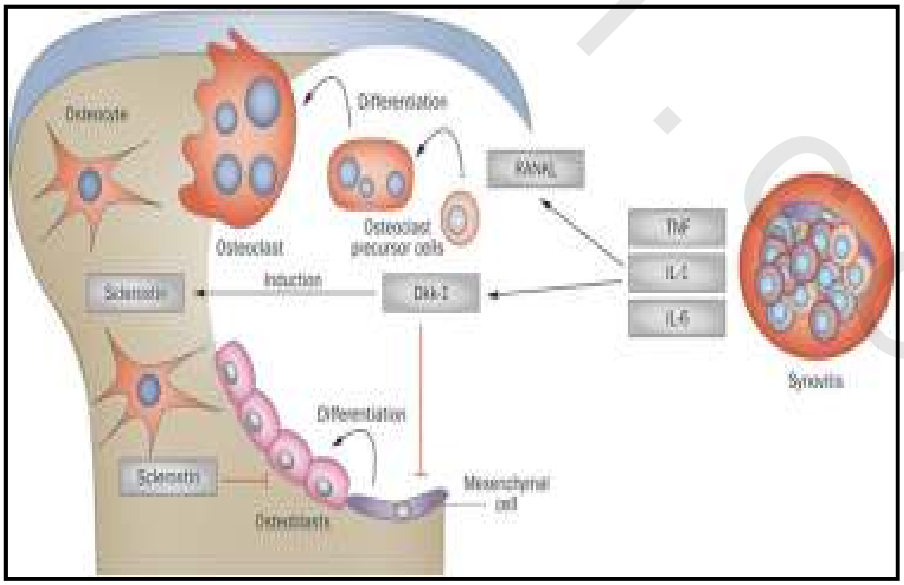

Figure (6): Disruption of bone homeostasis by synovitis.[90]

The success of B cell targeting therapy in RA patients has suggested the central role B cells play in the pathogenesis of RA.[89,91] Researchers proved that B cells in the RA synovium are capable of producing pro-inflammatory and bone-destructive cytokines including RANKL, TNF- α and Il-6.[92] Recently a distinct subtype of B cells ($FcRL4^+$ B cells) were identified in the synovium of RA patients that produces higher levels of TNF-α and RANKL messenger ribonucleic acid (mRNA).[93]

Remarkably, the localized and generalized bone loss as well as erosions share common pathways through cytokines', as TNF-α and the RANKL/RANK pathway, activation of osteoclast.[69,94,95] (Figure 6) This is supported by a study that showed reduced joint damage in all RA patients that were treated with methotrexate (MTX) and denosumab, a monoclonal antibody against RANKL, versus those treated by MTX and placebo. It was also noted that erosion (E) score was lower, while joint space narrowing (JSN) was unaffected.[96] Few studies have also suggested that anti-TNF therapy may prevent general bone loss.[97,98]

Radiographic progression in Rheumatoid arthritis

The marginal erosions of the joint margins and subchondral bone seen radiographically are the localized form of bone loss.[61] It is documented that erosions develop within the first months of the disease onset; nearly 50% of patients with RA have evident radiographic erosions within 6 months. The extent and severity reflect the cumulative disease activity and contribute to the disability of the disease.[99]

The long-term severity of RA is recognized from the longitudinal studies of clinical cohorts that showed continuous radiographic progression in up to 20 years follow up.[100,101] Several methods for the assessment of radiographic progression have been proposed over the years;[102] of them the two most widely used are the Sharp[103,104] and Larsen score[105] that provide a quantitative scale, rather than a qualitative measure for radiographic damage.

Plain radiographies of the hand and feet have been important in the evaluation of RA over the past years, as they provide permanent measures of damage in RA.[100,106] There are several limitations as radiographs change slowly, at least 6 months to a year is needed to assess change. Also with the emerging new therapies for RA the target is to treat patients before radiographic damage, limiting its role.[107] From this the value and sensitivity of MRI, computerized tomography (CT) and ultrasound (US) in detecting early structural changes in joints and surrounding structures is recognized.[108,109] Nearly 70% of the patients with early RA have erosions detected by MRI,[110] it also detects bone oedema that may accompany these erosions. Aspirates from these oedematous regions yielded CD34+ cells, potential osteoclast precursors.[111]

The only limitation for their use in daily practice is the high coast as well as the availability of the machine and/or a trained specialist.[108, 109]

Osteoporosis

Osteoporosis is the most common bone disease in humans, and it represents a major public health problem. It is characterized by low bone mass, deterioration of bone tissue, disruption of bone architecture, compromised bone strength and an increase in the risk of fracture.[112] (Figure 7)

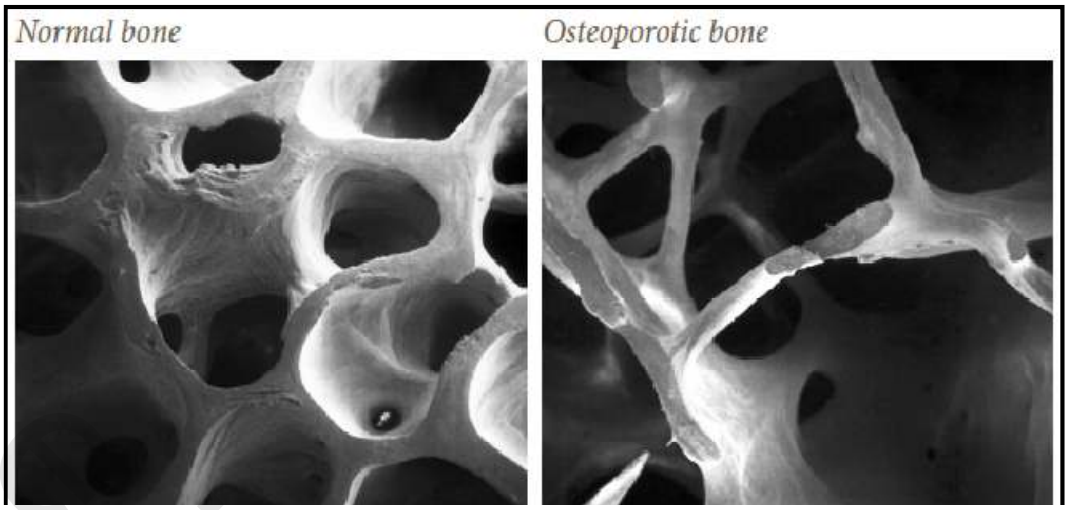

Figure (7): Macrographs of normal versus osteoporotic bone.[113]

Osteoporosis affects an enormous number of people, of both sexes and all races, and its prevalence increases with age. It has a higher incidence in the Caucasian race and in females, the prevalence of OP ranges from 9-15% in females and 1-4% in males based on total hip bone mineral density (BMD) and 16-38% in females and 3-8% in males based on spine BMD.[114]

In females one out of two will experience an OP-related fracture at some point in their lifetime and in men approximately one in five.[115] Several studies showed that the prevalence of OP in postmenopausal females is highest at the spine followed by the proximal femur in different races and ethnic groups.[116,117]

The prevalence of OP in RA increases about twofold compared with the general population especially in female RA patients.[118] The data about the prevalence of OP in men with RA are scarce, both clinicians and patients have less concern about OP in men, compared to it in women. Even in 2014, there is a significant difference in care of men versus women, men are less likely to be evaluated or treated for OP, despite worst outcomes after fracture.[119] A study of 94 male RA patients showed a two fold increase in the frequency of reduced bone mass similar to that in female RA patients.[120] Some studies showed that OP occurs in 15–26% at the hip and 19-32% at the spine of RA patients.[118,121] Unlike postmenopausal OP, OP in RA is more characterized by bone loss at the hip and the radius, while the axial bone is relatively preserved.[118,122] A higher decrease in BMD[123] plus an increased risk of both hip and vertebral fractures in patients with RA compared with patients without RA has been demonstrated in several studies.[124-126]

The morbidity of generalized OP in RA patients is reflected in the increased fracture risk.[126] OP in RA shows a higher incidence of fracture, which has a major impact both on the patients and society by increasing morbidity, mortality, and health care costs.[127]

Dual energy X-ray adsorbometery scan and bone markers in the diagnosis of OP

The World Health Organization (WHO) has established dual energy X-ray adsorbometery (DXA) scan as the best densitometric technique for assessing BMD and based the definitions of osteopenia and OP on its results. DXA allows accurate diagnosis of OP, estimation of fracture risk and monitoring of patients undergoing treatment.[112] The BMD

diagnosis of normal, osteopenia, OP and severe or established OP is based on the WHO diagnostic classification, which defines OP as BMD at the hip or spine that is less than or equal to 2.5 standard deviations (SD) below that of young normal mean reference population.[128]

In premenopausal women, men less than 50 years of age and children, the WHO diagnostic classification should not be applied. In these groups, the diagnosis of OP should not be made on the basis of densitometric criteria alone. The International Society for Clinical Densitometry (ISCD) recommends that instead of T-scores, ethnic or race adjusted Z-scores should be used.[128] The diagnosis of reduced bone mass is defined by BMD less than or equal to 2 SD below that of expected BMD for the patient's age and sex. A clinical diagnosis can often be made in at-risk individuals who sustain a low-trauma fracture.[112]

Bone turnover markers in the diagnosis of Osteoporosis

The bone is a dynamic biologically active organ, bone remodeling (or turnover) occurs throughout life to repair fatigue damage and microfractures in bone, to accomplish this function there must be tight coupling between bone resorption and formation.[129]

During bone resorption, constituents of bone matrix, mainly collagen (maturation products of collagen crosslinks), find their way into the circulation and then are excreted in the urine through the kidneys. On the other hand during bone formation, osteoblasts produce several markers for bone formation. These metabolites that measure bone building conditions or bone resorption state can be detected in the serum and/or in the urine, thus act as indices of the activity of the bone remodeling process, indicating whether bone formation or resorption is taking the upper hand or if there is a state of balance. The rate of bone formation or degradation can be assessed by measuring the enzymatic activity of osteoblastic or osteoclastic cells or by measuring components of bone matrix released into the circulation.[130]

Bone markers currently in use in clinical practice are serum osteoclcin (OCN), serum bone-specific alkaline phosphatase (BAP), urinary N-terminal of type 1 collagen (NTx), urinary C-terminal of type 1 collagen (CTx) and free deoxypyridinoline (Dpd). The introduction of automated analyzers for these markers improves reliability and availability of these markers in clinical chemistry laboratories.[131]

Each marker of bone formation reflects one of the three different phases of bone formation: matrix synthesis, matrix maturation or mineralization. The carboxy and aminoterminal propeptide of type I procollagen (PICP and PINP respectively) are liberated during the first phase.[132] The second phase is reflected by BAP, which is found in the membrane of osteoblasts. It is very stable and not affected by haemolysis.[133] While the third phase is reflected by OCN, which is the most abundant noncollagenous protein in bone.[134] (Table 1)

Ninety percent of the organic matrix of bone is type 1 collagen, it is responsible for the bone's mechanical strength. Procollagen is the biosynthetic precursor for type I collagen and there is a proportionate relationship between collagen deposition in bone and the procollagen propeptide released into the circulation. There are two procollagen peptides released into the circulation relatively unchanged originating from bone tissue, the PICP and PINP.[132] Although specific assays for PICP have been available longer than PINP, the new assay for intact PINP has turned out to be more reliable and show more dynamic variation with bone disease than PICP.[135] Any biological process that affects the amount of bone formation must also affect type I collagen.[132] The disease osteogenesis imperfecta is caused by genetic defects in type I collagen and many different mutations usually lead to this brittle bone disease.[136]

Alkaline phosphatase is the marker most commonly used to monitor bone formation. It is a bone specific enzyme and a product of tissue nonspecific alkaline phosphatase (TNAP) gene. The activity of BAP seems to be needed for the initiation of mineralization of the osteoid. Alkaline phosphatase is present in several isoforms, the most abundant are the liver and bone variants, as they are produced by the same TNAP gene. Difference in the glycosylation has made it possible to isolate the two forms by several methods including the immune-assay based methods that are specific and measure the BAP directly.[137]

Osteocalcin is a small protein that was previously thought of as bone formation marker as it is produced by osteoblasts during mineralization process (calcium deposition), but OCN knock-out animals showed surprising results of larger and better mineralized bones.[138] Osteocalcin in the circulation can come from either osteoblasts or as a degradation product of OCN found in the mineralized bone matrix. It is believed that most of the intact OCN found in the circulation results from its synthesis from osteoblasts. Only a small portion of the circulating OCN is intact, there are several different types of fragments found in the serum. This has lead researchers to consider OCN as a bone turnover marker.[134] (Table 1)

The majority of biochemical markers of bone resorption are based on the measurement of fragments of collagen type I, they constitute over 90% of the bone protein. There are other markers based on noncollagenous proteins or specific enzyme activities either in the serum or in the urine.[139] (Table 1)

Bone turnover markers are an established tool in the diagnosis and treatment of metabolic bone diseases as Paget's disease of bone, where BAP is superior to other markers.[140] The measurements for these markers have improved considerably over the last few years such that their use can be considered for patients with OP. There is evidence supporting that bone turnover markers can predict the rate of postmenopausal bone loss and the occurrence of OP fractures.[141,142] It has also been suggested that their measurement might be useful in selecting the type of therapy, whether antiresorptive or bone forming therapy.[143] It can also monitor the efficacy of treatment, for example estrogen therapy monitoring can be done by any bone formation marker.[135] Data obtained from several prospective studies indicated that increase in bone resorption markers are associated with increase all types of OP fractures (vertebral & non-vertebral and hip & non-hip fractures).[144,145] Increased skeletal fragility can occur due to increased bone resorption through 2 factors; prolonged increase in bone turnover after several years will lead to low BMD and increase in bone resorption above the upper limits of normal may induce microarchitectural deterioration of bone tissue leading to compromised bone strength.[142]

Table (1): Biochemical markers of bone remodeling.

FROMATION MARKERS:
Serum
• Bone specific alkaline phosphatase (BAP) • C – and N propeptide of type I procollagen (PICP, PINP)
RESORPTION MARKERS:
Plasma/serum
• Tartrate-resistant acid phosphatase (TRAP) • Free pyridinoline and deoxypyridoline (Dpd) • N- and C- terminal telopeptide of type I collagen (NTX, CTX) • Bone sialoprotein (BSP)
Urine
• Free pyridinoline and deoxypyridoline • N- and C- terminal telopeptide of type I collagen (NTX, CTX) • Calcium • Hydroxyproline • Galactosylhydroxylysine
TURNOVER MARKERS:
Serum
• Osteocalcin (OCN)

Bone markers testing is noninvasive, suitable for serial measurement and can detect changes in bone turnover sooner than that revealed by serial BMD measurements, any change in BMD by imaging needs at least one year.[130] Unfortunately there are some disadvantages to them as they are more costly than measurement of BMD, they give no information about cellular activity and are influenced by nonosseous sources, which may give false results.[146] Combining bone markers and BMD measurement may be more helpful for diagnosis.[147]

Risk factors for Osteoporosis

There are several risk factors for the occurrence of OP including age, sex, postmenopausal state, life style factors, drugs as Cs and clinical disorders as RA.[112]

In inflammatory diseases, as RA, several factors have emerged as important determinates of bone mass in these patients. These include background factors as age, gender, menopausal status and lifestyle and disease related factors as reduced mobility, disease duration, disease activity and anti-rheumatic drugs especially Cs.[148,149] (Figure 8)

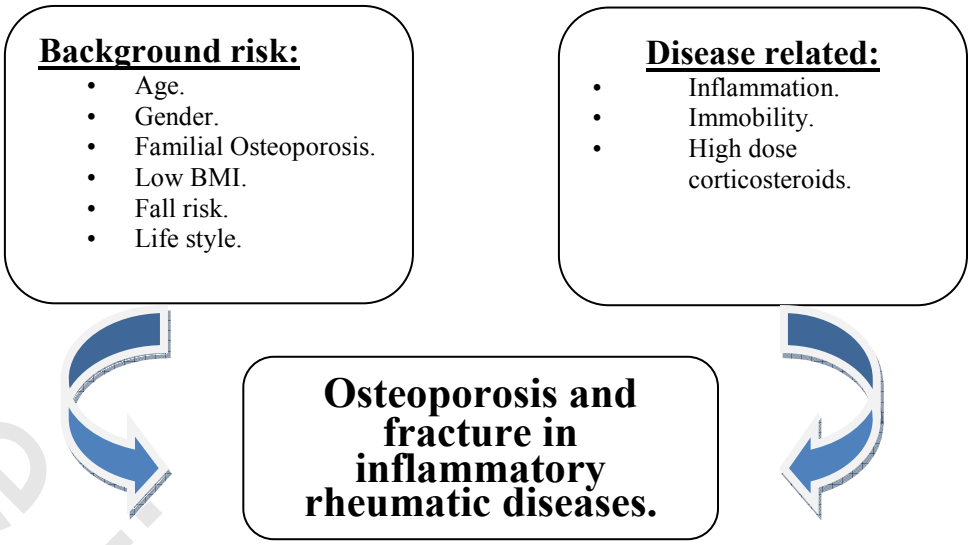

Figure (8): Risk factors for osteoporosis and fracture in inflammatory rheumatic diseases.[149]

Background factors as age is an important risk factor for RA,[9] similarly OP is a devastating disease frequently found in older people,[150] both diseases are more prevalent with increasing age. Bone loss in RA is also more prevalent with increasing age.[151]

Although OP is more prevalent in females in the general population,[114] the prevalence of decreased BMD is similar for both male and female RA patients at the hip, while a higher percentage of male RA patients had decreased BMD at the spine.[118,120] There is conflicting data about the effect of menopause on BMD in RA patients, a study by Compston et al [152] suggested that RA related bone loss occurs mainly in younger patients with RA. On the other hand a study by Butler et al,[153] found that the adverse effects of RA on bone mass are accentuated in the post-menopausal state, this is supported by the accelerated bone loss with sex hormone deficiency at the onset of menopause, that continues for 10 to 15 years after its onset in the general population.[154] In male RA patients, the reduction of BMD appears to be independent of serum testosterone.[120,155]

Hormonal and environmental factors heighten the risk for the development of OP, complex multifactorial genetic factors influence sensitivity to these factors and their interactions contribute to the end result of bone strength in later adult life.[150] Family studies have demonstrated that mothers with OP fractures have daughters with lower BMD.[156] Similarly polymorphism has been described in genes linking the development of RA and OP.[157]

Low BMI and low weight have been shown to predict OP risk and are associated with increased fracture risk in women,[158] also low BMI in RA patients was associated with higher risk of OP and its related fractures.[126]

The level of weight bearing activity may be an important determinant of bone mass in general. Extreme inactivity causes rapid loss of considerable amounts of bone, and most exercise intervention programs have shown either a reduction in bone loss or an increase in bone mass.[159] In RA patients femoral BMD is proportionate to quadriceps strength,[160] while non-weight bearing exercise programs have revealed no increase in BMD of the axial and appendicular skeleton.[161]

Several disease related factors including disease duration appear to be important determinants of bone loss especially in early RA. There seems to be an initial rapid rate of bone loss followed by a gradual reduction in the speed of bone loss, when RA patients were divided into 2 groups according to disease duration, patients with early RA (disease duration <1 year) showed significant loss in the amount of bone in comparison to the following years in their disease course.[162]

Several inflammatory mediators including TNF-α and IL-1 have been implicated in the pathogenesis of primary OP and high bone turnover.[163] In RA there is considerable evidence supporting that the pathophysiology of erosive joint damage, periarticular and generalized OP share common pathways.[69,129]

Severity of RA, in the form of elevated serum C-reactive protein (CRP), erosive joint changes and radiographic joint damage, has been linked to hand bone loss and bone loss at hip or spine, it has also been linked to vertebral and non-vertebral fracture risk.[164-166] This association with generalized bone loss has also been found in Cs naive patients. [167]

Higher functional impairment and disability as assessed by the Health Assessment Questionnaire (HAQ) is also related to decreased BMD in RA patients.[168]

Osteoporosis and increased fracture risk are recognized as one of the major complications of Cs therapy in both rheumatic and non-rheumatic diseases.[169,170] The effect of Cs on bone is both dose and duration dependent; the cumulative Cs dose was associated with decreased spine and hip BMD and increased fracture risk while the daily Cs dose showed controversial results regarding its effect on BMD. The onset of bone loss is rapid within the first months of starting CS therapy, slowing down after about one year; the only limitation is the variability in the daily dose of Cs. There is strong evidence that suggests that Cs-induced OP and its consequences are substantially reversible after CS therapy is stopped.[171]

In RA patients the effect of low-dose Cs therapy on bone loss remains controversial, they have negative effects on bone, but at the same time they reduces disease activity, joint damage and enhances mobility, effects that are antiosteoporotic. Therefore, the negative effects of low-dose Cs treatment on bone can be counterbalanced by their positive effects in suppressing disease activity.[172] Some studies have shown no increased risk of OP in Cs-treated patients compared with controls.[123,172]

Other studies have suggested that low dose Cs play a significant role in the OP and its related vertebral fracture in RA.[125,173] A study showed that long-term Cs therapy with doses no greater than 5 mg prednisolone per day increase the degree of OP in patients with RA. The same study showed that female RA patients receiving Cs have a greater risk of developing spinal OP.[174] Another study suggested that Cs bone loss is partially reversible, this was proven by the partial increase in BMD after discontinuation of Cs within 24 weeks.[173]

Studies on the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on BMD and fracture risk showed conflicting results; these inconsistencies can be attributed to the effect of differential cyclooxygenase (COX) inhibition on BMD.[175] A study by Carbone et al [176] showed that the combination of selective COX-2 NSAIDs and aspirin is associated with higher BMD at multiple skeletal sites in men and women.

Methotrexate has been reported to have negative effects on bone and the term ‘‘methotrexate osteopathy’’ has been used to describe a clinical syndrome characterized by stress fractures, diffuse bone pain and OP in children treated for malignancies.[177] In

animal studies high-dose MTX has been shown to induce apoptosis and suppress proliferation of the growth plate chondrocytes as well as proliferation of the osteoblasts and preosteoblasts.[178] Older studies of the effect of MTX (5–20 mg/week) in RA patients for prolonged periods have shown adverse effects on bone, particularly in post-menopausal women, but this was found in very few patients.[179,180]

However, more recent studies of a larger number of RA patients treated with MTX (5–20 mg/week) both in cross-sectional[168] and longitudinal [181] studies have not shown any negative effect of MTX on bone.

Sulfasalzine (SSZ) seems to have a protective effect on bone in RA patients, a study by Tengstand and Hafstorm[155] found that patients treated with SSZ had higher BMD in the trochanteric region.

The process of bone loss in RA is mainly mediated through the RANKL signaling system, which is up-regulated by numerous pro-inflammatory cytokines involved in the pathogenesis of RA.[82] The knowledge of the association between cells and cytokines and their relationship to bone remodeling has revealed several promising targets for the treatment of inflammatory bone loss in RA. The use of biologic therapies targeting inflammatory cytokines and/or lymphocyte activation has modified RA therapy not only by blocking local and systemic inflammatory cascades but also by providing beneficial effects against bone and joint degradation.[182] In RA patients treated with infliximab, bone loss is arrested in the spine and hip, but not in the metacarpal bones of the hand.[183] Adalimumab in combination with MTX were found to reduce periarticular bone loss independent of clinical response. These results support the hypothesis that TNF-α stimulates the osteoclast not only by the inflammatory pathway but also have a direct effect on the osteoclast.[184] Recent data suggest that aggressive anti-inflammatory treatment with biologic therapy reduces the rate of bone loss in RA, indicating that the burden of OP is reduced in RA patients treated aggressively.[185]

There are a number of effective, well-tolerated therapies that treat OP as well as significantly reduce risk for OP related fractures, in addition to lifestyle changes such as improved diet and increased exercise.[186] Bisphosphonate therapy is considered the first-line therapy for the treatment of OP, they are currently approved by the Food and Drug Administration (FDA) for the prevention and treatment of postmenopausal OP.[187] Alendronate and risedronate are also recommended for the treatment of Cs-induced OP.[186] Other types of therapies including hormone replacement therapy (HT)[187] and raloxifene,[188] are recommended for treatment of postmenopausal OP, while teriparatide is recommended for Cs-induced OP in high risk patients.[186] Newer therapies like Denosumab, a fully human monoclonal IgG2 antibody that binds RANKL, showed greater increase in BMD when compared to alendronate in females with postmenopausal OP.[189]

In RA, calcium alone has also been shown to be ineffective in preventing loss of bone,[148] while alendronate was found to prevent the loss of vertebral strength, primarily via its positive effect on the outer 2 mm of vertebral bone.[190] HT increases spinal BMD and maintains femoral BMD in postmenopausal RA patients.[191] Denosumab had similar effects to those found in postmeopausal females, where there was a significant increase in BMD and a sustained substantial decrease in bone turnover markers, as serum CTX.[96]

Several factors can alter the level of bone markers depending on the type of the bone disease and the type and duration of therapy the patient received. A large dose of Cs decreases serum PICP and OCN concentration in 3 hours.[192] Both β-CTx and RANKL were decreased in RA patients treated with infliximab, the decrease in serum β-CTx was

proportionate to the decrease in DAS 28 scores and CRP levels.[183,193] Markers of bone formation give conflicting results in patients with RA, while markers of bone resorption show more uniform results, with significant increase in patients with RA.[148]

The increase in the overall fracture risk in RA patients correlates with the postmenopausal status, the degree of disability, as assessed by the HAQ, and Cs use. An increased HAQ score was also associated with nonhip/nonspine fractures.[194]

Rheumatoid arthritis and OP are both very common and debilitating diseases; their concomitant presence highly increases morbidity and mortality.
The incidence and risk factors for the development of osteopenia or OP in postmenopausal RA patients has been studied extensively over the years, while research of its incidence in both premenopausal female and male RA has fallen short. For that incidence and risk factors for reduced bone mass, osteopenia and OP were studied.