Review Article

ARTHRITIS: CLASSIFICATION, NATURE & CAUSE - A REVIEW.

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ABSTRACT

This article describes several common features about arthritis regarding nature, various forms and probable causes for its occurrence in a simplified manner. Typically, it is a collection of diseases together nomenclatured as "Arthritis". Nearly 47 million people in the US alone are suffering from this disease. Globally, it imposes a huge financial burden. Considering medical condition, the disease exerts medium to severe problem at various bone-joints displaying inflammation as a common symptom which often turns serious, incapacitating the individuals through pain, swelling and inflexibility at those affected joints. Statistically, women over the menopausal stage fall as the major victims. Among the victims of either sex, about half suffers from Osteo arthritis (OA). Next in line, are those having the problem of Rheumatic arthritis (RA). Besides OA or RA, other categories of arthritis are also briefly illustrated in addition to their epidemiological survey. But the article emphasizes mainly on OA and RA for their severe role among the major population of sufferers. The likely reasons of developing calcification and its subsequent after-effect resulting in the progression of OA are discussed in semi-detail. Additionally, the role of autoimmune disorder along with its genetic predisposition which triggers the inflammation leading to RA is also included in the discussion. Simplistically, it is concluded that OA creates inflammation after wearing tearing of the cartilage tissue which is mechanically driven whereas RA is created out of the inflammation thereby imposing a problem. In that perspective RA is considered as an inflammatory autoimmune disease

Key words: *Osteo-arthritis, Rheumatic arthritis, Ankylosing Spondylitis, Gout, Lupus Arthritis, Psoritic Arthritis, Cartilage, Calcification, Proteoglycan, Collagen, Cysteine rich angiogenic inducer, Extra-cellular matrix, NO,TNF- α, Interleukins, Integrin, Aging, Cellular senescence.*

Running Title: Arthritis – a review.

Abbreviations: Osteo Arthritis (OA), Rheumatic Arthritis (RA), Ankylosing Spondylitis (AS), Lupus Arthritis (LA), Infectious Arthritis (IA), Juvenile Arthritis (JA), Psoriasis Arthritis (PS), Human Leucocyte Antigen (HLA), Major Histo-compatibility Complex (MHC), Tumor Necrosis Factor (TNF), Inter-Leukin (IL), International league against Rheumatism (ILAR), Community oriented program for the control of rheumatic diseases (COPCORD), Calcium pyrophosphate dihydrate (CPPD), Basic calcium phosphate (BCP), Micro vesicle (MV), Hydroxy apatite (HA), Nitric oxide (NO), Extra-cellular matrix (ECM), Cysteine rich angiogenic inducer (CCN), Nitric oxide synthase (NOS), Nucleotide pyro-phosphatase/phosphodiesterase - 1 (NPP-1), Tissue non-specific alkaline phosphatase (TNAP), Adenosine tri-phosphate (ATP), Uridine tri-phosphate (UTP), Lipopolysaccharide (LPS), Glycosamine glycan (GAG), Proteoglycan (PG), Prostaglandin E_2 (PGE_2), Archidonic acid (AA), Matrix-metalloproteinase (MMP), Insulin like growth factor-1 (IGF-1), Superficial zone protein (SZP), C-reactive protein (CRP), Endo-chondral ossification (EO)

INTRODUCTION

"Arthritis" is a combinatorial word originated by the mixing of Latin and Greek. In Greek, "*Arthron"* signifies joint and in Latin "*Itis"* specifies inflammation. Thus arthritis is normally viewed as a disease caused as a result of inflamed joints. Inherently, it is not just a single disease rather a collection of medical problems collectively termed as "Arthritis". Nearly 47 million adults and 300,000 children suffer in the US alone ***[1].*** The disease can incapacitate permanently if proper treatments are not provided in time. Globally, it imposes a huge financial burden through wage loss along with the cost of medications ***[2,3].*** Several treatment pathways are now available just to control the disease but no imminent cure is found yet. For proper understanding about the disease, it is worthy to know the mechanics of a bone joint.

Usually, when a bone moves or twists on similar piece(s) to maintain the functional flexibility, it is then characterized as a joint. During movement the ligaments act as elastic bands to help keep the bones in the same place. Under all situations whether in resting or moving, ligaments always hold them at the same place. Cartilage tissue covers the bone surfaces to prevent from direct rubbing thus smoothens the limb movement without causing pain or bone erosion due to friction. The cavity inside the joint is filled with synovial fluid produced by the cells from synovial membrane which is aligned with the ligaments within joint cavity (Figure1) ***[4].*** In case of arthritis, primarily the suffering starts due to faulty joints. The reasons that trigger the disease are many; A) possible cartilage damage, B) shortage of the synovial fluid, C) autoimmune attack, D) infections ***[5].*** By nature, arthritis is versatile. Here are the few common ones: **1.** Osteo-arthritis (OA), **2.** Rheumatoid Arthritis (RA), **3.** Gout, **4.** Ankylosing Spondylitis (AS), **5.** Lupus arthritis, (LA), **6.** Infectious arthritis (IA), **7.** Juvenile arthritis (JA), **8.** Psoritic arthritis (PA), **9.** Fibromyalgia. The most outbreaks are seen for OA, RA and gout or to a certain extent AS, whereas the remaining others are less frequent ***[6].***

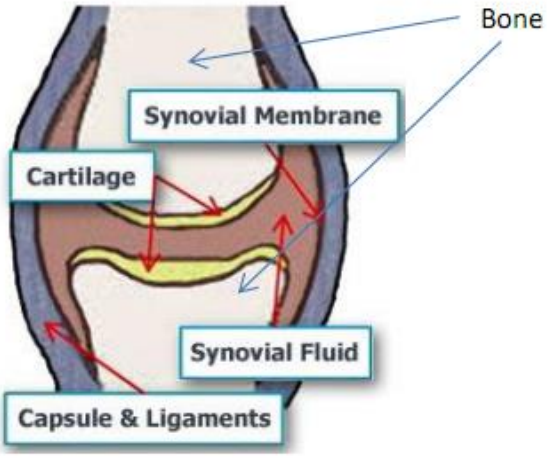


Figure1. Typical picture of a bone joint (Knee)

CLASSIFICATION:

FACTS AND FEATURES ABOUT SEVERAL COMMON ARTHRITIS

Osteo-arthritis (OA): In this disease, cartilage undergoes a slow damage due to stiffness developed by losing the elasticity ***[7].*** Therefore, it no longer can act as a proper shock absorber. Due to gradual erosion, ligaments face stretching that initiates the pain. As an outcome the bones start rubbing with each other adding agony and suffering. Initially, the symptoms advances slowly but worsens with time causing inflammation and creating more harm to the joint. Patients feel pain during and after the joint- movement. There is an aching sensation at the joints if attempting to move suddenly which usually occurs waking up at the morning. In most cases the development of stiffness is a common indication. The disease progresses with age ***[8,9].*** Along with its progression, patients lose flexibility and feel irritating sensation while flexing the joints. As a symptom, hard lumps or bone spikes appear at the joints under attack viz, knees, hands, hips or spines ***[10].***

Rheumatoid arthritis (RA): This is a widely known inflammatory disease ***[11].*** In RA, the synovium is inflamed owing to auto-immune attack producing stiffness, swelling, pain and deformity at the later stage ***[12].*** RA occurs three times more within the women than men at ages ranging from 40 – 60 but rarely, children are the victims ***[13].*** The affected joints are arms, fingers, wrists, knees or legs. The joints are swollen due to inflammation thus felt stiffness especially after waking up at morning. If touched, patients feel tenderness showing red or puffy colors at the affected areas. Patients often feel tired and experience weight losses. The disease can strike at several places simultaneously spreading from smaller to the larger joints; like wrists, ankles and feet to elbows, knees, hips, necks or shoulders ***[11].***

Gout: It is also categorized as a form of arthritis affecting the bone joints particularly at faraway places like toes. The disease is observed more among men but the level equalizes when women arrive at menopause state thus supporting a strong role of estrogen to prevent it ***[14].*** Gout is a painful and debilitating disease caused by the uric acid / urate crystal deposition within the joints like toes, fingers or ankles creating inflammatory gouty condition. The faulty purine metabolism producing Hyperuricemia or mal-excretion of the uric acid / urate due to impaired kidney filtration are the key factors that elevate the rise of serum uric acid level resulting in its deposit while inflicting severe pain and sufferings inducing the inflammation as well ***[14].***

Ankylosing Spondylitis (AS): It is also regarded as an inflammatory autoimmune disease of the spinal joints or between spine and pelvis ***[15,16].*** The inflamed joints perpetrate excruciating pain that increases with time. Along that course, spine experiences stiffness due to the fusion of bones. The exact cause remains unidentified but suspicion points it to be genetic. The disease affects more male than the female and often starts at the ages of 20 – 40 ***[17,18].*** The pain and stiffness are severe at night or morning but subsides during the day with start of physical activities. The disease onsets at the sacroiliac (spine and pelvis) joints and afterward affects the other places also. Patients lose mobility of the lower spine and cannot expand chest properly for taking a full breath. The other associated symptoms are; uveitis (swelling of the eye), pain in the hip, heel or other joints accompanied with low level fever, loss of appetite and weight loss ***[19].***

Lupus arthritis (LA): It is a systemic autoimmune disorder affecting nearly 1.5 million people in the US alone ***[20].*** Almost 90% of the lupus patients suffer from joint and muscle pain and about 35% of

them bear LA ***[21].*** The disease produces pain and swelling of the joints accompanied by morning stiffness. Occasionally fluid accumulates at the swelled joints. Besides serious damages, LA creates deformities and discomforts but does not attack neck or spine. Areas far away of the body are mostly affected eg, fingers, wrists, knees, feet, toes, elbows and hands. The effect of LA is symmetrical, for example, attacking identical joints on both sides of the body. Study indicates that anti-histone antibody is possibly linked to its occurrence ***[22].***

Infectious arthritis (IA): IA arises due to infection inside the synovium caused by bacteria, fungi or viruses. The infection spreads through circulation later affecting the joints. If patients already suffering from any arthritis, they would be prone to it which then synergizes the sufferings further. It might be the cause why patients with arthritis often become the prey to infection thus worsening the situation more. The symptoms are pain, swelling, inflammation of the joints followed by frequent fever; often starts with an injury. The areas falls under attack are knee, ankle, shoulder, wrist, elbow, finger etc. But IA affects single joint only ***[23].***

Juvenile arthritis (JA): Obviously, patients involved are the child. The symptoms involve occasional evening fever, poor appetite, weight loss followed by rashes on the arms and legs. The patients frequently limp and experience sore at the wrist, finger or knee. The joints appear larger due to swelling. The sufferings include pain and stiffness at the neck or hips. The frequent development of anemia is also detected ***[24].***

Psoriatic arthritis (PA): Generally, psoriasis is a well-known inflammatory skin disease, noticed within 1- 3% of the white European population. About 15% of the patients with psoriasis face PA expressing Human Leukocyte Antigen (HLA), HLA-B27 ***[25].*** The HLA – B27 is a Class-I surface antigen which is encoded by the B locus in Major Histocompatibility Complex (MHC) within chromosome - 6 presenting antigenic peptide to the T cells. HLA-B27 has a close link to the AS also. Studies show that Psoriasis and PA is noticeably common among those suffering from the inflammatory bowel disease / Crohn's disease. Genetic predisposition, both innate and adaptive immunity is involved in the pathogenesis of both Psoriasis and PA ***[25].*** In this regard the role of TNF-α is particularly important since this cytokine exacerbates the disease drastically. Based on that observation several approaches regarding the anti-TNF- α therapy are sought into practice. Either monoclonal antibody to TNF-α or the fusion proteins expressing soluble TNF-α receptors (TNF-α – R) are used as an effective therapy in controlling either the psoriasis or PA (Table2) ***[26].*** The usual symptoms for PA are; pain, swelling and stiffness at the joints displaying either redness or when felt warm if touched. Swellings appear as a sausage especially at the fingers and toes. Further, tendinitis is also occasionally developed in the Achilles tendon. Often pains are also felt either at the lower back or tail bone ***[25].***

Fibromyalgia: The disease is defined as a disorder originated due to musculoskeletal pain along with the fatigue. Many believe that it over-amplifies the pain sensation in comparison to normal perception. Often psychological stress, physical trauma or infection may initiate the disorder. Survey indicates that women are the major victims than men. A significant section of patients suffering from fibromyalgia also show the tension headaches, irritable bowel syndrome, anxiety and depression. Apparently, the disease runs in the families so there is a good possibility of genetic mutations involved in it. In many cases post-traumatic stress disorders or those suffering from RA tend to help develop the disease ***[27].***

Epidemiology of Arthritis: Numerous studies are conducted concerning the incidence of various forms of arthritis in western and eastern hemisphere. So far, no precise reason whether genetic predisposition or environmental stimulus plays any role has been identified so far. Studies performed by Helmick et al identifies that in the US alone > 21 % adults or ~ 46.4 million are diagnosed to be currently suffering from the arthritis. Further as reported in 2008, approximately 1.3 million of the US population have the RA which is somewhat less than that estimated (2.1 million) in 1995. The study also indicates that AS sufferer ranges from 0.6 to 2.4 million whereas the LA affects 161,000 to 322,000. In case of JA, the value is ~ 294,000. The study also shows that ~ 27 million of the US population possesses clinical OA which is up from 21 million compared to the year 1995. Regarding other kinds, about 5.0 million have Fibromyalgia and ~ 3.0 million carries the gout (up from 1995 which was 2.1 million) ***[28,29].***

A Canadian study in recent decade shows that in general, ~ 15% of the overall population suffers from any kind of arthritis. Among the victims, 48.8% are male and 51.2% are the female. The difference is claimed significant which is supported by other studies pointing the problem more toward females. The study further indicates that within the Canadian nationals, white Europeans / Caucasians bear a higher percentage (19.7%) than the Asians (5.5%) or other ethnic categories (8.8%, including Africans & other non-Caucasians). Several relating studies convince also that the Asian race have lower incidences of any arthritis irrespective of their age, sex or education level ***[28-31].*** In US, concerning the ethnicity, no exact consensus has been reached concretely but a few studies reflect that there is a distinguishable role regarding some forms of arthritis. For example as an average estimate, the incidence of RA is seen somewhat higher within the Hispanics community ***[28].***

As stated by Symmons et al that globally, in previous decades, arthritis is estimated to be the 40th leading cause of non-fatal burden. In the last decade just before changing of the century, it has been accounted that about 0.7% of the total years people lived with disability (YLD). In next decade following the World Health Report, just RA alone is considered to be the 31st leading cause of YLD globally and that percentage (0.7%) increases to greater than >1% ***[32].***

As published by Inoue et al, that in the hip joints OA are more prevalent within Caucasians than in Asians, particularly comparing to the Japanese ***[33].*** Studies performed in nineties covering up the last three decades indicate that among developing Asian nations the prevalence of RA is just about the same as for Western nations (0.75%) whereas according to Modi et al, in the case of India or Pakistan it is somewhat less, about 0.55% ***[32].*** The value is even remarkably low (0.4%) for China and Indonesia including both urban and rural population ***[32].*** Interestingly, in rural African nations RA is considerably low whereas it is extremely high in Jamaica (2%) and Latin American nations (1.5%) ***[34].*** The ecological factors or genetic variations are suspected to be largely responsible behind these differences. A number of studies show that the frequency of RA or its severity is somewhat less within Asians and West Africans ***[35].*** Studies conducted in the US with worldwide focus on RA alone showed that the prevalence is much higher in Europe and North America than in any developing nations ***[36].*** The major data collection by ILAR (International League against Rheumatism), for the developing nations was carried out mostly from China, Philippines, Malaysia, Indonesia and South Africa (not India or Pakistan) ***[31,37,38].*** The data from India or Pakistan remains questionable. According to some studies, no real difference exists when compared with the West-European nations ***[31,39].*** The genetic profile associated with RA is uniform for

both India and Pakistan but definitely not for the Chinese or other South Asians. The differences in HLA motif is considered to be the underlying reason ***[35].***

The degeneration of cartilage within bone joints sets the attack of OA which starts at the median age of 40. Studies showed that among the OA sufferers, the disease affects nearly 13.9% adults from the age over 25 or older and 33.6% around the age of 65 or higher which estimates about 12.4 million people in that age group. Concerning the incidence of OA correlating with age and sex, women show the higher rates than men mostly after the age of 50. In that way, men possess 45% lower risk of knee and 36% reduction in case of hip OA ***[28,29].*** The prevalence of knee OA is severe for the women than men. The widely famed Framingham study also validates the fact by judging the pictures of radiography of the knees. The higher incidence of OA for women with increasing ages in comparison to the men are distinctively noticeable which is supported by the other studies also ***[40].*** A follow up of Framingham study showed that the risk of knee OA turns 60% lower within the women who are using hormone replacement therapy than those abstaining from it. This very finding led to speculate that estrogen could have a chondro-protective role, which may disappear with the menopause. Several studies also favor the preventive role of estrogen ***[41].*** Since OA is linked to the aging so its incidence rate is higher among the women in Asian countries because they age and reach the menopausal stage earlier. Studies within Asian women show that the incidence depends further on their professions and living conditions. Thus the hip and knee OA within working Asian women are exceedingly common and associated with their occupational activity which often involves serious physical labor. For that they frequently show a higher incidence rate than men. The victims belong mostly to the poor and rural community ***[32].***

The Gout is also counted as an inflammatory arthritic disease, very common among the men. In the US, its incidence is higher within black than the white males, about 3.1 vs 1.8 of 1000 persons counted in each year for last 34 years. The Rochester Epidemiology Project shows that there is an increase of incidence from 45.0 out of 100,000 persons in 1977-78 to 63.3 in the year1995 -96. The ratio of male to female is 3.3 to 1.0 as seen in both cases whereas below the age of 65 the rate is 4 to 1 ***[42].***

The prevalence of ankylosing spondylitis (AS) is normally less compared to either RA or OA but certainly not ignorable. The epidemiological surveys were conducted in various populations and subpopulations and the value ranges from 0.036 % to 0.10%. The incidence is lower in Greece and Japan because of the low occurrence of HLA-B27 antigen ***[43-44].*** The involvement of antigen HLA-B27 expression is believed to be the common cause but that is not always the exact reason. Following the New York criteria, the prevalence of AS in Dutch population was seen 0.24% whereas the value for HLA-B27 is noted to be 0.1%. Surprisingly only a limited number among the AS sufferers corresponds to HLA-B27 positive. In previous Norwegian study within Lappish population the prevalence of AS was reported 1.1 - 1.4% and the male to female ratio was 4:1. In that particular study the prevalence of HLA-B27 antigen is noticed to be a common factor because it corresponds well, ~ 91%, signifying that this antigen could be the major cause of AS within them. In Asian region the average prevalence of OA is 0.11% which is almost equal to that of Chinese, Thai and average Caucasians but not for the Japanese who bears a significantly lower rate due to low prevalence of HLA-B27 antigen. The middle-east Arab population

shows a higher rate of AS compared to the south Asians. Further the diversity of HLA-B27 antigen regarding the subtypes is identified when Indonesian Chinese (HLA – B2704) are compared with the natives (HLA –B2705). In India, the study conducted by ILAR or Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) by Chopra et al showed that the prevalence of AS in rural Indian population is 0.09%. The study was conducted with 4092 adults of whom 18.5% expressed pre- rheumatologic complain ***[45,46].***

NATURE and CAUSES: As already mentioned that arthritis belongs to two main categories. OA which is the most prevalent one often starts due to wear and tear or rather say by the rupture of cartilage tissue. Whereas in case of RA, it is the body's immune system that creates the trouble by attacking cartilage. Considering that fact, the present day treatments are constructed which brings much success in controlling the disease. But in all cases the joints experience inflexibility along with the pain, swelling and bone erosion. For OA, the disease is viewed as a common ailment whose incidence goes up with the ages. The disease is identified by observing progressive degradation of the articular cartilage causing severe discomfort accompanied with pain and loss of mobility.

Physico-chemical factors behind the cartilage action: During flexing of the joints like, hip, knee or elbow, articular cartilage (synovial joints attaching the bones) provides smooth gliding. It is intimately attached to the bones thereby immensely influencing the surfaces to provide easy motion for coasting. The tissue consists of chondrocytes (cartilage forming cells), collagens (mainly type II and others), chondroitin / keratan sulfate and hylauronic acid. It also carries no nerve or blood vessels. As per physical appearance it is white and offers extreme amenability that helps distributing pressure between the opposing bones. If the tissue turns stiff then stress at the contact point raises high that brings discomfort during flexing of the joints ***[47].***

The chondrocytes in healthy joints secrete synovial fluid (~ 1ml in case of normal joint) with thick egg-white appearance needed for joint lubrication. The fluid contains hyaluronic acid / PGs (3-4 mg/ml) or lubricin (a heavily glycosylated protein, MW ~ 345KD secreted by the adjoining fibroblasts providing 50µm layer thickness which reduces the friction. Concerning the properties, the fluid possesses dilatant character therefore non-Newtonian by nature switching to higher viscosity under the applied shear force. Besides working as lubricant, the fluid also transports nutrient and wastes (CO_2 and other metabolites). As per chemical composition, the cartilage consists of ~70 – 80 % water, ~ 30 % PG and the rest is collagens primarily the type II. Considering its dry weight, 60 – 70 % is collagen and the rest 30 % is PGs. By nature PGs are highly glycosylated proteins bearing a small protein core covalently linked to glycosaminoglycan (GAG) chains via the serine residue (Figureure 2) ***[47,48].*** The architecture of collagen distribution varies along the depth of cartilage tissue (Fig – 3). In physiologic environment (pH ~ 7.5), PGs are highly charged poly-anions due to the ionization of Hylauronic acids, Chondroitin or Keratan sulfates therefore their mutual repulsion helps spreading off the molecules and forcing them to occupy a large space (Figure 2). But within the cartilage matrix volume taken up by aggregated PGs is limited so they are wrapped up with the frame works of collagen. So swelling of PGs against the collagen frame work is necessary during any mechanical response. If the cartilage is compressed the negative charges come closer increasing the repulsive forces that enhances the compressive stiffness. In case of normal tissue, PGs within the matrix is in aggregated state. The

non-aggregated PGs are not effective in resisting the compressive loads because they are not bound to the collagen frame work. Conceivably, any damage to the collagen frame work would reduce the compressive stiffness and that would disaggregate the PGs while holding them inefficiently. In a way, cartilage acts like a sponge and does not allow the easy fluid flow through it. So cartilage is a mixture of solid-liquid component and biphasic by nature. The solids are a mixture of PGs, collagens and cells clustered together to be in one phase whereas the other component, interstitial fluid being in liquid phase and incompressible offers the cushioning effect. Together, they are liable for the free joint movement. Essentially the normal cartilage matrix is incompressible as well as elastic and it does not allow the fluid to flow through, therefore impermeable by nature. If water easily flows through the matrix, then the solids would experience a huge stress therefore it may tend to break. As per clinical relevance, the permeability increase is seen only in arthritis ravaged cartilage associated with matrix deformation. The post-mortem study supports the fact showing that the cracks developed at bone – cartilage interface in OA when water can flow out completely from the matrix. Thereafter cartilage experiences wide lateral displacement during compression but its expansion is restricted due to adjacent bones thus allowing develop severe stress at the bone-cartilage interface. The failure of cartilage thus directly depends on the severity of stress ***[47-49].*** Due to its anisotropic nature, the cartilage acts differently under different types of stress eg, it may resist strongly during tension parallel to the collagen fibers whereas felt weaker while experiencing shear along the planes. The studies showed that most joint failures are primarily caused by the shear stresses. The ability to maintain tensile strength within the ankle is a key factor for its reduced incidence of OA in comparison to hip or knee ***[49].***

OA and cartilage function: The knowledge about basic function of a cartilage is important because this particular tissue provides smooth movement, offers low friction and load bearing or distribution. These are all possible due to its unique mechanical behavior. If by any chance there occurs any wear and tear the tissue can hardly regenerate by itself. One of the reasons is its metabolic activity is extremely poor. Concerning the structural aspect, the tissue is built up of chondrocytes that are surrounded by dense extracellular matrix (ECM). The ECM is largely composed of water as a major ingredient including collagens and PGs. The chondrocytes are normally elongated in shape and carry about 5 % of wet weight of the entire tissue whose metabolism is slow but important for the healthy maintenance. Anatomically, cartilage consists of organized layered structure having four zones: superficial zone, middle zone, deep zone and calcified zone (Fig – 3). The top superficial zone or tangential zone offers smooth sliding and resists any shear. It covers 10 – 20 % of the total cartilage depth having highest collagen content. In this zone, the collagen fibrils are thickly packed and arranged orderly being aligned parallel to the cartilage surface. The compressive modulus is very low so that it can be deformed easily, about twenty five times easier than the middle zone. The cells in this layer express a distinctive lubricating protein called superficial zone protein (SZP), necessary for smooth gliding of the surfaces. These chondrocytes are phenotypically different from those of the other layers. The middle zone or transitional zone covers 40 – 60 % of the cartilage volume and has relatively higher compressive modulus. Its collagen fibers are less organized and thicker than the previous zone but loosely packed and aligned in an oblique pattern. Here the chondrocytes are more rounded shape. The deep zone takes up about 30 % of the cartilage. The collagen fibrils are larger in diameter aligned perpendicularly to the surface. This zone has the highest PG and lowest water content for

that it bears the highest compressive modulus. The chondrocytes are arranged as a column parallel to the collagen fibers but perpendicular to the joint surface. Finally the deep zone carries calcified cartilage resting directly on the subchondrial bone. This calcified cartilage zone bears very small cells attached to the matrix that are sprinkled with the calcium apatite (Figure 3) ***[49].***

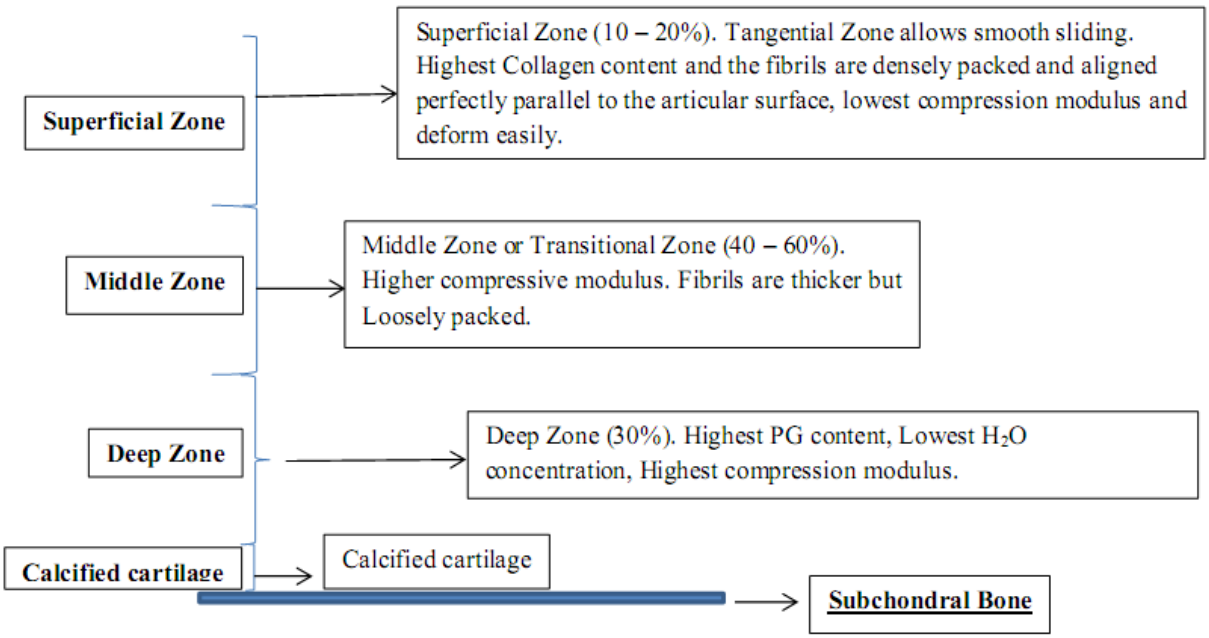


Figure 3: The schematic diagram depicting the four zones of an articular cartilage. The cells in those zones are phenotypically dissimilar as well as in sizes and shapes. The secretagouges at those layers are also distinctively different and they have their respective responsibilities in order to maintain the joint flexibility.

During OA attack the cartilage tissue steadily loses PGs relative to its collagen content. Therefore a large percentage of PGs becomes non-aggregated by detaching themselves from the hylauronates. The proteolytic degradation causes the lowering of PGs' chain-lengths subsequently inhibiting the normal macro-molecular complex formation. Thus with the progress of disease the PG / collagen ratio becomes severely lowered which eventually disturbs the matrix architecture causing its breakdown. This breaking-down event makes the matrix more water permeable which appreciably diminishes the hydraulic pressure, as seen in the case of OA infested cartilage consequently reducing the compressive stiffness also.

Unequivocally, OA is considered as a non-inflammatory arthritic condition created by the wearing and tearing of the cartilage tissue by the mechanical event which afterward acquires inflammation as a secondary episode exacerbating its painful progress. So the disease is mechanically driven which helps releasing the numerous chemical mediators, who later dictates the chondrocytes' behavior at the different zones within cartilage. As per outcome the cartilage breaks down further. Several of the chemical

mediators are enzymes MMPs, collagenases and Cathepsins. In addition to the deregulation of MMPs' expression triggered by the mechanical overload there is a release of other inflammatory cytokines (TNF - α, IL - 1β and IL - 6) which helps disrupt the cartilage tissue further in later stage. These cytokines modulate the chondrocytes in various ways either by inhibiting the synthesis of PG, collagens or allowing the over-expressions of proteolytic enzymes enabling to disrupt the matrix more. The progression of OA including the inflammation is usually assessed by the level of C-reactive protein (CRP) expressed along the pathway. Studies showed that the level of CRP is moderately elevated during OA but for RA the level shows steady increment following disease's progression ***[49].***

Chondrocytes and Ossification: Chondrocytes are known as being the cartilage forming cells located also within the cartilage matrix. These cells produce collagens and PGs which constitutes the matrix. The precursors of chondrocytes are the mesenchymal stem cells that can differentiate also to be an osteoblast, the actual bone cell, depending on the activation by the surrounding transcriptional stimulus during intra-membranous ossification whereas a cartilage tissue is generated during endochondral ossification (EO) ***[49].*** In that act, the undifferentiated mesenchymal cells lose some of their potentials but can proliferate and crowd the space in a dense pack which later differentiates to chondroblasts synthesizing the cartilage forming matrix. Afterward the cells occupy small space and surrounded by the matrix substances but stay no longer in contact with the extracellular fluid. The cells are now transformed to chondrocytes which are far more inactive but can secrete only the matrix forming or degrading components, depending on the response or condition. Further considering the nature of cartilage and location their phenotypes would change. Characteriscally, OA follows the similar course of chondrocyte differentiation pathway like that in EO occurring during skeletal development. In healthy cartilage the cells resist to proliferate and do not undergo any terminal differentiation. On the contrary, in course of OA chondrocytes proliferate unstoppably and eventually reaches to a different stage of maturation ending to the state of hypertrophy. Following that event there starts the process of vascularization through the invasion of blood vessels exerting the event of cellular apoptosis. The release of proteinases during apoptotic event changes the matrix architecture starting the process of mineralization therefore depositing the $CaPO_4$ crystals within the joint cartilage as seen in OA. Before arriving to final event of apoptosis, the steps involved during EO are identified by the expression of various types of collagens, proteins and glycans. Collagen I, III and V are seen in undifferentiated precursor, the mesenchymal cells. Once differentiated to the chondrocytes those collagen components are stopped being produced while starting to generate collagen II, IX, XI including the PGs or Aggrecan. At this stage, the sizes of chondrocytes are small but uniform in shape and they possess low proliferation rate. Afterward if the cells proliferate and divide few times then they would acquire a flattened appearance and are arranged in longitudinal columns. In this course they express collagen VI, Matrilin - 1 (a non-collagenous protein) including also the collagen type II, IX, XI and PGs. But just before reaching to the state of hypertrophy the Indian hedgehog protein appears. At the final stage of differentiation and reaching the state of hypertrophy, the cells stop producing collagens II, IX or IX while expressing, collagen X, MMP-13, alkaline phosphatase, vascular endothelial growth factor, Osteopontin and numerous other transcription factors. Collagen X, MMP-13 and alkaline phosphatase are identifiable markers of the hypertrophic stage. The hypertrophic

chondrocytes undergo apoptosis while releasing number of matrix degrading enzymes and simultaneously initiating the process of calcification. The uncontrolled calcification created out of the imbalance in any of the steps finally results in OA (Figure 4).

Calcification of articular cartilage and propagation of OA: The excessive deposition of Ca^{+2} due to uncontrolled mineralization at the bone-joints is suspected to create inflammation as its aftermath (Figure 4). The imbalance created between pro and anti-mineralization factors is liable for the excessive deposition which arises due to deviation from the normal course of EO. The responsibilities could lie on metabolic disorders, degenerative joint diseases, aging or any physical disturbances setting the conditions of uncontrolled calcification. The involvement of unidentified genetic factor is also suspected in this course (Figure 4) ***[50,51].*** Several other parameters taking part in this unrestrained calcification is also noted (Figure 4) ***[50].*** Among them hypertrophy and ECM modification play the major task (Figure 5). But, aging has also a significant role in pathological calcification since it releases number of ingredients identical to those seen during the OA ***[49].*** The high deposition of Ca^{+2} crystals in the form of calcium pyrophosphate dihydrate ($[Ca_2 (PO_3\text{-}O\text{-}PO_3)^4]; 2H_2O$) (CPPD) or basic calcium phosphate (BCP) like hydroxy apatite (HA) ($Ca_5 (PO_4)_3\{OH\}$) is considered to be the main biochemical reason behind the initiation of OA, although the exact reason still remains unknown (Figure4). So, preventing the calcification process could be an effective therapeutic measure in future.

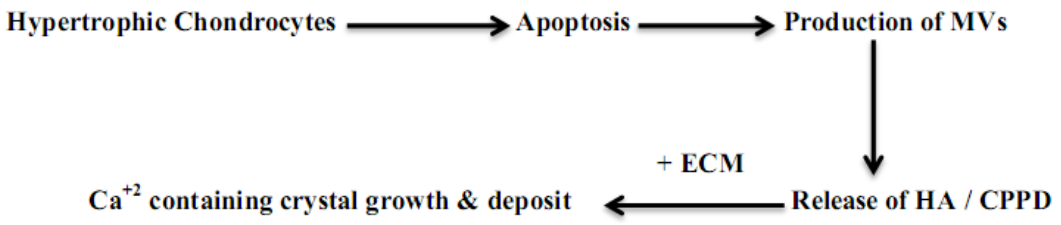
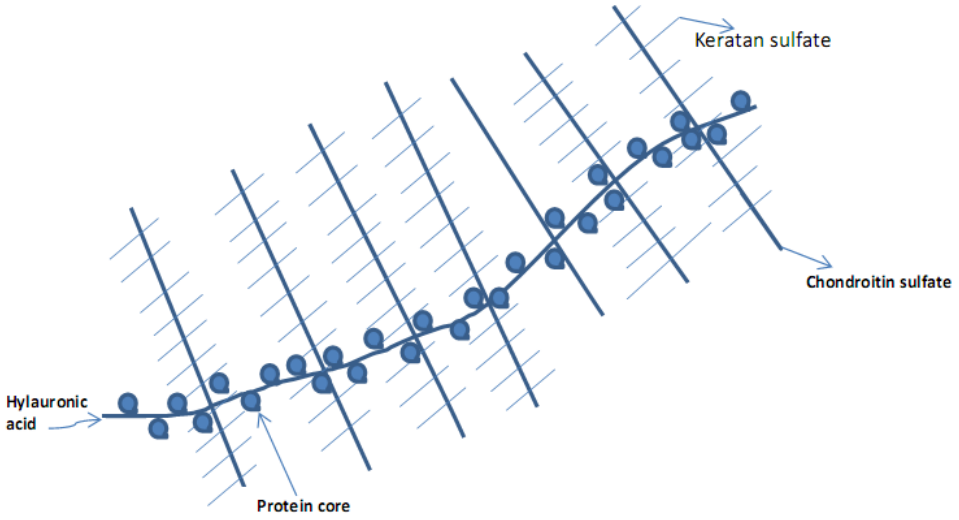
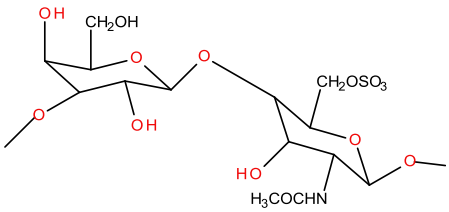


Figure 5 A simple ways to visualize the calcification process which is initiated during terminal differentiation of the hypertrophic chondrocytes after undergoing an apoptosis

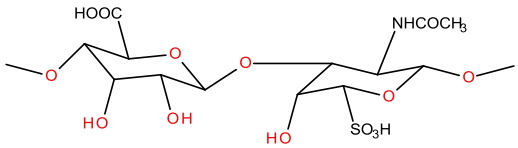
Mechanism behind calcification: Normally, endogenous PG has a potent inhibitory role in the event of calcification. In that regard the larger poly-anions are more effective than the smaller monomers (Figure 2) ***[52].*** The pathological calcification is naturally resisted during normal maintenance of the mature chondrocytes in the presence of well aggregated PGs. It is already mentioned that calcification occurs during longitudinal growth of the chondrocytes differentiation which also induces rapid proliferation mimicking the normal ossification but



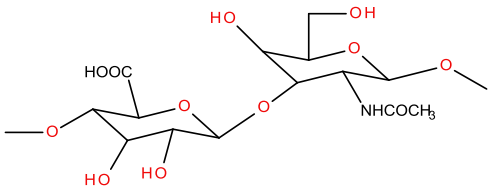
Physical structure of Proteoglycans (PG)



Keratan Sulfate



Chondroitin Sulfate



Hylauronic Acid

Figure 2: The PG is an aggregate with brush structure having Hylauronic acid backbone. The side chains consist of Chondroitin and Keratan sulfates that are attached to the protein cores. At physiological pH (7.5) molecules of Hylauronic acids, Keratan and Chondroitin sulfates are ionized to CO_2^- and SO_3^- anions making the PG highly charged poly-anion so the molecule is extended due to charge repulsion occupying large spaces in aqueous media.

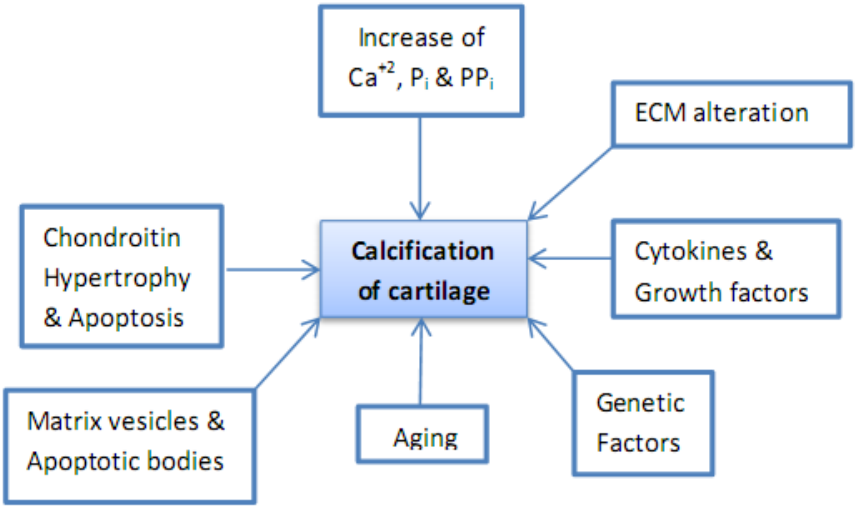


Figure: 4 Probable factors behind cartilage calcification leading to OA

the process goes uncontrolled due to cellular hypertrophy releasing the MVs through apoptosis inducing the crystallization of $CaPO_4$ in several forms ***[49,53].*** So as a therapeutic measure, Hylauronic acid or Glycosamine glycan (GAG) if used exogenously can offer protection from extra-ordinary calcification by lowering the level of free Ca^{+2} within the joint fluid and subsequently reducing the role of pro-inflammatory mediators ***[50,54].***

During calcification and in course of OA the chondrocytes experience terminal differentiation like that happened in the growth plate of cartilage while releasing the HA and CPPD ***[53-56].*** Thus in all cases of degenerative bone-joint problems the deposition of CPPD or HA crystals are visualized ***[50].*** Although pyrophosphate (PP_i) is considered to be the main source of basic phosphate (P_i) which can also prevent the apatite (HA) production or deposition. But the excess PP_i production also causes crystallization of CPPD which is viewed as an index for the OA. So, the P_i / PP_i ratio is a determining factor during physiological and pathological mineralization events. In course of pathological calcification the formation of both CPPD and HA occurs with the help of micro vesicles (MVs). The crystal composition depends on the values of P_i / PP_i ratio. If the value crosses over 140 then calcification takes place and HA would be the major component. But if P_i / $PP_i \leq 70$ then there will be no MV induced HA formation so there would be no calcification at all. Whereas if P_i / $PP_i < 3.0$ then CPPD would deposit as crystals. On the other hand, P_i / $PP_i > 30$ inhibits the CPPD deposit ***[50].***

The hypertrophic chondrocytes starts the mineralization event by releasing the MVs after undergoing an apoptosis that initiate the calcification process by crystallizing CPPD and HA (Figure – 5). The released crystals from MVs bind to

ECM allowing it to grow further. So, the ECM modification by the cells at terminal differentiation causes further deregulation of inorganic pyro-phosphate (PP_i) or phosphates (P_i) generation helping the calcification process which is inhibited beforehand in case of healthy chondrocytes ***[50,54-56].*** A subset of ECM called matricellular proteins has a primary regulatory role besides acting normally as scaffolding. In that category, there lies a family of CCN proteins (Cysteine rich angiogenic inducer, CCN1 - CCN 6) ***[57].*** They regulate several cellular acts eg, adhesion, differentiation, migration, survival, apoptosis, senescence and gene expression. Studies in patients show that CCNs are much involved in chondrocyte differentiation at the early stage of OA while exerting apoptosis also ***[57].*** In course of apoptosis, for ordinary tissues, debris created out of the dead cells are engulfed and cleared off by the incoming mono-nuclear phagocytes thereby preventing any further inflammatory responses. Disadvantageously, the articular cartilage is not so vascularized therefore provides hardly any phagocytes to serve that purpose. Contrarily, the attached chondrocytes encircled by the pericellular matrix therefore are lacking in the clearing ability of the apoptotic debris. It is known that MVs from normal epiphyseal growth plates have the roles in both bone and cartilage calcification. Interestingly, the electron microscopic and biochemical studies reveal that apoptotic cell debris bear unique similarity with the MVs from growth plates which by all nature are also the membrane enclosed small vesicles enabling to deposit the HA crystals in vitro. Instances indicate that MVs can be originated from the apoptotic cell debris also; in vitro experiments by using isolated MVs from different sources confirm the fact ***[58].*** Regarding biochemical nature, the MVs from all sources possess alkaline phosphatase and nucleoside triphosphate pyro-phosphohydrolaze enzymes. Experiments showed that isolated vesicles are functionally active and behave as same way incorporating ^{45}Ca; hydrolyzing the ATP or other nucleotide triphosphates to produce ortho-phosphates ($-PO_4^{-3}$). If the level of Ca^{+2} and phosphate products reaches above the solubility limit, it then allows the precipitation of Ca^{+2} phosphate crystals. In physiological and patho-physiological mineralization, the ratio of P_i / PP_i is regulated under biologic control which acts solely as the deciding factor ***[50].***

Concerning the mineralization event, nucleotide pyro-phosphatase/phosphodiesterase-1 (NPP1) and tissue nonspecific alkaline phosphatase (TNAP) have an antagonistic effect for their opposing roles while producing PP_i by NPP1 and its subsequent hydrolysis by TNAP creating the P_i ***[59,60].*** So, the metabolism of PP_i has a role in the skeletal matrix calcification since it is destined to act as a potent inhibitor during crystallization process inside the extracellular fluids. Normally, inside the cells, NPP1 provides PP_i from the hydrolysis of ATP and UTP. Ankylosing protein (ANK) transports PP_i from intracellular to extracellular matrix ***[61].*** The high accumulation of PP_i in cartilage causes deposition of CPPD crystals ($Ca_2P_2O_7$; $2H_2O$). As reported by many that NPP1 overexpresses in the chondrocytes of OA affected cartilage that increases the PP_i level to form CPPD crystals along with HA ***[50].*** The mineralization process plays a distinctive role in bone or cartilage growth and repair which is coordinated by the endogenous stimulatory and inhibitory factors. The uncontrolled mineralization only occurs either during aging or in any degenerative joint diseases which can be a result of genetic modifications or metabolic deregulations (Figure 6) ***[62].***

Cartilage degradation by apoptosis and the role of Nitric Oxide (NO*) free radical: Apoptosis is a natural event but for chondrocytes attaining to hypertrophy can initiate uninhibited calcification.

The degraded apoptotic cell bodies supply the MVs that essentially promote the process (Figure5) Therefore a proper knowledge about the chondrocyte apoptosis would help building up a therapy in future. So far, several important mediators are identified: 1) NO* free radical, 2) Fas

Record shows that chondrocytes generates NO* during the oxidation of L- Arginine by Nitric oxide Synthase (NOS) in presence of Intertleukin-1 (IL-1) ***[63].*** NOS can be produced constitutively (cNOS) or inducible way (iNOS). As reported, the former is produced in a Ca^{+2} dependent ways

The generated NO* also produces Prostaglandin E_2 (PGE_2). So the signaling pathway is IL-1 induces iNOS that catalyzes the NO production which afterward produces PGE_2 from the Archidonic Acid (AA). The PGE_2 thus produced exerts apoptosis by enhancing the intracellular cAMP level within chondrocytes cells ***[65].*** It is noticed that the inhibition of type-II collagen synthesis follows both NO* dependent and independent pathways whose mechanism is unclear ***[66].*** The inhibitory action of GAG or PG on calcification is stopped due to degradation by upregulated enzyme level, Aggrecanase ***[67]*** which is stimulated by both TNF-α and IL-1 but not NO while following the action of lipid messenger, Ceramide ***[68].*** Aggrecanase catabolizes PGs thereby destroys the cartilage matrix. The action of TNF-α / IL-1also induces the breaking down effect of Sphingomyelin to release Ceramide which then stimulates the MMP genes synthesizing Collagenase – 1 (MMP1) or Collagenase -3 (MMP3) or other matrix destroying proteinases. Both MMP1 and MMP3 destroy the Type II collagen within the cartilage matrix ***[68].***

The protein Integrin acts as a receptor(s) helping the cells attaching with the surrounding ECM or other cells. Integrins are versatile by nature and

[58].

(APO-1, CD-95) and the ligand Fas-L, 3) TNF-α and 4) Bcl-2/Bax proteins of the proto-oncogene family. Among those, NO* harms the most ***[58]***

whereas the latter is generated by following Ca^{+2} independent ways. Chondrocytes produces iNOS only when exposed to the cytokines IL-1 or TNF-α which afterward generate the NO* ***[63,64].*** The after effect of this NO* exposure inhibits a) cell proliferation, b) type-II collagen production, c) PG synthesis and d) integrin function ***[64].***

take part in signal transduction and also regulating the cell cycle. Chondrocytes bind to the ECM through its cell surface receptor (α5β1- Integrin). That binding to the ECM-Fibronectin helps assemble Focal Adhesion Complex (FAC) at subplasmalemmal level. Reports show that NO prevents this act by disrupting the FAC assembly. Since Chondrocytes survive only through their adherence to the ECM by receiving the surviving signal through the adhesion mechanism therefore, destruction of ECM brings their depletion ***[69].*** In a way, the generation of NO* creates a number of problems leading to OA.

Aging and OA: By far age is considered to be a major risk for setting the stage of OA [18]. An intense correlation between age and high incidence of OA shows that it as an age related disease. But in no way OA is inevitable in the aging process although it enhances the risk considerably ***[62].*** Definitely, aging changes the ECM structure showing cartilage disruption that increases the chances of OA attack. The reports show that aging alters the chondrocyte functions by lowering the PG synthesis, its proliferative actions and additionally decreasing its response to the growth factors or any other anabolic stimuli ***[70].*** So, over the age of forty, the incidence of OA is elevated significantly and the trend increases with time ***[8].***

The common age related changes are: **1)** Chondrocytes hypertrophy, **2)** Glycation causing increased stiffness of the Collagen matrix, **3)** The increase in the ratio of Keratin: Chondroitin sulfate in PGs, **4)** Increase in water content inside the matrix during OA whereas in case of normal aging it decreases, **5)** Decrease in chondrocytes number, **6)** Decrease in the size of PG molecules, **7)** Loss of cartilage elasticity.

As mentioned, the age related changes of ECM are highly linked to the chondrocytes hypertrophy. Further, changes of the matrix nature are visible also within the aggregating PGs which provide stiffness during compression. In that act the resistance and durability are duly affected in the aging process since size of the PG molecules decreases substantially with age due to enzymatic degradation. Additionally, aging increases the Collagen crosslinking thereby decreasing the hydrated water content so tissues lose elasticity. Moreover, the mitotic and synthesis events of the chondrocytes also decline with age. Noticeably, the anabolic response to Insulin like growth factor-1 (IGF-1) is lowered with the progression of age which might be liable for the declining of chondrocytes synthesis. On the contrary, the IGF receptor expression is enhanced ***[71].*** Identical incidents are observed in case of OA affected chondrocytes. The IGF-1 hypo-responsive is very critical for cartilage maintenance and repair. For plausible relation between aging and cartilage dysfunction, the following hypotheses are conceived; #1. Chondrocyte senescence, #2. Telomere erosion and #3. Oxidative stress ***[71].*** Even considering these possibilities it is certain that aging does not directly cause the OA. It only synergizes the process by limiting the metabolic or phenotypical events for maintenance or repair while expediting the deterioration of healthy chondrocytes. But importantly, aging allows the accumulation of MVs due to increment of apoptosis which enhances the calcification leading to OA or intensifying the existing one further ***[70].***

Relationship between inflammation and arthritis in general: In general arthritis is observed as being an inflammation of bone joints although not all members of the family follow the same course. Those who are created as a result of inflammation due to autoimmune attack are mainly RA, PA, GA, LA and AS whereas the OA or Fibromyalgia are different. These two show inflammation only after their infliction ***[72].*** Whereas in course of autoimmune disorders, body's immune system attacks the healthy tissues by mistake ***[72].*** If that happens at the joint tissues then it is defined as inflammatory arthritis eg, RA or its analogues, which exerts chronic pain through inflammation while continuously damaging the joints through bone erosion [19]. Individuals suffering from RA are diagnosed by the radiography or other imaging procedures. At start there is hardly any visible damage but later that changes with the passage of time ***[72,73].***

Probable causes behind RA: At present RA is universally recognized as an autoimmune disease ***[73,75].*** The endogenous immune system attacks the joint synovium causing a chronic inflammation which at later stage destroys the cartilage and associated bones. As a result, tendons and ligaments holding the joint assembly turns weak therefore stretched abnormally. With time joint loses shape and alignment. Many of the accomplices involved are known but the actual trigger remains unknown. Many suspect that environmental factors along with the pre-existing genetic predisposition make someone susceptible. The suspected triggering agents are often thought to be either bacteria or viruses from the environment but that is also questionable. Whichever may be the stimulus, malfunctioning of the immune behavior is overwhelmingly considered to be the major cause.

In this respect, B and T lymphocytes play the major roles. Normally, the T-cells after recognizing the antigen secretes cytokines that helps multiply the B - cells releasing antibodies. The circulating antibodies in the blood stream afterward attack the foreign objects that usually trigger an inflammation. In case of RA both T and B – cells are seen overactive.

As evidenced from the animal model, the T – cells can promote synovitis, the inflammation of synovium [74]. It is established that T-cells in close vicinity to macrophages within the cellular aggregates of synovial membrane does intercellular cross-talking which in turn activate them by locally releasing the cytokines like IL-12 & IL-18 through the process of co-stimulation or through the presentation of auto-antigens or both. The pathways depend on action of CD28, CD154 or CD47 cells [74,75]. A number of reports demonstrated that various T- lymphocytes can modulate the actions of other immune cell types just by its direct contact. The in vitro study shows that this property is enhanced by activating the T-cells with cytokines. Interestingly, the activation by IL-2, IL-1β and TNF-α of resting CD45RO+ and CD4+ T-lymphocytes can stimulate more cytokine production from the B-cells without the T-cell ligation. This emphasizes to hypothesize that the major role of T- cells within the synovium might be to activate the adjacent cells by its contact. To explain the situation in a simple way, a local autocrine loop has been imagined (Figure 6). Here membrane anchored as well as the secreted cytokines in addition to adhesion molecules control the synthesis of both pro and anti-inflammatory cytokines like, TNF-α and others [73-76]. Table 3 lists the impacts of T and B cells on immune behavior along with the other soluble pro-inflammatory products. It is recorded that contact interaction between lymphocyte and macrophage isolated from the circulating blood produces TNF-α in addition to IL-1β, IL-12 and several cytokine-inhibitors such as TNF receptor p75 and IL-1RA [73-76]. It is noticed also that T- cells undergo activation by interacting with the cells of

Effectors	**Actions**
T lymphocytes	Production of inflammatory cytokines Activation of synoviocytes by cell-cell contact Antigen-specific response Bone erosion by osteoclast activation
B lymphocytes	Production of inflammatory cytokines Auto-antibody production Antigen specific response Ectopic neolymphogenesis
Soluble molecules (IL-1β, TNF-α , IL-6, IL-12 Etc.)	Causing T cell activation Growth and differentiation of B cells Activation of osteoclast Activation of antigen presenting cells

Table3:

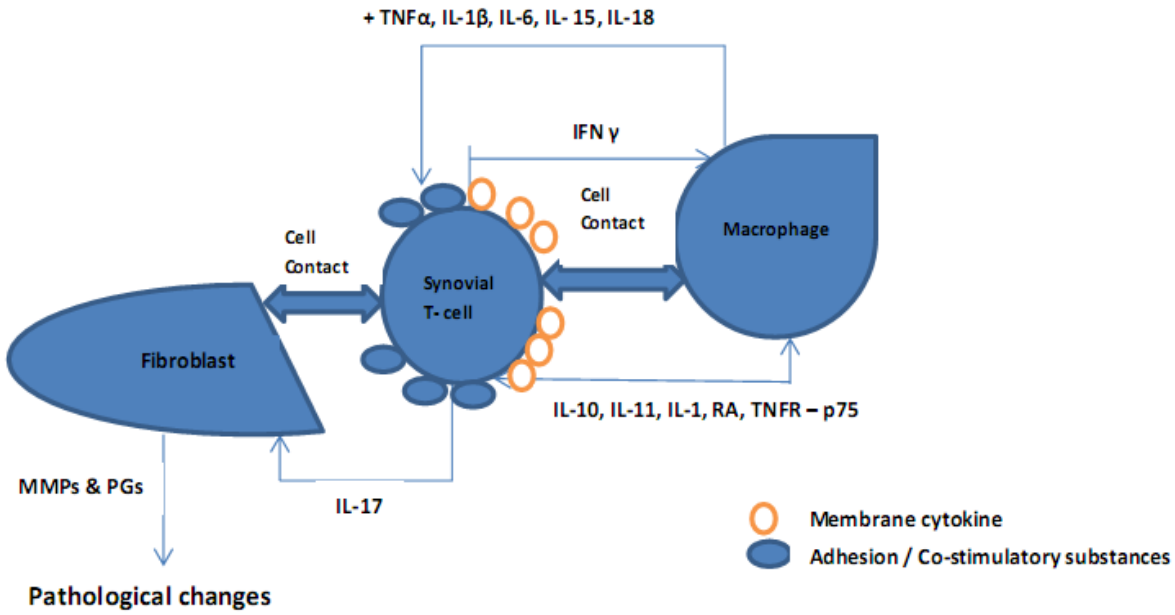


Figure 6: Possible existence of autocrine loop(s) and the role of various cytokines

endothelia due to its contact during transmigration. As per experiments using $CD45RO^{+}$ cells from the circulation, it is proven that they are activated during migrating through the endothelia ***[75,77,78].*** The experiments showed an important role of the adhesion molecules and cytokines expressed on the surface of endothelial cells. This is a powerful model providing a possible cause of inflammation inside the synovium.

Besides cytokines, the role of human leucocyte antigen (HLA) is also a much concerned factor due to its genetic affectivity ***[78,79].*** As per previous reports, the existence of this factor makes the subjects more susceptible in developing RA. Several HLAs are identified like, HLA-DRB1 or HLA-DR4 alleles. They are marked as RA-shared epitope and are not directly involved in developing the disease but normally used for identifications. Inheriting two copies of HLA alleles considerably increases the risk ***[78-80].*** In recent days the HLA epitope helps designing the anti-RA drugs ***[81,82].***

Treatment options and medications for OA and RA: As mentioned before that no known exact cure is still available for any of the arthritis. The current treatments only lower the pain and restrict its progression. Considering the nature of the disease and available knowledge in those areas, currently several treatment strategies are developed. Below is a list of drugs which are often used in the treatment of OA (Table1). In addition to drugs, physical therapies and avoiding of any joint stress are also recommended. Injecting either the cortisone or joint-lubricants (Hylauronic acid or modified derivatives) is often recommended by the doctors also. Additionally, surgical procedures like osteotomy (realignment of bones) or else the joint replacement offer helps to the severely affected OA sufferers. Like OA, the exact cure for RA is also not found. The drugs that are used can only reduce the

pain or inflammation or to a certain extent the progression of joint damages. Table 2 shows a list of common drugs used for treating the RA.

Medications	Nature	Side effects
Acetaminophen (Tylenol) Capsiacin ***[83]***	Lowers pain and helpful for mild OA.	**Continuous use at high doses can damage both liver and kidney.**
Non-steroidal anti-inflammatory drugs: Advil, Aleve etc.	Relieves pain and inflammation.	**Continuous use at high doses may cause stomach upset, enhances the bleeding problem, cardio-vascular, liver or kidney damage.**
Narcotic: Codeine, Oxycontin or similar kind ***[83***].	Provide relief from severe pain in case of extensive OA Problem.	**The excessive use brings dependency, nausea, constipation, sleepiness and lethargy.**
Non-addictive but opiate like. Tramadol (Ultram)	Provides pain relief but very much non-addictive.	**Higher doses can create nausea but no gastro-intestinal discomfort or ulceration.**

Table1.

Medications	Nature	Side Effects
Non-steroidal anti-inflammatory drugs: Ibuprofen (Advil, Motrin), Naproxen (Aleve), COX-2 inhibitors (Celebrex) ***[84].***	Relive pain and inflammation.	**Stomach irritation, bleeding, Cardiac problem liver and kidney damage.**
Corticosteroids: Prednisone	Reduces inflammation, pain and lowers the joint damage.	**Thinning of bones, induction of diabetes, cataracts and weight gain.**
Disease modifying drugs: Methotrexate (Trexal), Leflunomide (Arava), hydroxy chloroquine (Plaquenil), Sulfasalizine (Azulfidine), Minocycline (Dynacin, Minocin etc).	Slows down the progression of RA and save joints from any permanent damages.	**Can cause liver damage, reduces bone marrow level and exerts lung infections.**
Immunosuppressant: Azathioprine (Imuran, Azasan), Cyclosporine(Neoral, Sandimmune, Gengraf), Cyclophosphamide (Cytoxan).	These drugs intend to slow down the rapidly advancing Immune system which runs out of control in case of RA.	**These medications can enhance the susceptibility towards infection.**

Inhibitors of TNF-α: Etanercept (Enbrel: Monoclonal Antibody to TNF-αR2), Infliximab (Remicade: Monoclonal Antibody to TNF-α), Adalimumab (Humira: Monoclonal Antibody to TNF-α), Golimumab (Simponi: Monoclonal Antibody to TNF-α), Cetolizumab (Cimiza: PGEylated Monoclonal Antibody to TNF-α).	Reduces pain, morning stiffness, swelling of joints.	**Increases the risk of infections, congestive heart failure & Cancers.**

Table2:

In addition to others, the use of monoclonal antibody raised against a peptide mimicking docking sequence of the TNF-α or its receptor is also currently in use. This shows a great promise. As a further addition developing monoclonal antibody against a short sequence of MHC-1 antigen is also in progress. Considering the previous regimens the recent treatment strategy using the antibodies is seen far more effective but not without the undesired side effects. This treatment often creates immune deficiency which may produce serious problem making the patients more vulnerable toward any infectious diseases. So an extreme caution should be applied during its use by following the direction of a qualified physician. For aggressive treatment often a combination therapy is prescribed to halt the rapid progression and simultaneously relieving the pain. Surgery is authorized as a further option which mostly includes total joint replacement, tendon repair or else the joint fusion where surgical fusion of a joint is made for the realignment that often relieves the pain or inflammation.

CONCLUSION

Arthritis is a common disease and it expresses in several different forms. Among the major varieties OA and RA is seen much abundant whereas, the rests are considerably less prevalent. Concerning the pathophysiology, the disease falls into two main categories; one is mechanically driven and thus possibly arises due to wear and tear of the cartilage tissue as being the initiator which afterward creates serious inflammation inflicting a major problem at the joint. Whereas the other one, RA starts by the inherent autoimmune disorder. OA is seen to be the most prevalent. The underlying cause behind fragility of cartilage tissue in case of OA could be due to multiple reasons; uncontrolled calcification arises from the hypertrophic chondrocytes either due to aging or by some unknown means. In brief, the cells undergo apoptosis releasing the MVs and ECM cleaving enzymes that break down collagens and PGs enhancing the calcification process. Owing to the breakdown of PGs, the synovial fluid within cartilage tissue loses its lubricating nature exerting abrasive rubbing action to the bones within the joint. As a result, joint loses the flexibility or mobility and simultaneously adding discomfort bringing inflammation, pain and swelling. Whereas in case of RA, body's own immune system attacks the cartilage tissue destroying it relentlessly that eventually brings immobility while inducing also the bone-erosion. No significant proof relating to any genetic pre-disposition is ever identified in case of OA. In case of RA there are some evidences which can be cited as per its genetic support.

For treating the OA, anti-inflammatory and pain killer medications are often prescribed at higher doses. Surgery is also recommended as an

ultimate option. In case of RA or other auto-immune arthritis besides relief by the pain-killers or anti-inflammatory medicines, the antibody therapy is now successfully introduced. In that course, the monoclonal antibodies raised against a peptide epitope following the sequence of docking region of TNF-α or its receptor TNF-α-R are used. Notably, by neutralizing the cytokine's action can efficiently arrest the progress of RA.

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