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Oxidative Stress and Role of Antioxidant in Osteoarthritis & Rheumatoid Arthritis: A Review Article

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Abstract:
Arthritis is a generic term used for any of over hundred diseases of the joints which are accompanied by pain, stiffness and swelling. Many individual get crippled by arthritis, Arthritis thus refers to the pain and inflammation of the joints. The two most common and best known types of arthritis are Osteoarthritis, a wearing away of the cushioning cartilage in the joints: and Rheumatoid arthritis, an autoimmune disease that causes painful and often disabling joint inflammations. Free radicals and oxidants play a dual role as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. They are produced either from normal cell metabolism in situ or from external sources (pollution, cigarette smoke, radiation, medication). When an overload of free radicals cannot gradually be destroyed, their accumulation in the body generates a phenomenon called oxidative stress. This process plays a major part in the development of chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, arthritis, cardiovascular and neurodegenerative diseases. This review article shows the relation between oxidative stress and role of antioxidant in osteoarthritis and rheumatoid arthritis.

Keywords: *Arthritis; osteoarthritis; rheumatoid arthritis; oxidative stress; antioxidant; reactive oxygen species*

1. Introduction

Rheumatoid arthritis (RA) is a chronic syndrome of unknown etiology and is characterized by non-specific inflammation of the peripheral joints with swelling, morning stiffness, destruction of articular tissues and joint deformities. It affects nearly 1% of the population worldwide [1]. Studies have indicated that the development of RA is partly related to the excess production of reactive oxygen species and a lowered ability to remove oxidative stress [2-3]. A recent study indicated that pro- inflammatory cytokines such as IL- 1β and TNF- α are involved in the formation of toxic peroxynitrite by increasing the activity of nitric oxide synthase.

According to Muller- Lander et al.2005 & Sommer et al. 2005 Rheumatoid arthritis (RA) is a complex systemic disease and the most common inflammatory arthritis, affecting from 0.5 to 1% of the general population worldwide. Despite intensive work, only modest progress has been achieved in determining the cause of RA. The mediators of inflammation, cytokines, growth factors, chemokines, adhesion molecules and matrix metalloproteins have been carefully defined. These products attract and activate cells from the peripheral blood and evoke proliferation and activation of synoviocytes. Proteases can subsequently lead to behavior resembling a localized tumor, which invades and destroys articular cartilage, subchondral bone, tendons and ligaments [4-5].

Osteoarthritis (OA) results from the pathological imbalance of degradative and reparative process [Abramson and Krasnokutsky 2006] [6].OA the entire joint structure are affected. The cartilage, synovium, and bone can call be major sites for production of cytokines, growth factors, chemokines, and mediators, all classically associated with inflammation, which eventually promote progressive joint destruction [Pelletier et al. 2001; Loeser 2006] [7-8].

OA is commonly described as a non - inflammatory disease in order to distinguish it from RA [Benito et al. 2005] [9]. However in OA, the synovial compartment is also regarded as important since synovial proliferation and inflammatory changes are reported in some patients undergoing acute episodes of synovitis (Ayral et al. 2005) [10]. Despite this, it is still unclear whether inflammation is a feature of all patients with OA at some stage of their disease (Bonnet and Walsh 2005][11].

Osteoarthritis (OA, also known as degenerative arthritis, degenerative joint disease), is a clinical syndrome in which low-grade inflammation results in pain in the joints, caused by abnormal wearing of the cartilage that covers and acts as a cushion inside joints and destruction or decrease of synovial fluid that lubricates those joints. As the bone surfaces become less well protected by cartilage, the patient experiences pain upon weight bearing, including walking and standing. Due to decreased movement because of the pain,

regional muscles may atrophy, and ligaments may become more lax. [Conaghan, et.al; 2008**]** OA is the most common form of arthritis. [Conaghan, et.al; 2008**].** [12]

The term oxidative stress refers to the situation of a serious imbalance between production of reactive oxygen species/ reactive nitrogen species (ROS/RNS) and antioxidant defense. Attack of ROS upon proteins produces carbonyls as a marker of oxidative protein damage. It is based on the fact that several ROS attack amino acid residues in proteins to produce products with carbonyl content (CC) is actually the most general indicator of Peroxidation intensity and it has been observed in several diseases including Alzheimer's disease, diabetes, inflammatory bowel disease and arthritis [Renke et al. 2000; Dalle- Donne et al. 2003][13-14].

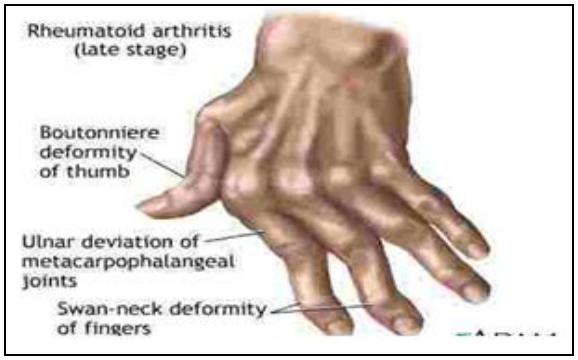
Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that most commonly causes inflammation and tissue damage in joints (arthritis) and tendons sheath, together with anemia. It can also produce diffuse inflammation in the lungs, pericardium, pleura, and the sclera of the eye, and also nodular lesions, most common in subcutaneous tissue under the skin. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility. It is diagnosed chiefly on symptoms and signs, but also with blood tests (especially a test called rheumatoid factor) and x-rays. Diagnosis and long-term management are typically performed by a rheumatologist an expert in the diseases of joints and connective tissues.

Various treatments are available. Non- pharmacological treatment includes physical therapy and occupational therapy. Analgesia (pain-killers) and anti- inflammatory drugs. As well as steroids, are used to suppress the symptoms, while disease – modifying antirheumatic drugs (DMARDS) are often required to inhibit or halt the underlying immune process and prevent long term damage[15].

Rheumatoid arthritis primarily affects joints problems involving other organs of the body are known to occur. Extra – articular manifestations other than anemia (which is very common) are clinically evident in about 15-25% of individuals with rheumatoid arthritis [16].

2. Joints of Rheumatoid Arthritis

The arthritis of rheumatoid arthritis is due to synovitis, which is inflammation of the synovial membrane that lines joints and tendon sheaths. Joint becomes swollen, tender and warm, and stiffness prevents their use. With time, RA nearly always affects multiple joints (it is a polyarthritis). Most commonly, small joints of the hands, feet and cervical spine are affected but larger joints like the shoulder and knee also be involved, differing per individual. Synovitis can lead of movement and erosion of the joint surface, causing deformity and loss of function.

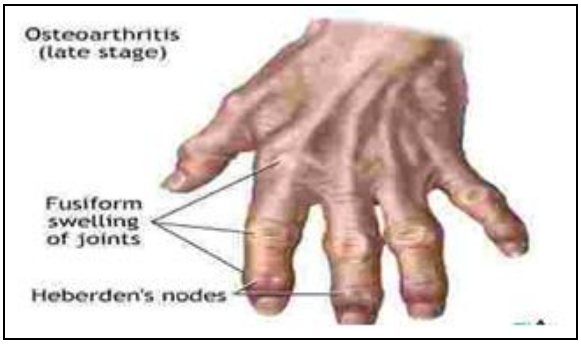


Inflammation in the joints manifest itself as a 'doughy' swelling, causing pain and tenderness to palpation and movement, a sensation of localized warmth, and restricted movement. Increased stiffness upon waking is often prominent features and may last for more than one hour. These sign help distinguish rheumatoid from non- inflammatory problems of the joint, often referred to as osteoarthritis or "wear and tear" arthritis. In RA, the joints are often affected in a fairly symmetrical fashion although this is not specific and the initial presentation may be asymmetrical [16].

Osteoarthritis (OA) is characterized by a breakdown of the extracellular matrix (ECM) of articular cartilage in the affected joints. The pathogenesis of OA involves multiple etiologies, including mechanical, genetic and biochemical factors. However, the precise signaling pathways in the degradation of articular cartilage ECM and development of OA are still not fully understood. Several studies have demonstrated the involvement of cytokines, such as IL-1 and IL-6, or tumour necrosis factor (TNF-α), in addition to proteases, such as matrix metalloproteases (MMPs) in the initiation and progression of articular cartilage destruction[17-18].

3. Epidemiology of Osteoarthritis

Osteoarthritis is caused by aberrant local mechanical factors acting within the context of systemic susceptibility. Systemic factors that increase the vulnerability of the joint to osteoarthritis include increasing age, female, sex and possibly nutritional deficiencies.



While epidemiological studies have shown a major genetic component to risk that is probably polygenic, the genes responsible have not yet been identified [19]. In people at risk, local mechanical factors such as misalignment, muscle weakness, or alterations in the structural integrity of the joint environment. (Such as meniscal damage) facilitate the progression of the disease. Loading can also be affected by obesity and joint injury, both of which can increase the likelihood of developing osteoarthritis or experiencing its progression.

3.1. Diagnosis of Osteoarthritis

Typically osteoarthritis presents as joint pain during a one year period, a quarter people aged > 55 have an episode of persistent knee pain, of whom about one in six consultants their general practitioner about it[20]. About half of these have radiographic knee osteoarthritis. Many of the remainder also probably has disease as yet undetectable on plain radiography or another source of knee pain such as pes anserine burstits or iliotibial syndrome.

The joint pain of osteoarthritis is typically described as exacerbated by activity and relieved by rest. In more advanced disease it is painful at rest and at night. The source of pain is not particularly well understood and is best framed in a biopsychosocial frame work [21].Of the local events in the joint, loss of cartilage probably does not contribute directly to pain as it is aneural . In contrast, the subchondral bone periosteum, synovium, and joint capsule are all richly innervated and could be the source of nociceptive stimuli in osteoarthritis.

3.2. Path Physiology of Osteoarthritis

Pathology of OA starts from fibrillation and ends at sclerosis.

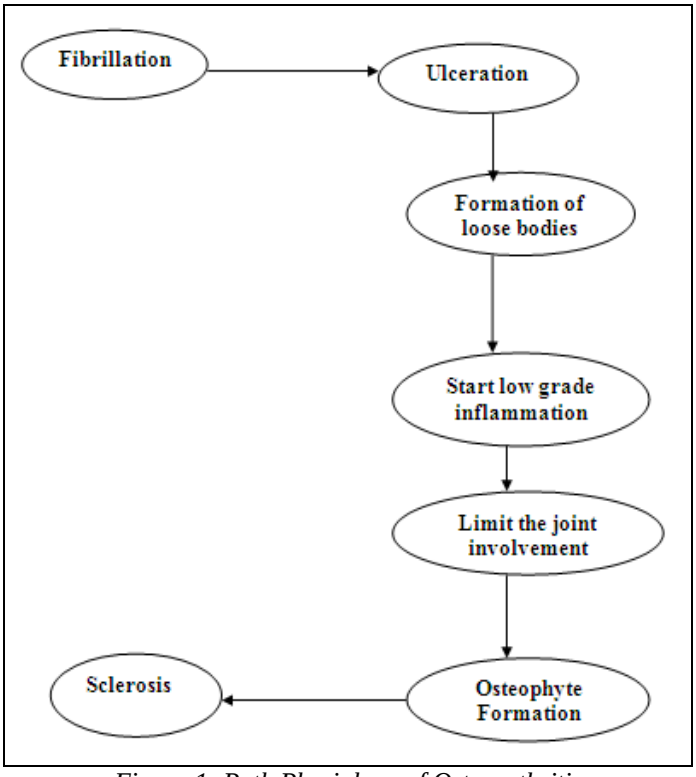


Figure 1: Path Physiology of Osteoarthritis

4. Oxidative Stress in Arthritis

Free radicals and oxidants play a dual role as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. They are produced either from normal cell metabolism in situ or from external sources (pollution, cigarette smoke, radiation, medication). When an overload of free radicals cannot gradually be destroyed, their accumulation in the body generates a phenomenon called oxidative stress. This process plays a major part in the development of chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, arthritis, cardiovascular and neurodegenerative diseases [Lien et al., 2008] [22]. The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/ or supplements. Endogenous and exogenous antioxidants act as "free radical scavengers" by preventing and repairing damages caused by ROS and RNS, therefore can enhance the immune defense and lower the risk of cancer and degenerative diseases [Valko M et al.,2006, Chatterjee et al.,2007] [23-27].

4.1. Characteristics of Free Radicals and Oxidants

ROS and RNS are the terms collectively describing free radicals and other non-radical reactive derivatives also called oxidants. Radicals are less stable than non- radical species, although their reactivity is generally stronger.

A molecule with one or more unpaired electrons in its outer shell called a free radical [Halliwell B et al.2007, Droge W.2002] [28-32]. Free radicals are formed from molecules via the breakage of a chemical bond such that each fragment keeps one electron, by cleavage of a radical to give another radical and, also via redox reactions [28-29]. Free radical include hydroxyl radical ($OH^{\bullet}$), superoxide ($O_2^{\bullet}$), nitric oxide ($NO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$), peroxyl (ROO•) and lipid peroxyl(LOO•). Also, hydrogen peroxide (H_2O_2), ozone (O_3), lipid peroxide (LOOH), are not free radicals and generally called oxidants, but can easily lead to free radical reactions in living organisms [33].

Biologically free radicals are thus highly unstable molecules that have electrons available to react with various organic substrates such as lipids, proteins, DNA.

4.2. Generation of Free Radicals and Oxidants

Formation of ROS and RNS can occur in the cells by two ways: enzymatic and non-enzymatic reactions. Enzymatic reactions generating free radicals includes those involved in the respiratory chain, the phagocytosis, the prostaglandins synthesis and the cytochrome P450 system [28-36]. For example, the Superoxide anion radical ($O_2^{\bullet -}$) is generated via several oxidase systems such as NADPH oxidase, xanthine oxidase, peroxidases. Once formed, it participates in several cellular yielding various ROS and RNS such as hydrogen peroxide, hydroxyl radical (OH•), peroxynitrite ($ONOO^-$), hypochlorus acid (HOCl), etc. H_2O_2 (non radical) is produced by the action of several oxidase enzymes, including aminoacid oxidase and xanthine oxidase. The last one catalyses the oxidation of hypoxanthine to xanthine, and of xanthine to uric acid. Hydroxyl radical (OH•), the most reactive of $O_2^{\bullet -}$ free radical in vivo, is formed by the reaction of $O_2^{\bullet -}$ with H_2O_2 in the presence of Fe^{2+} Cu^{+}. This reaction is known as the Fenton reaction[30-35].

Free radicals can be produced from non-enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing radiations. The nonenzymatic process can also occur during oxidative phosphorylation in the mitochondria [31, 32, 35].

4.3. Beneficial Activities of free Radicals and Oxidants

Low concentrations of, ROS and RNS are necessary for the maturation process of cellular structures and can act as weapons for the host defense system. Indeed, phagocytes (neutrophils, macrophases, and monocytes) release free radicals to destroy invading pathogenic microbes as part of the body's defense mechanism against disease [32- 36].

4.4. Deleterious Activities of Free Radical and Oxidants

When produced in excess, free radical and oxidants generate a phenomenon called oxidative stress, a deleterious process that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins, and deoxyribonucleic acid (DNA) (36-26).

Oxidative damage to DNA leads to the formation of different oxidative DNA lesions which can cause mutations. The body has several mechanisms to counteract these attacks by using DNA repair enzymes and/ or antioxidants (34-36). If not regulated properly, oxidative stress can induce a variety of chronic and degenerative diseases as well as the aging process and some acute pathologies (trauma, stroke).

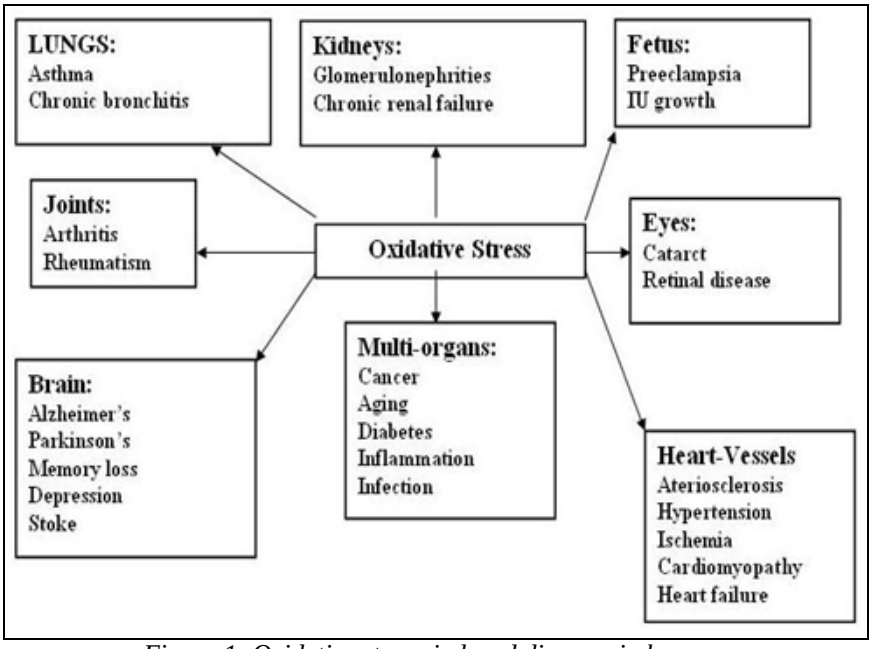


Figure 1: Oxidative stress-induced diseases in humans

4.5. Rheumatoid arthritis and oxidative stress

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation of the joints and tissue around the joints with infiltration of macrophages and activated T cells [31-38-39]. The pathogenesis of this disease is due to the generation of ROS and RNS at the site of inflammation. Oxidative damage and inflammation in various rheumatic diseases were proved by increased levels of isoprostanes and prostaglandins in serum and synovial fluid compared to control[39].

4.6. Osteoarthritis and oxidative stress

Osteoarthritis is a multifactorial process in which mechanical factors have a control role and is characterized by changes in structure and function of the whole joint.[40] Production of reactive oxygen species (ROS) generally is the result of tissue damage, and, in turn, causes tissue damage associated with osteoarthritis (OA) [Sowers, 2001][41]While epidemiological studies are complex and probably require further validated method development, expert do agree that ROS plays a key role in the degradation of cartilage, a key factor in the etiology of OA [Basu et al., 2001].[42] Elderly and aging populations, because of lower socioeconomic status, reduced nutritional intake, and lowered ability to ingest, adsorb and digest foods, generally take in reduced levels of antioxidants [Meyadani 2001] [43]. Poor intake of antioxidants, in cojunction with oxidative stress, has been associated with chronic disease states in the elderly [Miquel 2001].[44]

4.7. Antioxidant Protection for the joints

The generation of free radicals is increasingly being implicated in both cartilage aging and pathogenesis of OA [45-47]. In the joints chondrocytes are potent sources of reactive oxygen species, which cause degradation of joint cartilage matrix components such as proteoglycans and collagen, as well as synovial fluid.(47) The body defense itself against free radical damage with an integrated antioxidant defense system that utilizes antioxidants produced naturally within the body, such as superoxide dismutase, and from dietary antioxidants such as vitamin C and E.[47] These antioxidant can prevent matrix degradation and therefore may have a preventive or therapeutic value in OA .[45-46]

4.8. Vitamin E

Free radicals predominantly react with the polyunsaturated fatty acids that compose the lipid portion of cell membranes, leading to the eventual destruction of cell. One single free radical can destroy an entire membrane through a self-propagating chain reaction. Vitamin E, which is an important fat-soluble antioxidant, provides chain breaking free radical protection. Human studies shown that vitamin E is effective in reducing symptoms of OA [47-48]. While the mechanism of action of vitamin E has not fully elucidated, recent in vitro studies have shown that vitamin E, at physiological concentrations, significantly reduces cartilage matrix degradation caused by chondrocyte-derived free radical.[45-46]

4.9. Vitamin C

Vitamin C, or ascorbic acid, is required for the synthesis of collagen, an important structural component of joint cartilage. Ascorbic acid acts as a specific inducer of the collagen pathway, with a deficiency in vitamin C associated with poor collagen formation.[49-50] Vitamin C also functions as a very important water-soluble antioxidant and is capable of regenerating other antioxidants, especially

vitamin E.[47,51] In a study of participants in the Framingham Osteoarthritis Cohort Study, a higher intake of vitamin C was associated with a 3-fold reduction in risk of knee OA progression and a reduced risk of cartilage loss.[47]

4.10. Endogenous Antioxidant Enzyme

Superoxide dismutase (SOD) is an endogenous antioxidant enzyme that interferes with free radical generation in the initiation phase. There are two forms of SOD: copper-zinc SOD (Cu-Zn-SOD) is found in the cytoplasm, and manganese SOD (Mn-SOD) is found in mitochondria. SOD protects tissues by converting damaging Superoxide free radicals into hydrogen peroxide, which is in turn reduced to water and oxygen by peroxidases glutathione and catalase enzyme.[52] An adequate dietary supply of copper, zinc, and manganese is required for SOD enzymes to function. Research suggests that raising the intake of minerals needed for SOD induction may improve SOD activity.[53-54]

In osteoarthritis and rheumatoid arthritis, there is a focal loss of cartilage resulting from increased activity of catabolic pathways. This catabolic activity is stimulated, for the most part, by pro - inflammatory cytokines, like interleukin-1 and tumor necrosis factor alpha. In addition, reactive nitrogen and oxygen intermediates are involved in the extracellular- matrix-degrading activity and may also be responsible for the cartilage damage occurring in osteoarthritis and rheumatoid arthritis. [Mazzetti et al] [55]. Evaluated the oxidative stress related to reactive nitrogen and oxygen intermediates in osteoarthritis and rheumatoid arthritis patients. The results of this study suggested that nitric oxide plays a major role in altering chondrocyte (cartilage cell) function in osteoarthritis, while the harmful effects of radical oxygen intermediates are more evident in the chondriocytes from patients with rheumatoid arthritis. All of this comes from an imbalance in the ratio of oxidants to antioxidants.

[Evans and Halliwell][56] state that the damaging oxidative species (reactive oxygen, nitrogen and others) arise as by-products of metabolism and as physiological mediators and signaling molecules. The levels of these oxidative intermediates are held in check by the antioxidant defense system. The components of this defense system are micronutrients, like vitamin C and E, or are dependent on dietary micronutrients (e.g. Cu/ Zn and Mn Superoxide dismutase). The antioxidant defense is a coordinated system in which deficiency of the others. A deficiency in these micronutrients leads to oxidative stress, which leaves body tissues open to the damaging effects of the oxidative intermediates seen in arthritics.

[Kuo S et al] [57] reported that the copper, zinc and manganese are key components of the two major Superoxide dismutase enzymes which have been shown to fight against the reactive intermediaries that are linked to the joint damage in arthritis. Mitochondrial manganese Superoxide dismutase (Mn-SOD) is the primary cellular defense against damaging Superoxide radicals generated by aerobic metabolism and as a consequence of inflammatory disease. Elevated levels of Mn-SOD provide potent cytoprotective advantage during acute arthritic inflammation.

ROS is implicated in the pathophysiology of a number of common age related condition.[58]OA similarly can be regarded as a prototypical age related degenerative disease. There is evidence that cells within the joint produces ROS, and that oxidative damage is physiologically important.[59] [Surapaneni et al][60] assessed oxidative stress and antioxidant status in patients with osteoarthritis. Levels of erythrocyte lipid peroxidation products, GSH, ascorbic acid, plasma vitamin E; and activities of antioxidant enzymes were measured in patients with osteoarthritis. The study suggests higher oxygen-free radical production evidenced by increased MDA and decreased GSH, ascorbic acid, vitamin E and catalase activity support to the oxidative stress in osteoarthritis. The increased activities of antioxidant enzymes may be a compensatory regulation in response to increased oxidative stress. [60] Micronutrients might mediate the osteoarthritis process by blocking oxidative damage. Nitric oxide and reactive oxygen species inhibit collagen and proteoglycan synthesis, activated matrix metalloproteinase, increase the susceptibility of cartilage to injury by other oxidant, and induce apotosis.

Schwartz and Adamy reported a decreased level of active proteinase in the presence of ascorbic acid and found further that sulphated proteoglycans biosynthesis; a presumed measure of repair was increased in the cartilage in the presence of ascorbic acid. [61] [Manson et al] [62] suggested ascorbic acid stimulates collagen synthesis and modestly stimulates collagen synthesis and modestly stimulates synthesis of aggrecan (a proteoglycan present in articular cartilage). Framingham epidemiological study found a threefold reduction in risk of OA progression for both the middle and highest tertiles of vitamin C intake and an inverse association between vitamin C intake and cartilage loss.[63]

[Tiku et al][64] showed that when chondrocytes were submitted to an oxidative burst, vit E reduced the catabolism of collagen by preventing the protein oxidation mediated by aldehydic down products of lipid peroxidation. Epidemiological studies examining the role of antioxidants, specifically tocopherols, in human osteoarthritis are few. Several methodologically limited clinical trials have suggested that vitamin E supplementation might be superior to placebo and equal in effectiveness to anti inflammatory medication in relieving osteoarthritic symptoms, but other studies failed to show an effect.[65-69]

ROS can cause oxidative stress- major cellular damage produced as a result of chain reactions leading to a disruption of macromolecular structure. The unsaturated fatty acid components of the cell wall are a major target, easily reacting with ROS to accept an extra electron which induce covalent interaction between neighboring molecule and causing severe distruption to membrane function. This aspect of ROS activity is readily quantifiable by the measurement of lipid peroxidation products such as 4-hydroxynoneal and malondialdehyde. The latter can then react with lysine residues in proteins to produce immunogenic molecules which can exacerbate inflammation. 4- Hydroxynoneal can also directly suppress mitochondrial respiration [Picklo et al, 1999] [70] a monoamine transporter function [Morel & Baroiki, 1998] [71] both of which may further compromise cellular viability.

ROS may also damage nucleic acid structure, compromising cell survival directly and potentially modifying gene expression, leading to disorders of cell proliferation. The oxidation of thiols and the formation of carbonyl groups on proteins can lead to widespread deterioration in cell viability, with less of receptor, enzyme and transporter functions [Brown-Galatola & Hall, 1992].[72]

Nitric oxide the reaction of nitric oxide (NO) with Superoxide generates peroxynitrite [Beckman et al. 1994][73] which, under the acid conditions often found in regions of inflammation and ischemia, yields the hydroxyl radical $OH^{\bullet}$, the most highly reactive and toxic of the ROS. The study of experimental arthritis is animals has confirmed as increased activity of inducible NO synthetase (: NOS) [Mc Cartney- Francis et al 1993: Sakuri et al. 1995] [74-75] with a raised production of NO [Cannon et al.1996 Grabowski et al. 1996a: Yang et al. 1998].[76-77-78] the inhibition of NOS can suppress disease activity in parallel with a fall in plasma nitrotyrosine or nitrite [Mc Cartney Francis et al. 1993; Kaur & Halliwell, 1994; Conner et al. 1995; Cannon et al. 1996; Santos et al 1997; Stichtenoth & Frolich, 1998][72,79,80,76,81,82]. There is an increased activity of NOS in MRL- 1pr/1pr mice (a strain which shows pronounced lympo proliferative activity and develops severe autoimmune disorders) and enzyme inhibition reduces the degree of arthritis [Weinberg, 1998][83]

A number of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor – α (TNF α) appear to be associated with joint inflammation and their secretion can be suppressed by anti- inflammatory agents such as steroids [Barners & Adcock, 1993].[84] The plasma levels of TNF-α^ correlated directly with the ability of phagocytes to generate Superoxide [Miesel et al. 1996 a, b] [85] although there is no correlation with C-reactive protein. The removal of TNF- α by dialysis diminished superoxide generation to control levels in RA patients implying an important intermediate role for the cytokine. Both TNF- α and interferon – γ increase the secretion of hydrogen peroxide by rabbit chondrocytes [Tiku et al. 1996] [86]

Bone metabolism in rat osteoblasts, fibroblasts and chondrocytes as well as explants or cultures of human cartilage from patients with RA or OA, combinations of cytokines including IL-1β TNF-α and interferon -γ induce NOS activity [Grabowski et al, 1996 b; Murell et al. 1996; Miyaska, 1997; Amin & Abramson, 1998].[87-90] The release of NO & PGE_2 OA patients was reduced by IL-1β receptor antagonist, suggesting an essential role of IL-1β in their synthesis [Attur et al.1998].[91] Since the soluble TNF-α receptor did not share this action; this cytokine would appear to be less crucial. The levels of serum NO correlate with the amounts of TNF-α and IL-1β as well as disease activity, especially joint stiffness [Ueki et al. 1996].[92]The increased levels of NO suppressed osteoblast activity, as measured by the amount of DNA synthesis, cell proliferation [Hukkanen et al. 1995. Ralston, 1997], [93-94] depressed chondrocyte function and promoted apoptosis [Amin & Abrason.1998]. (90)

α- Tocopherol is the most biologically important form of vitamin E. It scavenges free radicals before these can initiate a destructive chain reaction. Such 'chain-breaking' antioxidants are consumed in the process, although vitamin E may be regenerated by GSH and by ascorbic acid. Most cells contain enzymes which reduce dehydroascorbate back to ascorbate using either reduced NADH or GSH. Since dihydroascorbate is a very unstable molecule, however, there is an overall loss of ascorbate at sites of oxidative damage [Chaudiere & Ferrai-Iliou, 1999]. [95]

Vitamin C and E also have not antioxidant effects. Ascorbate stimulates procollagen secretion [Henderson et al 1991] [96] and vitamin C deficiency is associated with defective connective tissue. Vit C is needed for the Vit-C dependent enzyme lysyl- hydroxylase for the post translation hydroxylation of specific prolyl and lysyl residues in procallogen – action necessary for the stabilization of the mature collagen fibril [Dowling et al, 1990].[96] Vit C is also thought to be necessary for glycosaminoglycan synthesis [Merry et al, 1991].[97]

Vitamin E blocks arachidonic acid formation from phospholipids and inhibits lipoxygenase activity, resulting in a mild anti-inflammatory effect. Benefits from vitamin E treatment have been claimed from several small studies of human OA [Doumerg, 1969; Mc Alindon and Felson, 1997] [98,99] However combined supplementation with Vit C and Vit E is more immuno potentiating than alone in healthy adults [Jeng et al. 1996].[100]

Osteoarthritis is an age-associated disease to which patients may be predisposed by weaker cartilage and in which ROS have been implicated. Several small studies in humans have suggested benefits from Vit E treatment. In a 6 week, double blind, placebo-controlled trial of 400 mg of α-tocopherol in fifty six patients with OA, those treated with Vit E experienced greater improvement in every efficiency measure [Blankenhorn, 1986] [101] intra-articular administration of SOD (orgotein), a Superoxide radical has long been used to treat equine osteoarthropathy and also, with benefit, in placebo controlled clinical trials in human OA.

The use of copper and zinc for RA may be justified by the requirement of these metals for the cytoplasmic form of SOD (Cu/Zn-SOD). Intra-articular injections of SOD reduce joint inflammation. It has proposed that D-penicillamine could extert its therapeutic effects by forming a complex with copper which then acts as a SOD-mimetic [Aeseth et al. 1998].[102] D-penicillamine also scavenges hydrogen peroxide and hypochlorus acid and suppresses the stimulated release of ROS from human neutrophils. [Ledson et al.1992].[103]

An important study by [Li et al. 1996] [104] revealed that several fatty acids, including EPA, DHA, linoleic and linolenic acid could potentiate the action of TNF α in promoting generation of ROS by human neutrophils. Such as effect could result in the activation of compensatory antioxidant enzymes, but the result emphasizes the greater potential for fatty acid effects in inflammatory conditions compared with normal individuals.

Anemia often occurs in patients with rheumatoid arthritis, and its cause is often multifactorial. The effect of erythropoietin on such anemia is controversial, and evidence exists that cytokines may affect haemopoiesis, possibly by affecting sensitivity to erythropoietin. [105,106]

4.11. Impact of Inflammatory Cytokines

Development of anemia of chronic disease in patients with RA appears to be related to inflammatory cytokines, which cause joint inflammation and interfere with normal red blood cell formation and destruction.[107-110]

Patients with RA make erythropoietin in response to the inflammatory anemia, as expected. However, the response is blunted in these patients, with both inadequate production of erythropoietin and inadequate bone marrow responses compared to people with similar levels of anemia and no inflammation. (105) Animal studies suggest that increased levels of the inflammatory cytokines interleukin- 1 (IL-1) and tumor necrosis factor-∝ (TNF-∝) inhibit erythropoietin production and interfere with erythroid colony-forming units in the bone marrow.[107,111,112]

According to [Cengiz Beyan and Esin Beyan] [113] Anemia of chronic disease (ACD), one of the most common syndrome in medicine, is observed in patients with chronic infections, inflammatory and neoplastic disorder. All of the factors involved in the development of ACD can be distributed to effects of cytokines, including shortened red cell survival, blunted erythropoietin response to anemia, impaired erythroid colony formation in response to erythropoietin and abnormal mobilization of reticuloendothelial iron stores. Tumor Necrosis factor-α (TNF α), which is important for the pathophysiology of ACD, may act directly on bone marrow, erythroid precursors. Hepeidin is a liver made peptide, and its synthesis is greatly stimulated by inflammation. The plasma level of erythropoietin (EPO) in anemic patients suffering from inflammation is often low in relation to the blood hemoglobin concentration interleukin 1 and TNF α suppress EPO gene expression.

ACD is most effectively treated via approaches directed against the underlying cause. There are also some reports addressing that iron supplementation and iron chelation therapy may be useful. If this is not possible, supportive career is given through red cell transfusion or use of recombinant human EPO. Patients with inflammatory disorders showed remarkable hematologic response to recombinant EPO, although a significant change in rheumatologic picture was not seen. [114]

Substantial evidence indicates that inflammatory cytokines observe a crucial role in joint destruction and disease propagation in rheumatoid arthritis (RA).(115) Among these cytokines, tumor necrosis factor α (TNF-α) has been considered as the pivotal factor to induce and sustain tissue damage by activating the inflammatory mediate cascade, stimulating the mechanism of angiogenesis and up-regulating the vascular endothelial adhesiveness. Apart from its detection in the inflamed synovial fluid, TNF-α is also found in elevated levels in patients sera, and cytokine concentration has been shown to correlate with disease activity. 116 Furthermore, circumstantial evidence suggests that increased local TNF-α production in the bone marrow may be implicated in the pathogenesis of anemia of chronic disease (ACD) seen in up to 50% of patients with RA.[117]

4.12. Nutritional Status in Arthritis

Patients with RA are considered to be at nutritional risk for many reasons. One cause of poor nutritional status in this patient population is thought to be the result of the weight loss and cochexia linked to cytokines production.[118] In patients experiencing chronic inflammation, the production of cytokines such as interleukin -1 and tumor necrosis factor, increases resulting metabolic rate and protein breakdown. The patient then is faced with the challenge of increasing both calorie and protein intake to meet the nutritional requirements of the increased metabolic rate. This is frequently difficult secondary to the pain and swelling associated with RA which frequently makes food preparation and purchasing difficult for those who live alone or have limited resources.

The effect of arthritis medications that are frequently taken long-term may also compound these nutritional problems. One example of this is observed in patient's reciving methotrexate, where patients are frequently identified with folic acid deficiency. Additionally, prolonged dosing of other RA medications may be associated with conditions such as gastritis or peptic ulcer, frequently reducing a person desire to eat.

The most commonly observed vitamin and mineral deficiencies in patients with RA are folic acid, calcium, magnesium, zinc and selenium.[119] Although food is always the preferred source for vitamin and minerals, it may be essential to use supplementation to assist in counterbalancing the outlined deficiencies and improving nutritional status for patients with RA. Increased intake of antioxidants such as selenium and Vitamin E may decrease free-radical damage to join lining, which diminish swelling and pain. However, to date, there have been no human clinical trials that convincingly prove or disprove the efficacy of antioxidant use. Supplementation of calcium and vitamin D is also recommended to decrease the risk of osteoporosis that results from nutritional loss of these supplements, from menopause and from concurrent steroid therapy.

In some patients, specific foods have been shown to exacerbate the symptoms of RA. Avoiding these foods or food groups has been shown to have limited, short term benefits long term. Even though different forms of dietary modification have reportedly improved symptoms in some patients, people with RA may have spontaneous temporary remissions. Therefore, it is important to perform double blind, placebo controlled trials to differentiate diet effect from spontaneous remission. Diet elimination therapy is a method of determining food hypersensitivities with patients. Elimination diets avoid a specific food or groups of foods such as milk, meat or processed that is known to be prime allergy suspects. These foods are eliminated from the diet for a specific period of time. Foods are then gradually reintroduced one at a time, to determine whether any of them cause a reaction. intake of antioxidants has been shown to improve OA symptom [Mc Alindon et al 1996 a].[121] ROS has been shown to oxidatively convert amino acid to F_2 – isoprostanes, malondialdehyde (MDA) and 4- hydroxynoneal (HNE), which are elevated in OA patients and induce damage to cartilage [Basu et. al. 2001].[42]

Keeping in view the work of the above researchers, the present study was performed oxidative stress marker and non - enzymatic antioxidant status and antioxidant enzyme and some trace mineral levels in anemic osteoarthritis and rheumatoid arthritis patients.

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