Review article **J Indian Rheumatol Assoc 2004 : 12 : 139 - 142**

ANTIOXIDANTS AND RHEUMATOID ARTHRITIS

Annil Mahajan*, Vishal R Tandon

*Post Graduate Department of General Medicine and Pharmacology and Therapeutics, Govt Medical College, Jammu, Jammu and Kashmir , India

Abstract : Free radicals can cause tissue damage. In normal physiology the endogenous free radicals produced in the body are neutralised by endogenous antioxidants. In inflammatory disease like RA free radicals may perpetuate tissue damage . The review disscuss the possible role of antioxidants in the treatment of RA

Key Words : Free radical, reactive oxygen species, inflammatory arthritis, treatment

Free radical (FR) can be defined as a chemical species, an atom or a molecule that has one or more unpaired electrons in its valance shell and is capable of existing independently. Free radical contains an odd number of electrons which makes it unstable, short lived and highly reactive, therefore it react quickly with other compounds in order to capture the needed electron to gain stability. Generally, free radical attacks the nearest stable molecule "stealing" its electron. When the attacked molecule looses its electron, it becomes a free radical itself, beginning a chain reaction cascade resulting in disruption of a living cell[1,2].

Most common radical derivatives of oxygen like superoxide free radical anion ($O_2^{\cdot-}$), hydroxyl free radical ($OH^{\cdot}$), lipid peroxyl ($LO^{\cdot}$), lipid alkoxyl ($LOO^{\cdot}$) and lipid peroxide (LOOH) as well as non-radical derivatives such as hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$) are collectively known as reactive oxygen species (ROS)[2]. These free radicals/reactive oxygen species are produced mainly from two important sources[1,2] in the biological system i.e. cellular metabolism like mitochondrial electron transport chain, endoplasmic reticulum oxidation, NADPH oxidase, xanthine oxidase, prostaglandin synthesis, reduced riboflavin, nitric oxide synthetase, reperfusion injury, cytochrome P_{450}, activated neutrophils and phagocytic cells and environmental sources like drugs, pesticides, transition metals, tobacco smoke, alcohol, radiations and high temperature.

Free radical and ROS production in the animal cell is inevitable. Normally, there is an equilibrium between a free radical/reactive oxygen species formation and endogenous antioxidant defense mechanisms, but if this balance is disturbed, it can produce oxidative stress[2-4]. This state of oxidative stress can result in injury to all the important cellular components like proteins, DNA and membrane lipids which can cause cell death.

Antioxidants are the compounds of exogenous or endogenous in nature which either prevent the generation of toxic oxidants or intercept any that are generated and inactivate them and thereby block the propagation of chain reaction produced by these oxidants[5]. These can be classified as enzymatic antioxidants, superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, non-enzymatic antioxidants like (nutrient antioxidants) beta-carotene, alpha-tocopherol, ascorbic acid, bioflavonoids and (metabolic antioxidants) like glutathione, ceruloplasmin, albumin, bilirubin, ferritin, transferrin, uric acid and lactoferrin. In re-

Address for correspondence
Dr Annil Mahajan, Assistant Professor
Postgraduate Department of General medicine
Government Medical College, Jammu (J & K) 180001
Email: annil_mahajan@rediffmail.com

cent years increasing experimental and clinical data has provided compelling evidences for the involvement of FR/ROS in large number of pathophysiological states[1,2,6] including rheumatoid arthritis (RA)[7-12]. This has led to increased interest amongst the researchers globally to evaluate role of antioxidant therapy in RA. We had made an attempt to understand the role of reactive oxygen species in pathogenesis of rheumatoid arthritis and protection provided by antioxidant supplementation in RA in the present review article.

Reactive oxygen species hypothesis of rheumatoid arthritis:

It is well established now that free radicals/reactive oxygen species play an important role in inflammation[13]. Nitric oxide (NO) has a role in the regulation of vascular tone, contributing to cardinal signs of inflammation, superoxide free radical ($O_{2.}$-) in fibroblast proliferation and hydrogen peroxide (H2O2) in the activation of transcription factors such as NFkappa B, an important transcription factor controlling the transcription of a number of cytokine genes including IL-2 and TNF-α. Other control mechanisms which may be perturbed in inflammation include: the oxidative modification of low density lipoprotein, the oxidative inactivation of alpha-1-protease inhibitor, DNA damage, lipid peroxidation and heat shock protein ciated with the activation of neutorphil, NADPH oxidase and endothelial cell xanthine dehydrogenase, which contribute significantly to the inflammatory process[13].

Rheumatoid arthritis is a systemic disease characterized by progressive, erosive, and chronic polyarthritis. Cellular proliferation of the synoviocytes and neo-angiogenesis leads to formation of pannus which destroys the articular cartilage and the bone[14]. Recent studies[7-12] provide evidences for the involvement of FR/ROS in the pathogenesis of rheumatoid arthritis.

A recent study[7] indicated that increased oxidative stress and/or defective antioxidant status contribute to the pathology of rheumatoid arthritis. The study showed raised levels of Malondialdehyde and low levels of endogenous antioxidants in patients of rheumatoid arthritis. Plasma catalase had also been reported to be significantly lower in patients with RA[8]. Another study reported impaired glutathione reductase activity in synovial fluid in rheumatoid arthritis[9]. In active RA[10] and juvenile idiopathic arthritis[11], increased oxidative stress and decreased levels of antioxidants have been reported.

An epidemiological study[12] suggested that low selenium status may be a risk factor for rheumatoid factor-negative RA and low alpha-tocopherol status may be a risk factor for RA independently of rheumatoid factor status. Another study[15] suggested that ROS generation can be decreased via inhibition of an enzyme (thioredoxin reductase) by gold thioglucose in RA. Overall it is well evident that there is increased state of oxidative stress in RA, which proposes the use of antioxidant supplementation in such patients.

Antioxidant supplementation in RA:

In view of the recent animal studies strongly suggesting anti-inflammatory role of antioxidants like superoxide dismutase[16] and vitamin E[17] in experimentally induced arthritis, antioxidant therapy strategies have been proposed for the prevention and treatment of RA[18-24].

Vitamin E seems to uncouple joint inflammation and joint destruction in the transgenic KRN/NOD mouse model of RA, with a beneficial effect on joint destruction[18]. Therapeutic value of adding a high dose of vitamin E or an antioxidant combination to the treatment regimen of the rheumatoid disease suggested that the symptoms of arthritis were better controlled from

the first month and by the end of the second month better control of disease was achieved[19]. Furthermore, another study suggested that therapeutic co-administration of antioxidant along with conventional drugs to RA patients result in statistically significant increase in the post- treatment concentration of these antioxidants, decrease in the concentration of MDA along with improved symptoms[20]. Similarly antioxidants and few fatty acids have been suggested to ameliorate RA and related disorders[21]. In a randomized, controlled Mediterranean dietary intervention study[22] in patients with RA, it was observed that plasma levels of vitamin C, retinol and uric acid inversely correlated with variables related to disease activity. Thus proposing even dietary antioxidant interventions in patients of RA.

This fact was supported by other studies[23,24]. Another study suggested that proper dietary antioxidant nutrient intake may reduce FR generation and improve antioxidant status in RA patients[23]. In another recent study[24], intake of certain antioxidant micronutrients particularly beta-cryptoxanthine and supplemental zinc and possibly diet in fruits and cruciferous vegetables were suggested to have protective role against the development of RA.

Problems associated with antioxidant supplementation:

The biggest doubt, which antioxidants raises is that of suicidal oxidative stress, induced by certain antioxidants[25-27]. These antioxidants can act as pro-oxidants in certain conditions like presence of transition metals[25,26] or at high concentrations[27] and can cause the cell to undergo severe oxidative stress ultimately resulting in suicidal cell death. Hence, irrational and non-judicial use of antioxidants can also increase the risk of potential toxicity. In addition number of questions like appropriate timing of administration, dosage and duration of antioxidant therapy still need to be determined. As one of the study[28] pointed that different timing of administration, dose and duration of antioxidant vitamins have variable effects on serum markers of the study. Delivery at specific site of FR generation and to understand the riddle that FRs are cause or consequence of disease, still remains a challenge.

Present status of antioxidants in RA:

This review suggests a preventive and an adjuvant role of antioxidant supplementation or intake of natural dietary antioxidants in RA patients. However, therapeutic efficacy, dose, duration and appropriate timing of administration of antioxidant supplementation to derive best possible results or still not established. Therefore, there is need of conducting larger, adequately powered clinical trials in this direction to find out answers for all these unsolved questions.

References:

1. Cheeseman KH, Slater TF. An introduction to free radical biochemistry. In: Cheeseman KH, Slater TF, Editors. Free radical in medicine.New York: Churchill Livingstone; 1993. pp 481 – 93.
2. Mitchell RN, Cotran RS. Cell injury, adaptation, and death. In: Kumar V, Cotran RS, Robbins SL, Editors. Robbins. Basic Pathology. 7th ed. New Delhi: Harcourt (India) Pvt. Ltd. 2003. pp 3-33.
3. Murray RK, Granner DK, Mayes PA, Rodwell VW, Editors. Harper's biochemistry. New York: McGraw -Hill, 2000.
4. Sen CK. Oxygen toxicity and antioxidants: State of the art. Indian J Physiol pharmacol 1995; 39: 177 – 96.
5. Rangan U, Bulkley G B. Prospects for treatment of free radical-mediated tissue injury. In: Cheeseman KH, Slater TF, Editors. Free radicals in medicine. New York: Churchill. Livingstone; 1993. pp 700-18.
6. Pillai CK, Pillai KS. Antioxidants in health. Indian J Physiol Pharmacol 2002; 46: 1-5.
7. Karatas F, Ozates I, Canatan H, et al. Antioxidant status and lipid peroxidation in patients with

rheumatoid arthritis. Indian J Med Res 2003; 118: 178-181.
8. Kamanli A, Naziroglu M, Aydile K, et al. Plasma lipid peroxidation and antioxidant levels in patients with rheumatoid arthritis. Cell Biochem Funct 2004; 22: 53-57.
9. Bazzichi L, Ciompi ML, Betti L, et al. Impaired glutathione reductase activity and level of collogenase and elastase in synovial fluid in rheumatoid arthritis. Clin Exp Rheumatol 2002; 20: 761-766.
10. De Leo ME, Tranghese A, Passantino M, et al. Manganese superoxide dismutase glutathione peroxidase and total radical trapping antioxidation capacity in active rheumatoid arthritis. J Rheumatol 2002; 29: 2245-2246.
11. Gotia S, Popavici I, Hermeziu B. Antioxidant enzymes levels in children with juvenile rheumatoid arthritis. Rev Med Chir Soc Med Nat Iasi 2001; 105: 449-503.
12. Knekt P, Heliovaara M, Aho K, et al. Serum selenium, serum alpha-tocopherol and the risk of rheumatoid arthritis. Epidemiology 2002; 11: 402-405.
13. Windrow VR, Winyard PG, Morris CJ, et al. (Editors). Free radicals in inflammation: second messengers and mediators of tissue destruction. In: Cheeseman KH, Slater TF, editors. Free radicals in medicine. New York: Churchill. Living stone; 1993. pp 506-22
14. Edwards CRW, Bouchier IAD. (Editors). Davidson's Principles and Practice of Medicine. Chirchill Livingstone UK. 16th edition, 1994.
15. Kerimova AA, Atalay M, Yusifov Ey, et al. Antioxidant enzymes: Possible mechanism of gold compound treatment in rheumatoid arthritis. Pathophysiology 2002; 7: 209-213.
16. Salvemini D, Mazzon E, Dugo L, Serraino I, De Sarro A, Caputi AP, Cuzzocrea S. Ame lioration of Joint disease in a rat model of collogen induced arthritis by M40403, a superoxide dismutase mimitic. Arthritis Rheum 2001; 44: 2909-21.
17. Behaska AA, Wu D, Serafini, Meydani-SN. Mechanism of vitamin E inhibition of Cyclooxygenase activity in mocrophage from old mice: role of peroxynitrite. Free Radic Biol Med 2002; 32: 503-11.
18. Bandt MD, Grossin M, Driss F, et al. vitamin E uncouples joint destruction and clinical inflammation in a transgenic mouse model of rheumatoid arthritis. Arthritis Rheum 2002; 46: 522-532.
19. Helmy M, Shohayeb M, Helmy MH, et al. antioxidants as adjuvant therapy in rheumatoid disease. A preliminary study. Arzneimittelforschung 2001; 51: 293-298.
20. Jaswal S, Mehta HC, Sood AK, et al. Antioxidant status in rheumatoid arthritis and role of antioxidant therapy. Clin Chim Acta 2003; 338: 123-129.
21. Darlington LG, Stone TW. Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. Br J Nutr 2001; 85: 251-269.
22. Hagfors L, Leanderson P, Skoldstam L, et al. Antioxidant intake, plasma antioxidants an oxidative stress in a randomized, controlled, parallel, maditerranean dietary intervention study on patients with rheumatoid arthritis. Nutr J 2003; 30: 2: 5.
23. Bae Sc, Kim SJ, Sung MK, et al. Inadequate antioxidant nutrient intake and altered plasma antioxidant status of rheumatoid arthritis patients. J Am Coll Nutr 2003; 22: 311-315.
24. Cerhan JR, Sagg KG, Merlino, et al. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. Am J Epidemiol 2003; 157: 345-354.
25. Koshy h, Dwarkanath BS, Raj HG, et al. Suicidal by certain antioxidants. Indian J Experiment Biol 2003; 41: 1273-8.
26. Cao G, Sofic E, Prior RL. Antioxidant and proxidant behaviour of flavonoids structure activity relationship. Free Radic Biol Med 1997; 22: 749.
27. Offer T, Russo A, Samuni A. The prooxidative activity of SOD and nitroxide SOD mimes. FASEB J 2000; 14: 1215.
28. Carvoll MF, Schade DS. Timing of antioxidant vitamin ingestion alters postprandial proatherogenic serum markers. Circulation 2003; 108: 24-31.