East African Scholars Journal of Medicine and Surgery
Abbreviated Key Title: EAS J Med Surg
ISSN: 2663-1857 (Print) & ISSN: 2663-7332 (Online)
Published By East African Scholars Publisher, Kenya

Volume-2 | Issue-7| Jul-2020 | DOI: 10.36349/EASJMS.2020.v02i07.002

OPEN ACCESS

Research Article

Soothing Effect of Antioxidants in Rheumatoid Arthritis

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Article History
Received: 01.07.2020
Accepted: 19.07.2020
Published: 31.07.2020

Journal homepage:
http://www.easpublisher.com/easms/

Quick Response Code

Abstract: Recent progress regarding the potential benefit of dietary antioxidants in the treatment of chronic diseases with a special focus on immune system and neurodegenerative disorders will be discussed here. It is well established that reactive oxygen species (ROS) play an important role in the etiology of numerous diseases, such as atherosclerosis, diabetes and cancer. Among the physiological defense system of the cell, the relevance of antioxidant molecules, such as glutathione and vitamins is quite well established. Recently, the interest of researchers has, for example, been conveyed on antioxidant enzyme systems, such as the heme oxygenase/biliverdin reductase system, which appears modulated by dietary antioxidant molecules, including polyphenols and beta-carotene. These systems possibly counteract oxidative damage very efficiently and finally modulate the activity of oxidative phenomena occurring, for instance, during pathophysiological processes. Although evidence shows that antioxidant treatment results in cytoprotection, the potential clinical benefit deriving from both nutritional and supplemental antioxidants is still under wide debate. In this line, the inappropriate assumption of some lipophylic vitamins has been associated with increased incidence of cancer rather than with beneficial effects. ***Background:*** This study aims to investigate the effect of antioxidants supplement on clinical outcomes and antioxidant parameters in rheumatoid arthritis (RA). ***Methods:*** The pre-post study was conducted on 40 female patients with RA in 12 weeks that taken daily one Selenplus capsule contained 50 µg selenium, 8 mg zinc, 400 µg vitamin A, 125 mg vitamin C, and 40 mg vitamin E. About 5 mL venous blood sample was taken from all participants and disease activity score (DAS) was determined by DAS-28 formula and high-sensitive C-reactive protein (hs-CRP). Glutathione peroxidase (GPX) and superoxide dismutase (SOD) were measured by spectrophotometric kit and catalase (CAT) was measured by Abei method. Total antioxidant capacity (TAC) was determined by spectrophotometric kit. Distribution of the variables was assessed using histogram with normal curve as well as Kolmogorov-Smirnov test and data were analyzed with paired *t*-test for differences between pre-post data using SPSS software version 13.5.***Conclusions:*** Our findings showed that antioxidants may improve disease activity significantly, but it did not affect the number of painful and swollen joints and increased erythrocyte antioxidant levels. Antioxidants may be useful for controlling of clinical outcomes and oxidative stress in RA.

Keywords Antioxidants, dietary supplements, nutrition, oxidative stress, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that about 0.5%-1% of world population are affected by its complaints (Gill, T. M., & Feinstein, A. R. 1994). The prevalence of RA in females is 3 times higher than males. The RA affects blood vessels, heart, lungs, muscles, and joints, resulting in bone deformity and osteoporosis. Several studies have reported that oxidative stress and production of oxygen-free radicals have important role in RA development (Karatas, F. *et al.*, 2003; & Pattison, D. J. *et al.*, 2004) and epidemiologic studies have revealed a reverse relationship between dietary intake of antioxidants and RA incidence (Rennie, K. L. *et al.*, 2003; & El-barbary, A. M. *et al.*, 2011) and due to reduction of intake and absorption of dietary

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antioxidants in RA patients, the levels of blood antioxidants are decreased too. The antioxidants supplements such as vitamin E (Helmy, M. *et al.,* 2001; & Karlson, E. W. *et al.,* 2008), vitamin C (Pattison, D. J. *et al.,* 2004; & Meki, A. R. M. *et al.,* 2009), and selenium[10,11] may control the disturbance of lipid peroxidation and loss of antioxidants markers in patients with RA. Vitamin E can interact with nitric oxide and may trigger the gene expression of catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD) enzymes (Gill, T. M., & Feinstein, A. R. 1994), vitamin C may demolish the peroxides of macrophage activities, zinc may strengthen the immune system (Karatas, F. *et al.,* 2003) and selenium has an important role as a cofactor of GPX enzyme in reduction of oxidative stress. In past 30 years, controlled trials have conducted to compare the effect of dietary antioxidants and antioxidant-rich diets in controlling of RA clinical outcomes (Rennie, K. L. *et al.,* 2003); however, they could not find a clear statement about antioxidants in RA prevention and treatment due to difference in study period, dose, and different types of antioxidants (Westaway, M. S. e al 2008). Regarding to integrity of antioxidant defense system and few clinical studies on combined antioxidant supplements in RA, the aim of this study is to evaluate the effect of combined antioxidant supplements as daily oral capsule on clinical outcomes and antioxidant parameters in female patients with RA for 3 months.

ANTIOXIDANTS IN IMMUNE SYSTEM

During the inflammatory process, activation of phagocytes through the interaction of proinflammatory mediators, or bacterial products with specific receptors results in the assembly of the multicomponent flavoprotein NADPH oxidase which catalyzes the production of large quantities of the superoxide anion radical (O_2^-) (Gill, T. M., & Feinstein, A. R. 1994). In addition to classical reactive oxygen metabolites, activated neutrophils and monocytes release the hemoprotein myeloperoxidase (MPO) into the extracellular space, where it catalyzes the oxidation of Cl^- by H_2O_2 to yield hypochlorous acid (HClO) (Westaway, M. S. *et al.,* 2008). HClO is a non-specific oxidizing and chlorinating agent that reacts rapidly with a variety of biological compounds, such as sulphydryls, polyunsatured fatty acids, DNA, pyridine nucleotides, aliphatic and aromatic aminoacids and nitrogen-containing compounds (Karatas, F. *et al.,* 2003; Pattison, D. J. *et al.,* 2004; & Rennie, K. L. *et al.,* 2003). Moreover, apart from their direct toxic effects, neutrophil-derived oxidants may promote tissue injury indirectly by altering the protease/antiprotease equilibrium that normally exists within the intestinal interstitium. The oxidative inactivation of important protease inhibitors, coupled to the oxidant-mediated activation of latent proteases, creates a favorable environment for neutrophils that allows degradation of the interstitial matrix through elastases, collagenases and gelatinases, as well as injury to epithelial cells (El-barbary, A. M. *et al.,* 2011; & Helmy, M. *et al.,* 2001). However, not only immune cell produce ROS necessary for the microbicidal activity, but they are also sensitive to external ROS, due to their high polyunsaturated fatty acids (PUFA) content. Immune cells are atypical, as compared with other somatic cells, in that they contain high levels of antioxidant vitamins, presumably providing protection against lipid peroxidation and immunosuppression, both of which are well known risks posed by high PUFA content (Karlson, E. W. *et al.,* 2008). The reactivity of immune cells to exogenous ROS has been shown to be age-dependent. In fact, lymphocytes from elderly individuals appear to be more sensitive to exposure to hydrogen peroxide than those from young adults (Meki, A. R. M. *et al.,* 2009). Moreover, it has been demonstrated that a micronutrient deficiency can be the cause of suppression of immune function affecting both innate T-cell-mediated immune response and adaptive antibody response, thus altering the balanced host response. Therefore, an adequate intake of vitamins and antioxidant elements seems to be essential for an efficient function of the immune system. Micronutrient deficiency occurs in various conditions, such as eating disorders, tobacco smokers, chronic diseases, aging. During aging, changes in the immune system are frequent and associated with increased susceptibility to infections. Antioxidant vitamins and trace elements contribute to maintain an effective immune response (Pattison, D. J. *et al.,* 2004). For example, administration of vitamin E supplement to healthy elderly patients produced an increased antibody titer to both hepatitis B and tetanus vaccine (Gill, T. M., & Feinstein, A. R. 1994), thus enhancing T-cell mediated functions. In conclusion, maintaining adequate antioxidant status may provide a useful approach in attenuating cell injury and dysfunction observed in some inflammatory/autoimmune disorders (Pattison, D. J. *et al.,* 2004).

METHODS

A pre-post clinical trial was conducted on female patients with RA for 12 weeks. The study group was selected from 100 registered RA patients in Govt. Medical; College & Hospital, Amritsar. The inclusion criteria were RA diagnosis by rheumatologist according to American College of Rheumatology guidelines-1987, 40-60 years old, no change in treatment approach in past 2 months. The exclusion criteria were diabetes mellitus, hypertension, thyroid disorders, liver and kidney failure, Cushing syndrome, severe infection, gastric illnesses, smoking, and exposure to daily smoking at home. We followed-up the intake of daily supplement use and type and dose of medications by regular phone calls, so change in type and dose of drugs and antioxidant supplement resulted in omission from study. Five milliliter fasting venous blood samples (8-12 h after fasting) were taken from all participants and

were kept in -70°C freezer (Snider's, Germany) until conducting biochemical measurements. Biochemical measurements including GPX and SOD were measured by spectrophotometric kit (Ransel, Randox laboratories ltd, UK) and autoanalyzer apparatus (and CAT was measured by Abei method (Meki, A. R. M. *et al.,* 2009). TAC was determined by spectrophotometric kit (Randox TAC kit, Randox laboratories Ltd, UK). Serum high-sensitive C-reactive protein (hs-CRP) was quantified by photometric kit.

MATERIAL

A total of 39 patients sustained in the study after 12 weeks. The baseline characteristics and dietary intake have been reported in reference no. 20 (Westaway, M. S. *et al.,* 2008). One was left in reason of unrelated medical problem. Table 1 indicates basic characteristics of the subjects at the start point of trial and the median of the duration of the disease was 72 months [Table 1]. The pharmacotherapy regimen did not change during the period of the study in the selected patients and any changes in the dose and type of the drugs resulted in the omission of the study. Dietary intake of energy and selected nutrients during 12 weeks of intervention did not differ significantly [Table 2] and in the linear regression findings, no significant linear relationship between dietary antioxidants values with biochemical indices was observed.

RESULTS

In our study, antioxidants supplement for 12 weeks reduced significantly serum hs-CRP and DAS-28 score. The literature review indicates that zinc and selenium supplementation have been used in RA remission and prevention for several years (Gill, T. M., & Feinstein, A. R. 1994) and the similar results of these studies were resulted from multicomponent antioxidants and nutrients as Koracevic *et al.,* (2008) showed concurrent supplementation with 37.5 mg vitamin E, 150 mg vitamin C, 1.4 g eicosapentaenoic acid, 0.2 g docosaenoic acid, and 0.5 g gamma linolenic acid could not significantly reduce the number of swollen and painful joints (Westaway, M. S. *et al.,* 2008). As the results of alike studies revealed intake of simultaneous antioxidant micronutrients can have a helpful effect against RA progress (Westaway, M. S. *et al.,* 2008). In another similar study, 300 mg vitamin C, 5 mg zinc, 25000 International Unit vitamin A for 12 weeks reduced the disease activity ($P < 0.0001$) (Karatas, F. *et al.,* 2003). Also, Pretez *et al.,* (2001) study showed that 12 weeks selenium supplementation decreased the number of swollen and painful joints; however, the results were not statistically significant. Some studies have used higher doses of one antioxidant although they did not observe significant improvement in clinical outcomes (Pattison, D. J. *et al.,* 2004). It seems that the reason of these findings is due to no increase in antioxidants levels in polymorphonuclear leukocytes and antioxidant defense system in blood cells (Rennie, K. L. *et al.,* 2003). As Onal *et al.,* (2011) study indicated the pharmacotherapy in patients with RA results in lower levels of zinc and selenium and higher levels of copper in red blood cells, so intake of oral drugs such as corticosteroids and chloroquine elevates the required amount of the antioxidants to suppress inflammatory-like substances. Antioxidants supplement for 12 weeks reduced significantly serum hs-CRP and DAS-28 score. The literature review indicates that zinc and selenium supplementation have been used in RA remission and prevention for several years (Gill, T. M., & Feinstein, A. R. 1994) and the similar results of these studies were resulted from multicomponent antioxidants and nutrients as Koracevic *et al.,* (2008) showed concurrent supplementation with 37.5 mg vitamin E, 150 mg vitamin C, 1.4 g eicosapentaenoic acid, 0.2 g docosaenoic acid, and 0.5 g gamma linolenic acid could not significantly reduce the number of swollen and painful joints (Westaway, M. S. *et al.,* 2008). As the results of alike studies revealed intake of simultaneous antioxidant micronutrients can have a helpful effect against RA progress (Westaway, M. S. *et al.,* 2008). In another similar study, 300 mg vitamin C, 5 mg zinc, 25000 International Unit vitamin A for 12 weeks reduced the disease activity ($P < 0.0001$) (Karatas, F. *et al.,* 2003). Also, Pretez *et al.,* (2001) study showed that 12 weeks selenium supplementation decreased the number of swollen and painful joints; however, the results were not statistically significant. Some studies have used higher doses of one antioxidant although they did not observe significant improvement in clinical outcomes (Pattison, D. J. *et al.,* 2004). It seems that the reason of these findings is due to no increase in antioxidants levels in polymorphonuclear leukocytes and antioxidant defense system in blood cells (Rennie, K. L. *et al.,* 2003). As Onal *et al.,* (2011) study indicated the pharmacotherapy in patients with RA results in lower levels of zinc and selenium and higher levels of copper in red blood cells, so intake of oral drugs such as corticosteroids and chloroquine elevates the required amount of the antioxidants to suppress inflammatory-like substances. Erythrocyte antioxidant markers including TAC, GPX, SOD, and CAT increased significantly during 12 weeks supplementation due to probable direct effect of oral antioxidants on antioxidants levels. Similarly, Shinde *et al.,* (2001) have shown that 400 mg vitamin E and 500 mg vitamin C could increase the reduced form of erythrocyte glutathione ($P < 0.001$), probably because vitamin E is the most important fat-soluble antioxidant and protects the cell membranes against oxidative stress just as vitamin C preserves cytosol and membranes of free radicals activity (Karlson, E. W. *et al.,* 2008). Furthermore, the results of Meki, A. R. M. *et al.,* (2009) study indicated that 400 mg alpha-tocopherol, 10 mg lycopene, 5 mg alpha carotene, 10 mg lutein, and 200 mg vitamin C for 12 weeks increased plasma levels of vitamin E, lycopene, lutein, alpha-carotene, and vitamin

C and reduced F2-isoprstanes as the oxidative stress marker. Shah *et al.,*. illustrated that there is a strong association among the disease activity with antioxidant enzymes markers and they have showed that production of reactive oxygen substances can disturb the immune defense system and modulate inflammation processes to reduce the antioxidant molecules in blood cells. It seems that mixture of antioxidants help to reduce required dose of pain killer drugs and diminish the complaints of disease. Since autoimmune diseases such as RA are accompanying with reduction of cellular immune level that results in high coincidence of other chronic diseases, healthy antioxidant-rich diet can improve immune system and compensate the inadequate intake of micronutrients, especially antioxidant-rich supplies of RA patients in northwest of Iran (Helmy, M. *et al.*, 2001; & Karlson, E. W. *et al.*, 2008) Also, consumption of antioxidant micronutrients in the form of dietary items or supplements may be helpful in enhancement of enzymatic and nonenzymatic antioxidants due to strengthen the antioxidant defense system of the body (Meki, A. R. M. *et al.*, 2009; & Karatas, F. *et al.*, 2003). Lack of the control group is the major limitation in this pre-post clinical trial due to limited financial support. One of the strengths is the high response rate of participants (97.5%) and low loss to follow-up during the intervention. Also, mild to moderate severity of RA was considered as a criterion of the study and the dietary intake of antioxidants was supposed as confounding factors.

CONCLUSION

The combined antioxidant supplement may improve DAS-28 score significantly, but it did not change the number of painful and swollen joints statistically significant during 12 weeks, while it could increase TAC, GPX, SOD, and CAT levels. It seems that supplementation with antioxidants may be useful as a complementary treatment in control of clinical outcomes and oxidative stress in patients with RA. In our study, DAS-28 score and serum hs-CRP have changed during 12 weeks of intervention ($P < 0.01$), while the number of swollen and painful joints did not change significantly [Table 3]. The antioxidant markers of patients including TAC, GPX, SOD, and CAT increased significantly after 12 weeks supplementation ($P < 0.01$) [Table 4].

Table 1. The Basic Characteristics of Subjects in the Study

VARIABLES	STUDY GROUP
GENDER NUMBER	FEMALE (40)
AGE	54.9 ±5.9
	98 ±14
WEIGHT	
HEIGHT	150 ±11
BMI	30
DISEASE DURATION	5
ORAL USE OF PREDNISOLONE	72(18,435)
ORAL USE OF METHTREXATE	35(88)
ORAL USE OF SUFASALAZINE	34(85)
ORAL USE OF CHLOROQUINE	6 (15)
ORAL USE OF CYCLOSPORINE	16(42.5)
ORAL USE OF	1(0.025)
NSAIDS	4(10)
ORAL IMURAN USE	1(2.5)

Table 2. Dietary Intake of Selected Nutrients before and After 12 Weeks Intervention

VARIABLES	BEFORE STUDY (N=40)	AFTER STUDY(39)	P VALUE
ENERGY K.CAL	1235 (99,4006)	1603.0 (876,3500)	0.59
PROTEIN G	48.3	43.3	0.45
CARBOHYDRATE G	187	156	0.95
FAT G	75.8	76.9	0.87
ZN MG	5.2	5.8	0.78
VITAMIN A (IU)	4700.8	4090.9	0.49
VITAMIN E(MG)	32.8	32.3	0.76
VITAMIN C (MG)	102	98	87

Table 3. The Changes of Clinical Outcomes in Subjects of Study before and After 12 Weeks Intervention

VARIABLE	BEFORE STUDY(40)	AFTER STUDY (N=39)	P VALUE
DISEASE ACTIVITY	3.1± 2.1	2.87 ±1.76	0.019
NUMBER OF PAINFUL JOINTS	1	1	0.839
NO. OF SWOLLEN JOINTS	0	0	0.736
HS-CRP (MG/L)	5.87± 0.8	4.87± 0.12	0.003

Table 4. The Changes of Erythrocyte Antioxidant Parameters in Subjects of Study before and After 12 Weeks Intervention

VARIABLE	BEFORE STUDY(40)	AFTER STUDY (N=39)	P VALUE
GLUTATHIONE PEROXIDASE U/L	2.87 12.9	298 23.8	0.011
SUPEROXIDE DISMUTASE U/L	2.98 0.98	3.56 0.87	0.009
CATALASE U/L	23.89 5.98	25.76 7.98	0.008
TOTAL ANTIOXIDANT CAPACITY MMOLES/L	1.02 0.65	1.98 0.98	<0.001

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