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Status of oxidants and antioxidants in rheumatoid arthritis patients of north Karnataka

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ABSTRACT

Background: Oxidant stress as a result of increased production of reactive oxygen species (ROS) or a reduction in the body's endogenous antioxidant defense system is a hallmark of chronic inflammatory diseases including rheumatoid arthritis (RA). The objective of the study was to establish the status of oxidative/nitrosative stress in RA patients of north Karnataka.
Methods: Thirty RA patients and equal number of healthy individuals (controls) were included in the study. The morning stiffness (MS) and disease activity score 28 (DAS28) of RA patients were examined. Erythrocyte sedimentation rate (ESR) and hemoglobin (Hb) levels were estimated. Biochemical parameters uric acid, lipid peroxide (LPO), nitric oxide (NOx), vitamin C & E, erythrocyte superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were measured.
Results: Significant increased ESR (11.20 mm/hr vs. 40.97 mm/hr, 265.80%), uric acid (3.85 mg/dL vs. 6.73 mg/dL, 74.81%), LPO (1.12 µmol/L vs. 2.35 µmol/L, 109.82%) and NOx (16.19 µmol/L vs. 45.43 µmol/L, 180.61%) levels with significant decreased of the levels of Hb (12.59 g/dL vs. 10.16 g/dL, 19.30%), vitamin C & E (11.20.mg/L vs. 3.87.mg/dL, 65.45% and 13.01 mg/L vs. 7.05 mg/dL, 45.81%), SOD (3757.90 U/g Hb vs. 2201.20 U/g Hb, 41.42%) and GSH-Px (1.81 U/g Hb vs. 0.92 U/g Hb, 49.17%) were observed in RA. There was direct correlation found between MS, DAS-28 and ESR with serum LPO and NOx in RA patients. A significant negative correlation was detected between activity parameters with biochemical parameters in RA patients.
Conclusions: Increased oxidants level and decreased non-enzymatic/enzymatic antioxidants level in RA patients of north Karnataka confirm an association between oxidative/nitrosative stress and rheumatoid arthritis.

Keywords: Rheumatoid arthritis, Oxidative stress, Nitrosative stress, Antioxidants

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects nearly 1% of the world population. RA is a crippling disease, associated with severe pain, suffering, and diminished function, thereby detracting from an optimal quality of life.[1] Although the etiology is unknown, RA is certainly associated with autoimmune disorders, and its pathogenesis has been well investigated.[2] Reactive oxygen species (ROS) have been considered as aggravating factor for autoimmune diseases,[1] as there is a significant relation between the oxidative stress and such diseases.[2] ROS include superoxide, peroxide, hydroxyl radicals and reactive nitrogen species (RNS).[3] ROS could be produced as a result of inflammation which leads to the destruction of cartilage and bone, neutrophils degranulation and release a variety of potentially harmful enzymes and peptides.[4] Because of the highly reactive nature of ROS and RNS, it is difficult to directly demonstrate their presence in vivo. It is considerably more practical to measure the 'footprints' of ROS and RNS, such as their effects on

various lipids, proteins and nucleic acids.[5] Nitric oxide (NO) has been shown to regulate T cell functions under physiological conditions, but overproduction of NO may contribute to T lymphocyte dysfunction.[6]

Several investigators found correlations between serum nitrite concentration and RA disease activity or radiological progression while others did not find such correlations.[7,8] Cells have different antioxidant systems to defend themselves against free radical attacks. Circulating human erythrocytes possess the ability to scavenge O_2^- and H_2O_2 generated extracellularly by activated neutrophils, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px)-dependent mechanisms. The results about antioxidant state of patients with RA are inconsistent, since studies have reported increased, decreased and unaltered activity of antioxidant enzymes in RA patients.[9-11] Hence, this study was carried to establish the status of oxidative/nitrosative stress in RA by measuring the markers of free radical production and levels of non-enzymatic/enzymatic antioxidants in north Karnataka patients.

METHODS

Study design

The present study was carried out in the Department of Physiology, Al Ameen Medical College Vijayapur, Karnataka, India during January to June 2016. Samples were collected from Al Ameen Medical College Hospital Vijayapur, north Karnataka region under the guidance of the specialist. The study protocol was approved by Institutional Ethical Committee and consent was obtained from all the subjects before the study being started. All the subjects were matched according to socio-economical status and dietary habits. Thirty healthy control individuals of both the sexes were included for the study. Thirty Rheumatoid arthritis (RA) patients (classical rheumatoid arthritis according to American Rheumatism Association criteria and had disease duration of 2 to 8 years) of both the sexes were taken for the study.[12] All the reagents and chemicals used were of analytical grade and were purchased from Merck Chemical Company, Germany. Except serum vitamin E all the above biochemical evaluations were carried by using UV-VIS double beam spectrophotometer (SL 159), Elico, India. Serum vitamin E estimation was carried out by using ELISA Reader (ERBA-Lisa Scan II), Elico, India.

Inclusion criteria

Subjects, who gave informed consent for the study, having no history of any type of arthritis, non-smokers, don't under any medical treatment (anti-inflammatory drug) or taking antioxidant supplement for at least 1 month prior to blood collection were included.

Exclusion criteria

Patients with diabetes mellitus, hepatic disease, hypertension, those taking antioxidant vitamin supplements or non-steroidal anti-inflammatory drugs and with other connective tissue disease like systemic sclerosis and osteoarthritis were excluded.

Sample collection

Two milliliters of fasting venous blood was collected and transferred to the EDTA vials for estimation of hemoglobin and erythrocyte sedimentation rate. Fasting 5 ml of venous blood was added in EDTA tube and centrifuged in laboratory centrifuge machine (R-4C), Remi, India. Red blood cells were washed 3 times with ice-cold normal saline (0.9% sodium chloride) and used for the estimation of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). Fasting 5 ml venous blood was added in plain test tubes and serum was separated. Serum was used for the estimation of uric acid, lipid peroxide (LPO), nitric oxide (NOx), vitamin E (α-tocopherol) and vitamin C (L-ascorbic acid).

Demographic data

Body mass index (BMI) was calculated by using Quetelet's Index.[13] All patients were subjected to careful history taking and thorough clinical examination with assessment of duration of morning stiffness (MS) in minutes and Disease Activity Score 28 (DAS28) was determined for the evaluation of current RA activity.[14] The DAS28 considers 28-joint count for tenderness, a 28-joint count for swelling and erythrocyte sedimentation rate (ESR) for the patient's overall assessment of well-being. DAS28 was then calculated using Webculator. Hemoglobin was estimated by Cook RD method.[15] Erythrocyte sedimentation rate was measured by Westergren's method.[16] Serum uric acid is estimated by the standard kit method (Crest Biosystem, India).[17]

Biochemical analysis

The serum LPO was measured by the method of Satoh K.[18] The serum NOx was measured by the method of Moshage et al[19] with little modifications. The serum vitamin C was estimated by the method of Roe and Koether[20] and serum vitamin E was estimated by the plain non-antibody coated ELISA plate method of Jargar et al.[21] The erythrocyte superoxide dismutase was estimated by the method of Winterbourn et al.[22] The erythrocyte glutathione peroxidase was estimated by the method of Paglia and Valentine.[23]

Statistical analysis

Standard statistical methods were used to determine the mean and standard deviation (SD). Paired t-test was used to compare the results of various study parameters in the

two groups. All the values were quoted as the mean±SD. The p value of <0.05 was considered statistically significant different and represented by asterisk '*' between two groups. Correlation between the variables was examined using the Pearson's correlation coefficient.

Over all 70 patients of colorectal malignancies were included in this study. The detailed records were obtained from MRD section. The patients were also contacted by post or by telephone as and when necessary for their follow-up. All the data were analysed using the necessary statistical calculations, the result were then presented.

RESULTS

The demographic and clinical data in both the groups RA patients and healthy controls were listed in Table 1. A total of 30 RA patients (14 males, 16 females), their ages ranged from 40 to 68 years (mean age 52.73±7.74 years). The mean disease duration was 6.07±1.80 years. There was no statistically significant difference in age (54.27 years vs 52.73years, 2.84% reduction), sex (14 males/16 females vs. 14 males/16 females), weight (62.37 kg vs. 68.10 kg, 9.19% elevation) and BMI (22.86 kg/m^2 vs. 25.33 kg/m^2, 10.80% elevation) mean values between healthy controls and RA patients. But there was statistically significant difference in Hb (12.59 g/dL vs. 10.16 g/dL, 19.30% decreased), ESR (11.20 mm/hr vs. 40.97 mm/hr, 265.80% increased) and uric acid (3.85 mg/dL vs. 6.73 mg/dL, 74.81% increased) mean values between healthy controls and RA patients. In RA patients, the mean disease activity score (DAS-28) was 5.15±0.92 with a mean value of the morning stiffness (MS) which was 57.63±6.93min.

In Table 2 the RA patients showed highly statistical significant increase in mean serum lipid peroxide level (2.35 µmol/L) which is 109.82% elevated as shown in Figure 1 as compared to healthy control individuals (1.12 µmol/L). The RA patients also showed high statistically significant increase in mean serum nitric oxide level (45.43 µmol/L) which is 180.61% elevated as in Figure 1 as compared to healthy control individuals (16.19 µmol/L).

The RA patients showed statistically significant decrease in both mean erythrocyte superoxide dismutase (2201.20 U/g Hb) and erythrocyte glutathione peroxidase (0.92 U/g Hb) levels which are reduced by 41.42% and 49.17% as compared to healthy control individuals (3757.90 U/g Hb and 1.81 U/g Hb) respectively as shown in Table 3 and Figure 2. Table 3 also depicts the mean serum vitamin E (3.87 mg/dL) and vitamin C (7.05 mg/dL) levels decreased significantly (p <0.05) in RA patients as compared to healthy control individuals (11.20 mg/L and 13.01 mg/L) respectively. The percent change in vitamin E and vitamin C showed 65.45% and 45.81% reduction respectively as compared to controls as shown in Figure 2.

As regards correlation matrix as in Table 4, there is direct correlation between MS, DAS-28 and ESR with serum LPO and serum NOx in RA patients.

Table 1: Demographic data of RA patients and healthy controls.

Demographic data	Control (n=30)	RA Patients (n=30)	p value
Age (years)[Range: 40 to 68 years]	54.27±8.22	52.73±7.74	0.089 [NS]
Sex (Male/Female)	14/16	14/16	1.000 [NS]
Weight (Kg)	62.37±6.56	68.10±7.25	0.078 [NS]
BMI (kg/m^2)	22.86±1.82	25.33±1.98	0.068 [NS]
Hb (g/dL)	12.59±1.41	10.16±1.40*	0.037
ESR (mm/h)	11.20±5.10	40.97±8.32*	0.001
Uric acid (mg/dL)	3.85±0.51	6.73±0.84*	0.001
Duration of disease (years) [Range: 2 to 8years]	--	6.07±1.80	
DAS28 (score)	--	5.15±0.92	
MS (min)	--	57.63±6.93	

RA: Rheumatoid arthritis; BMI: Body mass index; Hb: Hemoglobin; ESR: Erythrocyte sedimentation rate; DAS28: disease activity for 28 joint indices score; MS: morning stiffness. All the values quoted as the Mean ±S D. Paired t-test was used to compare the results between two groups. The *p* value of <0.05 was considered statistically significant different and represented by asterisk '*'. NS: statistically not significant.

Table 2: Serum oxidative and nitrosative stress markers from RA patients and healthy controls.

Oxidative/ Nitrosative stress markers	Control (n=30)	RA Patients (n=30)	P value
Serum lipid peroxide (µmol/L)	1.12±0.16	2.35±0.25*	0.001
Serum nitric oxide (µmol/L)	16.19±3.33	45.43±8.84*	0.001

RA: Rheumatoid arthritis. All the values quoted as the Mean ± SD. Paired t-test was used to compare the results between two groups. The *p* value of <0.05 was considered statistically significant different and represented by asterisk '*'.

Table 3: Enzymatic and non-enzymatic antioxidants levels in RA patients and healthy controls.

Enzymatic and non-enzymatic antioxidants markers	Control (n=30)	RA Patients (n=30)	p value
Erythrocyte SOD (U/g Hb)	3757.90±733.02	2201.20±353.24*	0.001
Erythrocyte GSH-Px (U/g Hb)	1.81±0.20	0.92±0.14*	0.001
Serum vitamin E (mg/dL)	11.20±2.49	3.87±1.13*	0.001
Serum vitamin C (mg/dL)	13.01±1.52	7.05±1.43*	0.001

RA: Rheumatoid arthritis; SOD: superoxide dismutase; GSH-Px: glutathione peroxidase. All the values quoted as the Mean ± SD. Paired t-test was used to compare the results between two groups. The *p* value of <0.05 was considered statistically significant different and represented by asterisk '*'.

Table 4: Correlation between the clinical parameters and biochemical parameters in the RA patients.

Biochemical parameters	Clinical parameters			P value
	DAS-28	MS	ESR	
LPO	r = 0.645*	r = 0.744*	r = - 0.752*	*p* < 0.001
NOx	r = - 0.813*	r = - 0.78*	r = - 0.668*	*p* < 0.001
Vitamin E	r = - 0.462*	r = - 0.587*	r = - 0.586*	*p* < 0.001
Vitamin C	r = - 0.524*	r = - 0.554*	r = - 0.615*	*p* < 0.001
SOD	r = - 0.448*	r = - 0.540*	r = - 0.548*	*p* < 0.001
GSH-Px	r = - 0.786*	r = - 0.685*	r = - 0.648*	*p* < 0.001

RA: Rheumatoid arthritis; DAS28: disease activity for 28 joint indices score; MS: morning stiffness; ESR: erythrocyte sedimentation rate; LPO: serum lipid peroxide; SOD: erythrocyte superoxide dismutase; GSH: erythrocyte glutathione peroxidase. * Values were calculated using Pearson's correlation coefficient.

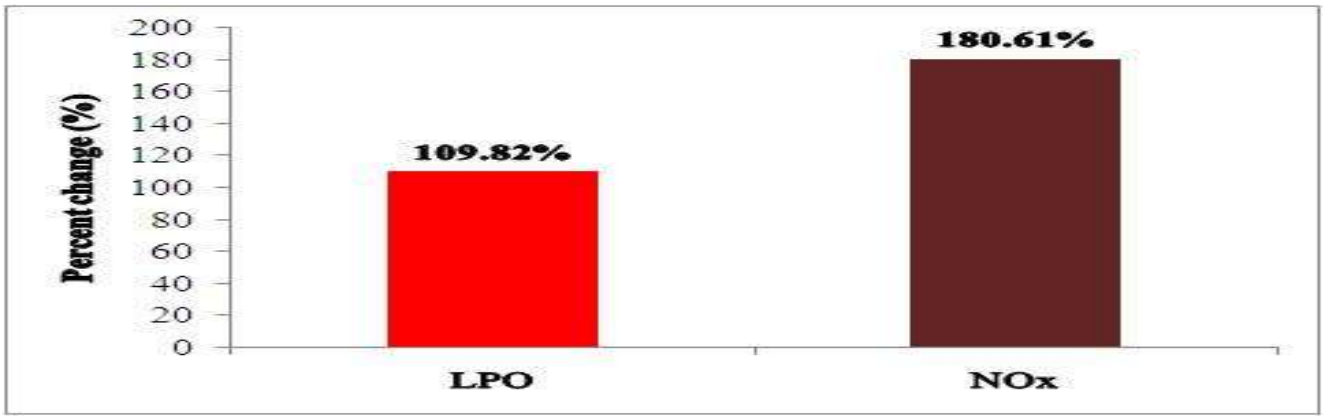

Figure 1: Percent change graph of serum lipid peroxide (LPO) and nitric oxide (NOx) in RA patients verses healthy controls.

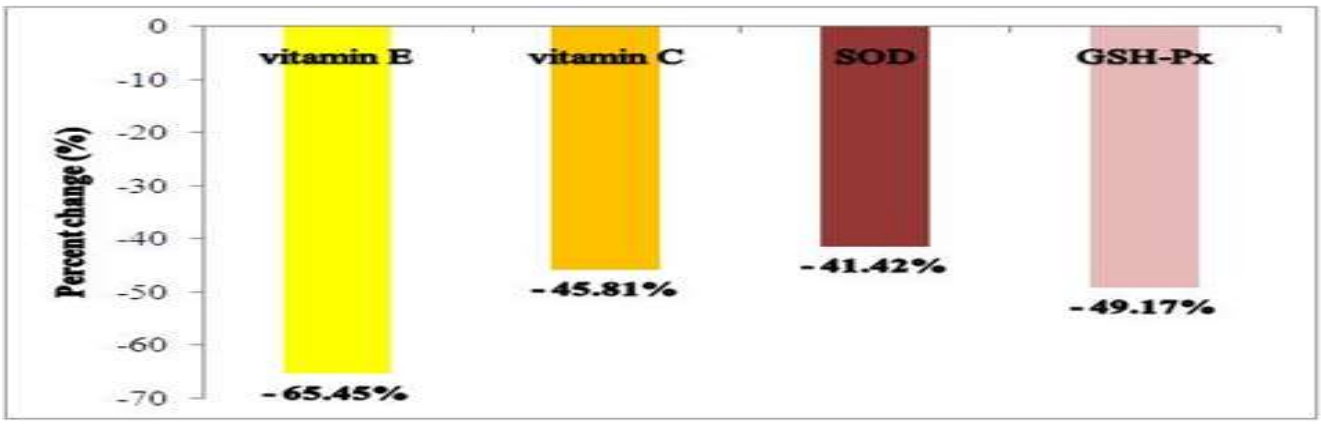

Figure 2: Percent change graph of non-enzymatic and enzymatic antioxidants in RA patients verses healthy controls.

A significant negative correlation is detected between activity parameters with serum vitamin E, serum vitamin C, erythrocyte SOD and erythrocyte GSH-Px level in RA patients. As regards intra-correlation coefficients (r values) between chemical parameters studied in patients with RA, there is positive correlation between oxidative/nitrosative stress parameters also between non-enzymatic/enzymatic antioxidants parameters ($P < 0.001$).

DISCUSSION

The pathogenesis of RA disease is due to the generation of ROS and RNS at the site of inflammation. In our study inflammatory markers i.e. ESR and DAS28 were increased in RA patients as in Table 1. The mean Hb level in the RA patients was statistically significant decreased than that of the healthy controls as in Table 1. Low levels of Hb are also reported in earlier studies.[24] Akyol et al found no differences between Hb values of RA patients and healthy controls.[25] The systemic effect of this disease is shown by marked increase in ESR and decrease in Hb levels. RA patients in our study showed statistically significant increased serum uric acid level when compared with healthy controls as given in Table 1. This finding is in accordance with the Mahajan et al.[26] The increased level of uric acid shows that it contributes to scavenging the free radicals.[27] Increased uric acid level in RA patients may be a compensatory response to combats the low levels of major non-enzymatic antioxidants like vitamin C and E.

A primary source of ROS in RA is leukocytes (i.e. activated macrophages, neutrophils, mast cells and lymphocytes) that are recruited to, and that accumulate within, the synovium. There is increasing evidence that ROS/RNS contributes to the phenomenon of pain, such as chronic arthritic pain in RA patients. In the current study serum LPO was found in significantly high levels in RA patients than in healthy controls as seen in Table 2 and Figure 1. Akyol et al found a remarkable elevation in lipid peroxide levels in patients with RA compared to controls; this was also observed in many published reports. [25,27,28] On the other hand, Olivieri et al reported no change in lipid peroxide in RA.[29] Significant rise in nitric oxide (NOx) level, a nitrogen reactive species product, in our patients is indicative of elevated nitrosative stress in RA patients as observed in Table 2 and Figure 1. The reaction of nitric oxide with superoxide generates peroxynitrite which, under the acid conditions often found in regions of inflammation and ischemia, yields the hydroxyl radical OH•, the most highly reactive and toxic of the ROS.[6] There is an increased activity of NOS in MRL- 1pr/1pr mice (a strain which shows pronounced lympho proliferative activity and develops severe autoimmune disorders).[30] The study of experimental arthritis in animals has confirmed as increased activity of inducible NO synthetase (NOS) with a raised production of nitric oxide.[31] The inhibition of NOS can suppress disease activity in parallel with a fall in plasma nitrotyrosine or nitrite.[32] Oxidative stress (OS) and nitrosative stress (NS) may contribute to the pathogenesis of RA in a variety of ways including: induction of membrane oxidation and instability, irreversible damage to proteins and DNA, cartilage damage and induction of bone resorption.[33]

In the present study we investigated the serum levels of non-enzymatic antioxidants vitamin C and E along with LPO and NOx in patients with rheumatoid arthritis. In the present study, a significant increase in oxidative stress and nitrosative stress along with significant decrease in antioxidant vitamin C and E as viewed in Table 3 and Figure 2 was observed in RA patients compared to controls, revealing that there is an increased oxidative/nitrosative damage in these patients. 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.[34] Vitamin E helps to trap free radicals and interrupt the chain reaction that damage the cells whereas regeneration of vitamin E depends on Vitamin C. The decrease in the levels of vitamin C and E (non-enzymatic antioxidants) may be due to the increase turn over, for preventing oxidative damage in RA.[25] Due to increased oxidative stress and nitrosative stress in RA there may be increased consumption of both of these vitamins C and E.[35] This implies that antioxidative defense mechanisms are of particular importance for patients with RA. While the mechanism of action of vitamin E has not fully elucidated. In-vitro study have shown that vitamin E, at physiological concentrations, significantly reduces cartilage matrix degradation caused by chondrocyte-derived free radical.[36]

Among the enzymatic systems of protecting the cell against free radical injury, SOD and GSHPx play a crucial role in the final detoxication of H_2O_2 to H_2O. In present study antioxidant enzymes SOD and GSH-Px levels were statistically significant lower in RA patients compared to healthy controls (Table 3 and Figure 2), this agrees with Nivsarkar and Banford et al.[10,37] There are controversial reports on erythrocyte SOD and GSHPx activities in patients with RA, as increased and unaltered, SOD activity has been reported.[9,11] During phagocytosis granulocytes and macrophages produce large amounts of O^{2-} and H_2O_2.[38] In reactive arthritis patients, SOD, an enzyme destroying O^{2-}, given systemically or locally, induces a decrease of inflammation.[39] It appears that increased levels of superoxide and other radicals are not detoxified in patients with RA due to decreased efficiency of antioxidant enzymatic and non-enzymatic mechanisms.

CONCLUSION

The systemic effect of RA disease is shown by marked increase in ESR and decrease in Hb levels. Increased

lipid peroxide and nitric oxide levels in patients with RA probably depend on their inflammatory response. The low level of antioxidants vitamin C and E, superoxide dismutase and glutathione peroxidase suggests that, it is being consumed for scavenging of free radicals and elucidating the mechanism of disease pathogenesis. These findings confirm an association between oxidative/nitrosative stress and rheumatoid arthritis. More studies involving large population from north Karnataka could provide vital information.

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