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Antioxidant Vitamins and indices of oxidative Stress in sera positive for Rheumatoid Factor

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ABSTRACT

Background: Rheumatoid factor (RF), an autoantibody, is often present in sera of patients suspected of having arthritis, liver diseases, auto-immune disorders, certain viral and bacteria infections and few healthy individuals. Up till now, factors responsible for the RF presence are not fully understood but the involvement of oxidant-antioxidant imbalance has been suggested. Therefore, this study was carried out to determine the serum levels of selected vitamins and oxidative stress indices in RF-positive patients

Methods: Indices of oxidative stress [malondialdehyde (MDA), total peroxide (TP), total antioxidant potential (TAP)] and vitamins C and E were spectrophotometrically determined in 28 patients with RF-positive sera and 28 age-matched apparently healthy adults whose sera were RF-negative (controls). Thereafter, oxidative stress index (OSI) was appropriately calculated. Presence of RF was determined using latex agglutination method. Student's t-test was used to compare differences in means while Pearson's correlation analysis was used to establish the correlation between RFtiter and the biochemical indices.

Results: The mean serum levels of TP, MDA and OSI were significantly elevated in RF-positive sera compared with controls. In contrast, the mean serum levels of TAP and vitamin E were significantly lower in RF-positive seracompared with controls.

Conclusion: It could be concluded from this study that increased oxidative stress and reduced antioxidant activity in RF-positive sera may contribute to RF related diseases. Thus, monitored co-administration of antioxidants supplement or increased intake of antioxidant containing diets with conventional drugs might be beneficial inpatients with RF related diseases.

Keywords: Rheumatoid factor, auto-antibodies, nutrition, inflammation.

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Introduction

Rheumatoid factors (RFs) are autoantibodies directed against the fragment crystallizable (Fc) portion of immunoglobulin G (IgG) (Mageed*et al*., 1997). They were identified more than 70 years ago and were so named because they are commonly found in patients with rheumatoid arthritis. However, it is now known that RFs can be found in autoimmuneand nonautoimmune diseases. Also, it is found in up to 30% of apparently healthy individuals (Kyburz*et al*., 1999; Ingegnoli*et al*., 2013).

Although RF can be found in healthy and unhealthy conditions, the type of RF B cells found in normal individuals appears to be different from what is found in RF-associated diseases such as rheumatoid arthritis (RA). Kyburz*et al*. (1999) reported that low affinity RF B cells, which are nonpathogenic, are found abundantly in lymph nodes of normal individuals whereas in RA patients, high affinity RF B cells, which are pathogenic, are usually found accumulated in the inflamed synovium where they can form immune complexes and induce Complement fixation. Although the reasons for this difference is still unknown, it could be suggested that other factors such as oxidative stress may play a role in the pathogenesis of joint destruction in RA.

Alteration in oxidative status and DNA damage have been reported in RA patients (Mateen*et al*., 2016). Recently, similar alteration was also observed in the brain, liver and vascular tissues of experimental animals with arthritis (Bracht*et al*., 2016; Schubert *et al*., 2016). Furthermore, the National Center for Complementary and Alternative Medicine reported that dietary supplements may be beneficial in the treatments of RA(Rheumatoid Arthritis and Complementary Health Approaches, 2013).A study also reported that intake of certain antioxidant micronutrients particularly, beta-cryptoxanthine and supplemental zinc via fruits and cruciferous vegetables ameliorate the symptoms of rheumatism(Knekt*et al*., 2000; Jaswal*et al*., 2003). Overall, these evidences indicate that there is alteration in oxidative status inpatients with RA. However,it is presently unknown if oxidative stress plays a role in RF generation in different disease conditions. This study was therefore, carried out to determine the levels of selected vitamins and oxidative stress indices in the sera of RF-positive patients.

Materials and Methods

Venous blood samples collected into bottles without anticoagulants were sent to the Immunology Unit Laboratory, University of Ibadan, Nigeria for the detection of RF presence in the samples. After obtaining the serum, the titer of RF was determined using latex agglutination method as described by the manufacturer (Cromatest, Linear Chemicals, LOT 232301, Spain).

Twenty eight consecutive samples that were positive for RF were selected for this study. The samples were from 19 males and 9 females between the ages of 30 and 62 years with arthritis related symptoms (swollen joints, stiffness and pains). The patients were age-matched with 28 apparently healthy individuals with no symptoms or history of arthritis. Verbal informed consent was obtained from the study participants or their relatives after explaining the purpose of the study to them. Sera from patients already on medication, organ transplant, underlining infections and auto-immune disorders were excluded from the study.

Serum levels of vitamins E and C were determined spectrophotometrically as described by Halliwell and Gutteridge(1998). Also, total peroxide (TP) level,malondialdehyde (MDA)and total antioxidant potential (TAP)were determined spectrophotometrically as described by Satoh (1978), Harma*et al*. (2003) and Erel (2004).Thereafter, the percent ratio of the peroxide level to the level of TAPwas regarded as the oxidative stress index (OSI).

All results are expressed as mean ± standard deviation (SD). Differences in means were determined using the Student's t-test. Spearman's correlation analysis was used to establish correlation between RFlevels and other parameters. *P*-values less than 0.05 were considered to be statistically significant.

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Results

Table 1 shows the levels of selected vitamins and indices of oxidative stress in the study participants. The mean levels of MDA, total peroxide and OSI were significantly higher while the mean levels of TAP and vitamin E were significantly lower in RF-positive patients compared with controls. The mean level of vitamin A was similar between the 2 groups.

Only MDA had significant positive correlation with RF titer (Table 2).

Table 1: Serum levels of selected vitamins and indices of oxidative stress in RF-positive patients and controls

	MDA (µmol/L)	Total peroxide (µmol H_2O_2/L)	TAP (µmolTrolox equiv./L)	OSI (%)	Vitamin C (mg/dL)	Vitamin E (ug/mL)
RF-positive patients (n = 28)	14.4 ± 2.8*	11.4 ± 2.8*	1130.0 ± 400.0*	1.0 ± 0.7*	0.6 ± 0.2	7.0 ± 3.0*
Controls (n = 28)	4.7 ± 2.5	9.8 ± 0.2	2030.0 ± 200.0	0.5 ± 0.1	0.6 ± 0.3	10.0 ± 2.0

*Significantly different from controls at $P<0.05$, MDA=malondialdehyde, TAP=total antioxidant potential, OSI=oxidative stress index

Table 2: Correlation between the RF titer and indices of oxidative stress and selected vitamins

RF Titer	r-values
Total peroxide	0.11
TAP	0.21
OSI	0.24
MDA	0.76*
Vitamin C	0.29
Vitamin E	0.35

*Significant at $P<0.05$

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Discussion

The vicious cycle between oxidative stress and inflammation is well established (Winrow*et al*., 1993). It has been shown that inflammation triggered by oxidative stress plays important roles in the pathogenesis of most human chronic diseases (Pashkow, 2011).It is known that RF combines withIgG to form immune complex which activates various inflammatory cells to producefree radicals which in turn, increase lipid peroxidation and cause tissue injury (Kapitany*et al*., 2008; Khansari*et al*., 2009).

Elevated levels of reactive oxygen species has been reported in the synovial fluid of inflamed rheumatoid joints and has been implicated in destructive and proliferative synovitis (Hitchon and El-Gabalawy, 2004). The observed elevated MDA level in RF-positive samples supports the reports of Chandankhede and Gupta (2013) and Mateen*et al*. (2016).This observation indicates that there is increased lipid peroxidation which can aggravate inflammation in patients with RF related diseases thereby, exposing them to increased risk of tissue damage. Darlington and Stone(2001) reported that MDA, the product of lipid peroxidation, can react with lysine residues in proteins to produce immunogenic molecules, which can exacerbate inflammation.

Total peroxide level reflects the total sum of peroxides in a biological sample. The observed elevated levels of TP and OSI in RF-positive patients corroborate the report of Isik and Selek, 2007). This observation indicates that there is heightened oxidative stress in RF-positive patients. This notion is further reinforced by the observed elevated TAP level and the positive correlation between MDA and RF titer in the patients. The abundance of free radicals exhibited by the elevation in the serum levels of MDA, TP and OSI could act as a second messenger which will stimulate nuclear factor kappa B-dependent expression of pro-inflammatory cytokines thus, forming a loop that feeds back to advance the production of additional free radicals (Hirao*et al*., 2012).

Vitamin E is a fat soluble antioxidant vitamin that plays a vital role in free radical quenching(Song and Kang, 2010).By limiting free-radical production, vitamin E prevents and delays chronic diseases associated with free radicals(Traber, 2007). The observed lower vitamin

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E level in RF-positive patients is in line with the report of Karatas*et al*. (2003).This observation could be due to the role of vitamin E in limiting free radical generation with a view to reducing tissue damage. Wagner *et al*. (1996) reported that vitamin E slows the role of free radical-mediated lipid peroxidation.

Conclusion

There is increased lipid peroxidation and oxidative stress as well as reduced antioxidant activity in sera of patients with positive RF. This alteration in oxidative status may contribute to generation of rheumatoid factor. Therefore, monitored co-administration of antioxidants supplement or increased intake of antioxidant containing diets with conventional drugs might be beneficial in patients with RF-positive sera.

Conflict of interest

Author declare to have had no conflict of interest

Dedication

This study is dedicated to the late Professor L.S. Salimonu who initiated most of routine investigations carried out in Immunology Unit, University of Ibadan, Nigeria.

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