Original Article

Total Oxidants, Lipid Peroxidation and Antioxidant Capacity in the Serum of Rheumatoid Arthritis Patients

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Abstract

Rheumatoid arthritis (RA) is a chronic disease characterized by the presence of inflammatory events and triggered immunity. Oxidative stress has been linked to the deterioration of many pathological conditions and involved in the presence of serious health risks. Reactive oxygen species (ROS) is involved in beneficial and harmful effects to the biological system. When the levels of ROS are increased the harmful effects appeared in different levels of oxidative damage. The oxidative damage of the lipids is termed lipid peroxidation and can be screened by measuring one of the final products called malondialdehyde (MDA). Antioxidants are the materials that responsible for the detoxification of ROS and prevent their harmful effects. In this article, we aimed to determine the levels of MDA, total oxidant status (TOS), and total antioxidant capacity (TAC) in patients with RA disease. Furthermore, we goaled to investigate the relationship of oxidative stress with RA disease, and the possibility of using oxidative stress indicators as diagnostic markers for the disease. The results have shown increase in the oxidation state of RA patients. The levels of MDA and TOS were significantly elevated in the serum of RA patients, in addition to this, the level of TAC was significantly reduced. This shift in the redox balance towered the oxidants indicate for sure the development of oxidative stress in RA patients. Furthermore, MDA, TOS, and TAC were observed to be excellent sensitive biomarkers for the diagnosis of RA disease. From this results, the administration with antioxidants is very important in the treatment of RA patients to control the disease and prevent any associated risks.

Keywords: Rheumatoid arthritis, TOS, TAC, MDA.

1. Introduction

Rheumatoid arthritis (RA) is a symmetric polyarticular arthritis which mostly affects the hands and feet's small diarthrodial joints. The aggressive front of tissue known as pannus invades as well as destroys local articular structures in additional to inflammation in the synovium, which is the joint lining. In its natural state, the synovium is a comparatively acellular structure with a fragile intimal lining [1].

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Synovial inflammation as well as hyperplasia ("swelling"), autoantibody production (rheumatoid factor and anti–citrullinated protein antibody [ACPA]), bone and cartilage destruction ("deformity"), as well as systemic features such as cardiovascular, pulmonary, psychological, and also skeletal disorders characterize rheumatoid arthritis [2]. The cause of rheumatoid arthritis is unknown, however it is thought to be caused by a complex interaction of environmental and hereditary factors. The severity of a disease is also influenced by genetics. Joint inflammation is caused by a triggering event, which could be autoimmune or viral. Joint degradation as well as systemic consequences are mediated by complex interactions among multiple immune cell types and also their cytokines, proteinases, as well as growth factors [3, 4]. Multiple studies have found that RA patients had a higher risk of cardiovascular events [5, 6]. The processes causing this risk could be linked to cytokines that promote endothelial activity as well as render atheromatous plaques more unstable. Total cholesterol, low-density cholesterol, as well as high-density cholesterol levels are all lower in patients with active untreated RA [7]. The brain is affected by RA, which causes fatigue as well as reduced cognitive function; the lungs are affected by inflammatory and also fibrotic disease; the exocrine glands are affected by secondary Sjogren's syndrome; the skeletal muscles are affected by sarcopenia; as well as the bones are affected by osteoporosis. Finally, persons with RA may be more susceptible to cancer, particularly hematologic as well as renal malignancies [8, 9].

Oxidative stress is a condition in which the redox balance in the biological system is disturbed [10]. Free radicals as well as reactive oxygen species (ROS) are increased in the cells, leading to oxidative reactions with the components of the cells including, proteins, lipids, and nucleic acids [11, 12]. Nevertheless, ROS considered important regulators when their levels maintained at low concentrations as signaling messengers [13, 14]. ROS can be produced in the cells of the body at normal levels but these levels can increased in certain pathological conditions, leading to the appearance of oxidative damage (stress) [15, 16]. The responsible of detoxifying ROS are materials called antioxidants [17]. These antioxidants are produced to the biological system from endogenous and exogenous sources [18-20]. When these antioxidants are failed to detoxify ROS, the oxidative damages would appeared rapidly [21]. The oxidative damage of the lipids called lipid peroxidation, and one of the stable final product is malondialdehyde (MDA) which can be used as indicator of oxidative stress [22, 23]. In this article, we aimed to determine the levels of MDA, total oxidant status (TOS), as well as total antioxidant capacity (TAC) in patients with RA disease. Furthermore, we goaled to investigate the relationship of oxidative stress with RA disease, as well as the possibility of using oxidative stress indicators as diagnostic markers for the disease.

2. Experimental Part:

2.1. Patients

The RA patients were documented in the consultancy of Baghdad Hospital at the Medical City (Baghdad, Iraq). They were informed about the standard criteria of the research and agreed to become a volunteers in this work. 60 patients with RA were selected for the study from May to August 2021, and controlled with 30 healthy volunteered people. The subjects were in equal gender distribution in each group.

2.2. Methods

The RA patients and healthy control people were donated a vein blood. The blood then centrifuged in a medical centrifuge (4000 rpm for 10 minutes), as well as the serum was kept in a deep freezing at -20 °C to be analyzed for MDA TOS, and TAC by using a spectrophotometric method (Apel PD-303, Japan). The level of MDA was analyzed according to the method of Benge and Aust [24], while the TAC as well as TOS levels were determined through using Erel's method that have been reported in Abod et al. study [25].

2.3. Statistics

The data were processed statistically on the computer by a program from IBM called SPSS version 26.0, for mean comparisons in an independent sample t-test, and the relationship between MDA, TOS and TAC were calculated according to the Pearson correlation. At last, the sensitivity of MDA, TOS and TAC as diagnostic markers for RA was determined by the receiver operating characteristic (ROC) curve through measuring area under the curve (AUC) of each variable.

3. Results

The characteristics of the volunteered people are contained in Table 1. Age was shown non-significant (P>0.05) differences between the RA patients (43.40±9.86 year) and control people (42.07±9.44 year). Also, the body mass index (BMI) was non-significantly (P>0.05) different between RA patients (25.63±2.56 kg/m2) and control people (25.32±2.70 kg/m2).

Table 1. Volunteered people characteristics.

Parameter	RA	Control	*P*-value
N	60	30	-
Age (year)	42.07±9.44	43.40±9.86	0.536
BMI ($kg.m^{-2}$)	25.32±2.70	25.63±2.56	0.606
MDA (µmol/L)	0.70±0.20	2.21±0.63	0.0001
TOS (µmol H_2O_2 Eq/L)	1.33±0.14	2.72±0.51	0.0001
TAC (µmol vitamin C Eq/L)	2.02±0.49	1.17±0.20	0.0001

The levels of MDA were significantly (P<0.05) elevated in the serum of RA patients (2.21±0.63 µmol/L) compared to the serum of control people (0.70±0.20 µmol/L). Also, the levels of TOS were significantly (P<0.05) increased in the serum of RA patients (2.72±0.51 µmol H2O2 Eq/L) compared to the serum of healthy control (1.33±0.14 µmol H2O2 Eq/L). While, the levels of TAC were significantly (P<0.05) lower in the serum of RA patients (1.17±0.20 µmol vitamin C Eq/L) compared to the serum of control people (2.02±0.49 µmol vitamin C Eq/L).

The results have shown significant positive association between MDA and TOS in the serum of RA patients, as shown in Table 2. Furthermore, RA patients had shown significant negative correlation between TOS and TAC in their serum.

Table 2. Correlation in RA patients.

Parameter	MDA		TOS		TAC	
	r	*p*-value	r	*p*-value	r	*p*-value
TOS (µmol H_2O_2 Eq/L)	0.305	0.018	-	-	-0.348	0.006
TAC (µmol vitamin C Eq/L)	-0.085	0.517	-0.348	0.006	-	-
Age (year)	-0.230	0.077	0.036	0.785	-0.002	0.985
BMI ($kg.m^{-2}$)	0.174	0.185	0.064	0.624	-0.168	0.198

The ROC curve of MDA has indicated the usefulness of this biomarker in the diagnosis of RA disease. MDA has shown excellent sensitivity (AUC = 1.0, P<0.0001) in the diagnosis of RA patients comparing to the healthy controls, as shown in Figure 1.

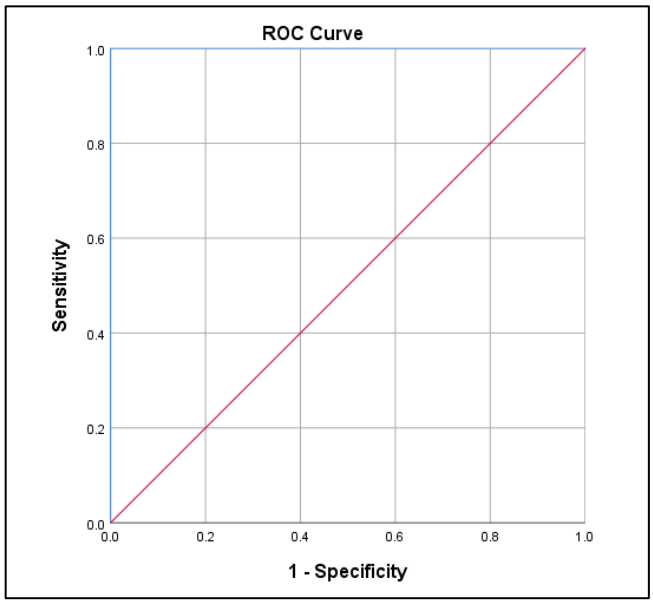

Figure 1. The ROC curve of MDA in the diagnosis of RA disease.

The ROC curve of TOS has indicated the usefulness of this biomarker in the diagnosis of RA disease. TOS has shown excellent sensitivity (AUC = 0.981, P<0.0001) in the diagnosis of RA patients comparing to the healthy controls, as shown in Figure 2.

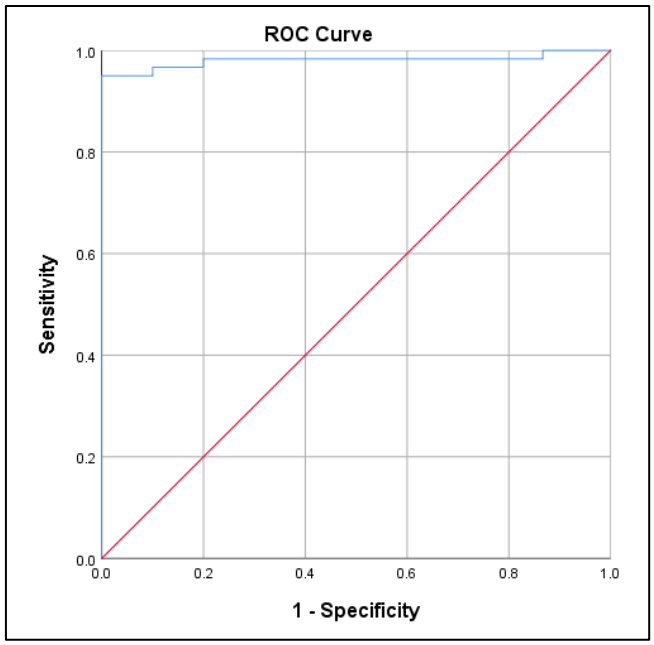

Figure 2. The ROC curve of TOS in the diagnosis of RA disease.

The ROC curve of TAC has indicated the usefulness of this biomarker in the diagnosis of RA disease. TAC has shown excellent sensitivity (AUC = 0.970, P<0.0001) in the diagnosis of RA patients comparing to the healthy controls, as shown in Figure 3.

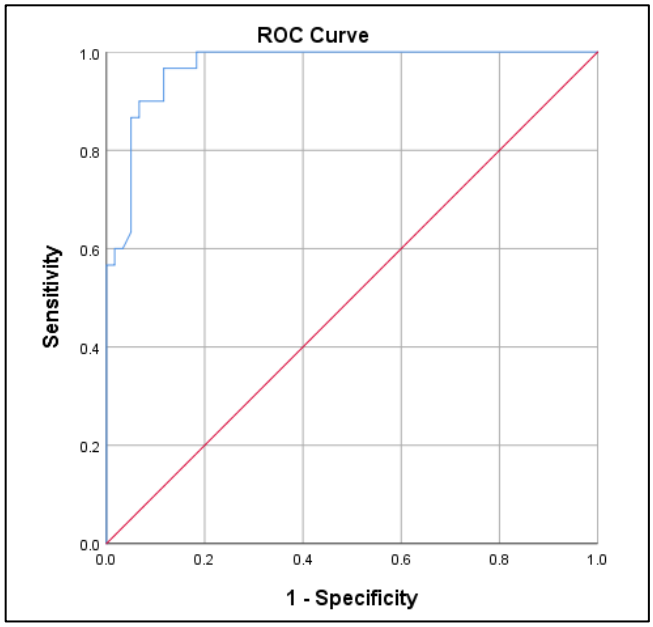

Figure 3. The ROC curve of TAC in the diagnosis of RA disease.

4. Discussion:

The present study has indicated the development of oxidative stress in RA patients. The serum levels of MDA as well as TOS were significantly elevated while the serum level of TAC was significantly reduced. Vasanthi et al. have reported significant elevated levels of MDA with nitric oxide in RA patients. Also, they have found a reduction in the circulation level of vitamin E in these patients. The authors have concluded that oxidative stress in RA may involve in the degradation of connective tissues and play a role in the pathophysiology of the disease [26].

Veselinovic et al. have reported that RA patients showed a significant increase in the oxidant markers MDA as well as hydrogen peroxide, indicating the usefulness of oxidative stress markers in the screening of RA disease [27], which was agreed with our results. Additionally, in a study performed on Iraqi patients with RA disease, the workers have revealed a significant elevated levels of MDA. The authors have linked this elevation to the immunity status of the RA patients [28]. Another study was performed on Iraqi RA patients has experimented the levels of TAC and MDA in the serum of patients. The workers have found that MDA was elevated significantly, while TAC levels was reduced [29].

Moreover, we have found a positive relationship between MDA and TOS, which indicates that lipid peroxidation takes a major part of the oxidative injury in RA patients. But, the negative correlation between TOS and TAC indicates the depletion of the antioxidant system to fight and detoxify oxidants properly. Also, we have found that MDA, TOS, and TAC can be used as excellent markers for the diagnosis of RA disease[30, 31].

5. Conclusions:

The results have shown increase in the oxidation state of RA patients. The level of MDA as well as TOS were significantly elevated in the serum of RA patient, in addition to this, the level of TAC was significantly reduced. This shift in the redox balance towered the oxidants indicate for sure the development of oxidative stress in RA patients. Furthermore, MDA, TOS, and TAC were observed to be excellent sensitive biomarkers for the diagnosis of RA disease. From this results, the administration with antioxidants is very important in the treatment of RA patients to control the disease and prevent any associated risks.

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