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Review Article

A Systematic Review on Association of Oxidative Stress in Rheumatoid Arthritis Based on Cross-Sectional Case-Control Studies

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ABSTRACT

Background: Rheumatoid Arthritis (RA) is a chronic form of inflammatory disorder where the immune system causes the destruction of bones and cartilage in joints and impacts the quality of life. Few studies have explored the possibility of the involvement of oxidative stress markers in the pathophysiological process of disease progression in RA as well as the beneficial effect of antioxidants. It was discovered that no systematic review had been carried out to support this idea over the previous five years. **Aim:** This review is intended to analyse the participation of oxidative stress markers in the origination and development of RA so that they can be a potential biomarker for supportive therapy**. Materials and Methods:** This systematic review was carried out as per the PRISMA guidelines. The authors executed a systematic literature search in different search engines for cross-sectional case-control research studies during the period from January 1, 2018 to November 30, 2022. Following inclusion and exclusion criteria, 16 articles have been selected for final analysis. **Results:** The evaluated biomarkers in the aforementioned studies countenance the participation of oxidative stress in RA with disease progression. However, additional research will be needed in the future to determine how oxidative stress contributes to the progression of RA and the potential role of antioxidants. **Conclusion:** Oxidation biomarkers may be an important tool in the early diagnosis of RA starting at the preclinical stage as well as in determining how the disease is evolving, offering new promise for employing these biomarkers as a focal point for supportive therapy.

Keywords: Rheumatoid Arthritis, Biomarkers, Malonandehyde, ROS, Oxidative Stress, SOD.

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INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic disease that has roots in 19th and 20th century genealogy.[1] It's a long-persisted autoimmune arthritis that impacts quality of life and life expectancy by destructing the cartilage and bones, which includes inflammatory changes in tissues within the joints.[2] RA can also lead to some other manifestations corresponding to cardiovascular disease, osteoporosis, as well as diminishing cognitive function in the brain. Osteoporosis and progressive joint destruction expose RA patients to a greater risk of progressive vertebral and non-vertebral fractures.[3] The American College of Rheumatology (ACR) recommends basically the clinical findings based on physical examination for the diagnosis of RA. About 1% of the total population worldwide suffers from RA, where women are found to be more on that list.[4] This disease is associated with a mean reduction in life expectancy of about 3 to 10 years, including premature death.[5] The pathogenesis of RA is significantly influenced by a number of autoantibodies, including Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA). These antibodies can be detected prior to the onset of RA. That is why they have a predictive, diagnostic and prognostic role. But unfortunately, as only 70% of the patients produce these antibodies, therefore, such corresponding biomarkers cannot be the ultimate choice for an accurate diagnosis of RA.[6] Although the main aetiology of RA is considered to be very complex and still needs to be apprised, certain aspects are under consideration. In brief, certain activated immune cells known as T helper cells, monocytes and neutrophils release a number of proinflammatory cytokines into the synovial fluid and membrane. These, in turn, trigger the B cells to produce RF and ACPA antibodies.[7] Reactive

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Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are known as free radicals as their outer shells contain unpaired electrons and have been found to be involved in the pathological processes of numerous diseases.[8] ROS include Superoxide (O_2^-), Hydroxyl (OH•), Peroxyl (ROO•) and hydrogen peroxide (H_2O_2) and are highly reactive.[9] Nitric oxide (NO•) and Nitrogen dioxide (NO_2•) are called RNS.[10] ROS and RNS are also involved in a number of pathways for regulation in cellular growth, differentiation, apoptosis, inflammation, oxygen sensing and the immune response against pathogenic microorganisms.[11] To withstand the deleterious effects instigated by free radicals, the role of antioxidants come into play. An antioxidant is capable of inhibiting the oxidation process or scavenging free radicals.[12] Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase (GPx), Glutathione Reductase (GR) and Thioredoxin Reductase (TR) are some enzymatic antioxidants in the human body that act vigorously to neutralise the free radicals generated in various biological processes.[13] These are found to be generated by either an exogenous source such as cigarette smoke, air pollution, heavy metals, ozone, ultra violet light, ionising radiation, or an endogenous enzyme, namely NADPH oxidase, lipooxygenase and cyclooxygenase, along with cellular respiration.[14] There is always a balance between the formation of ROS, RNS, prooxidants and counteracting mechanisms in living organisms, while unbalancing results in excessive formation of such components, resulting in an upsurge in oxidative stress.[15] Reactive Oxygen Species (ROS) are one of the main components behind the harmful consequences of oxidative stress.[16] Direct measurement of ROS levels in cells using fluorescent probes requires high accuracy and precision as they have a shorter half-life and are extremely reactive.[17,18] Therefore, another method was employed to evaluate the oxidative stress by considering the oxidative damage to lipids, proteins and nucleic acids caused by these species.[19,20] In continuation, oxidative damage to lipids can be measured by estimating the Malonaldehyde content.[21] Another strategy involves measuring the total antioxidant capacity as well as the quantification of certain free radical counteracting enzymes known as Catalase, Superoxide Dismutase, Glutathione Peroxidase and Glutathione Reductase *in vitro* and *ex vivo* in living tissue.[15] This article examines the involvement of oxidative stress in the pathological process and progression of rheumatoid arthritis after gathering and thoroughly examining the evidence from numerous research studies.

MATERIALS AND METHODS

Search Strategies

The literature for this article was searched systematically in "PubMed", "Google Scholar", "Science Direct" and "Web of Science" following the PRISMA guidelines. Few keywords such as "Free radicals and Rheumatoid arthritis", "Oxidative stress and Rheumatoid arthritis" and "ROS, RNS and Rheumatoid Arthritis" were included while searching for literature in the scientific database.

Inclusion and Exclusion Criteria

All the articles that were published in English between January 1, 2018 and November 30, 2022 were included in this study. The articles that directly or indirectly focus on the participation of free radicals or oxidative stress in the pathophysiology or progression of RA are included. The articles that are mainly considered for this review are only cross-sectional case-control studies attributed to *ex vivo* experiments with human volunteers and RA patients. The studies are discarded if the full-text version of the studies is not written in the English language, if it's a review article, case report, or letter to the editor, if it's an abstract published in scientific events or the full-text version is not available, or if the articles were published before 2018. Additionally, clinical research on rheumatoid arthritis that involves interventions is not covered in this review.

Study Selection and Appraisal of Quality

Following the previously mentioned predetermined inclusion and exclusion criteria, all of the titles and abstracts were reviewed. To determine whether the study was appropriate, the entire text of each article was examined and duplicates were eliminated. The methodology adopted for the selection of research articles is depicted in Figure 1. The search covered papers from January 2018 to November 2022 in the aforementioned electronic databases as well as clinical studies written in English. The references

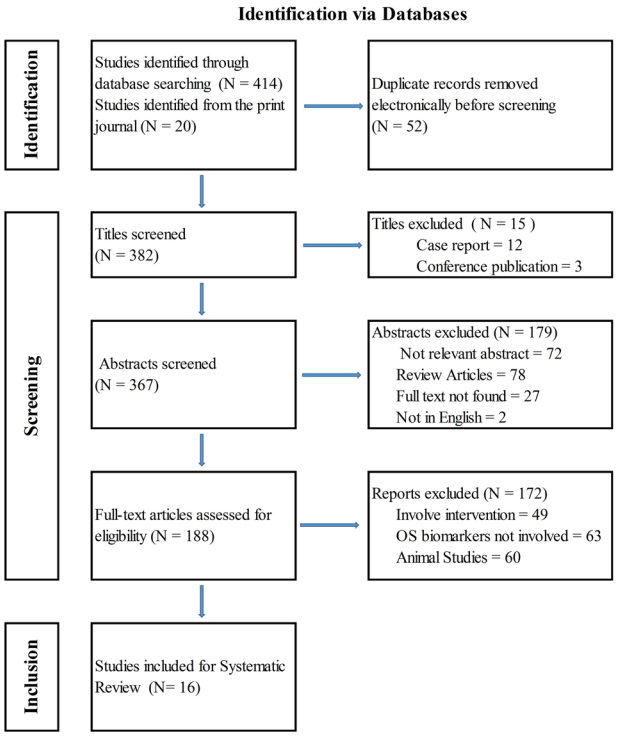

Figure 1: Schematic Representation of the selection of research articles for systematic review as per PRISMA Guidelines.

to the chosen articles were manually searched for further pertinent studies and documented. Information on study design, methodology, number of participants, cases and patients, as well as disease complications, was evaluated to assess the quality of the studies. The diagnostic parameters that were implemented were looked at carefully to examine the severity of the diseases.

Data Extraction

The selected research articles were reviewed and the following information was retrieved and tabulated: First author, Year of publication, Sample size, Mean Age and Age Range in Years for both Patients and Control, Types of samples, Oxidative markers that were analysed, Results, Main findings and outcomes.

RESULTS AND DISCUSSION

Description of the Selected Studies

A total of 16 clinical studies have been selected out of 434 studies after screening and all the selected studies fulfil the inclusion and exclusion criteria. All of the articles that were chosen are of moderate to high quality. A total of 877 patients with Rheumatoid arthritis and 722 normal human volunteers demonstrated as "control" took part in these selected research studies to be reviewed, of which 10 patients were the lowest carried out by Nawaz H. *et al.*[22] in the year 2021 and the highest number of patients, 164, were engaged by Baasu S. *et al.*[23] in the year 2020. The number of healthy human volunteers ranges from 20 to 127. Chetia P. *et al.*[24] did not disclose the number of healthy volunteers in their study. Few articles indicated the mean age of the patients and controls, whereas few articles mentioned the age range. The age of the patients suffering from Rheumatoid arthritis varies from 18 years to 74 years and the disease period is a minimum of 3 years. The control group, containing normal human volunteers, belonged to 30-65 years of age. In all the studies, human blood has been collected as a sample. But only in one study, urine[25] and in another study, a cell line of Fibroblast-Like Synoviocytes (FLS)[26] along with a blood sample, were collected to evaluate the parameters of oxidative stress (Table 1).

EVALUATED OXIDATIVE STRESS MARKERS IN RHEUMATOID ARTHRITIS

Malonaldehyde

It's the most evaluated marker in a blood sample. In 13 studies out of 16, Malonaldehyde (MDA) content was estimated. It's one of the aldehyde products of greatest interest from lipid peroxidation, along with 4-Hydroxynonenal (HNE). MDA is a typical indicator of oxidative stress since it is formed in large quantities during Lipid Peroxidation.[38] Oxidised lipids, which are frequently obtained in response to oxidative stress, can be particularly harmful as they can affect numerous proteins, lipid membranes and nucleic acids following their relatively lengthy half-lives.[39,40] In all the studies, MDA content was found to increase significantly, except for one. The study executed by Baasu S *et al.*[23] confirmed a non-significant increase in MDA level in RA patients than that of the control group.

8-Isoprostane

Urinary isoprostane was analysed by Duarte G *et al.*[25] in rheumatoid Arthritis patients and normal volunteers. The amount of 8-isoprostane, which is isomeric to prostaglandin F_2 and produced during arachidonic acid peroxidation processes, is directly correlated with the level of free radicals generated. Chemically stable isoprostane detected in plasma and urine is a dependable biomarker for peroxidation induced through free radicals.[41] Research evidence suggests that it is a promising index for inflammatory disorders promoted by cyclooxygenase.[42,43] The researcher found lower in urinary 8-iso-$PGF_{2\alpha}$ content in RA patients than that of a normal individual, which was significant.

Enzymatic Endogenous Antioxidants

Three enzymes Glutathione Peroxidase, Superoxide dismutase and Catalase are categorised as first line protective system capable of neutralising the free radicals.[44] Superoxide dismutase catalytically converts the superoxide radical or singlet oxygen radical to Hydrogen peroxide (H_2O_2) and molecular Oxygen (O_2). Finally, glutathione peroxidase takes the responsibility to convert H_2O_2 to water and lipid peroxides to the appropriate alcohols in mitochondria.[45] Among 16 studies, GPx was analysed by 5 researchers while SOD and Catalase were 7 and 4 respectively in the serum of patients with RA and normal human volunteers. All the researchers except one who studied these enzymatic endogenous antioxidant markers selected in this review reported significant reduction of GPx, SOD and Catalase in rheumatoid arthritis patients than normal human volunteers. Ogul Y *et al.*[30] in his studies reported non-significant decrease in catalase level in Rheumatoid arthritis group than that of the control group composed of normal human volunteers.

Non-Enzymatic Antioxidants

In addition to the above mention oxidative stress markers, non-enzymatic metabolic antioxidant such as Reduced Glutathione (GSH), nutrient antioxidant such as Vit E and Vit C were also analysed by different researchers selected in this review article. It is found that 6 researchers qualified GSH in RA patient's blood serum as well as in normal human volunteers. Das DC *et al.*[29] is the only researcher found in this review who carried out the estimation of Vit. C for both RA patients and normal human volunteers. The respective researchers found significant decrease in GSH level as well as Vit C in case of the patients suffering from Rheumatoid Arthritis in comparison with the control group consisting of normal human volunteers. Tocopherols and tocotrienols, a class of lipid-soluble antioxidants with the highest biological activity in Tocopherol (-TOH), are together referred to as vitamin E. Free radicals can also be neutralised by vitamin C

Table 1: Briefing of revealed oxidative stress marker investigated in both patients with RA and Normal human individual (Control).

References	Sample size (M+F)		Mean Age/ Age Range in Years		Duration of Disease in Years	Sample	Oxidative stress Marker Analyzed	Results			Main Findings / Outcomes
								RA Patients	Control	*p** Value	
	P	C	P	C							
Duarte G *et al.*, 2022[25]	51	55	55.6	35.6	18.8	Blood	GPx (U/gHb)	38.5 (33.5-43.6)	52.0 (48.1-55.9)	<0.001	Both the enzyme activity was found low in RA group compared to Control that proves increase in oxidative stress in RA patients. Isoprostane was found to be decrease in the urine of RA patients. Albunim content was also low.
							SOD (U/gHb)	1316.4 (1197.0-1235.7)	1741.0 (1600.5-1881.5)	<0.001	
							Albumin (mg/dL)	4.2 (4.1-4.3)	4.5 (4.5-4.6)	0.004	
						Urine	Isoprostane (8-iso PGF2a) (ng/mmol of creatinine)	111.3 (91.8-130.9)	137.9 (122.3-153.5)	0.004	
Ahmed R *et al.*, 2022[27]	80	80	30-65	30-65	4.7	Blood	MDA (ng/mL)	237.8±108.9A	22.1±18.31C	0.001	MDA was elevated in RA patients while Total Antioxidant was found to be decreased
							TAOS (U/mL)	1.150±1.01	1.133±0.872	0.882	
Anwar K. *et al.*, 2022[28]	50	50	45-70	30-50	__	Blood	MDA ng/dL	4.57±1.22	0.96±0.0392	0.015	MDA and NO were appeared as high value in RA patients in comparison to healthy volunteers whereas SOD, GSH and Catalase were significantly lower.
							SOD ng/dL	0.118±0.0018	1.056±0.056	0.035	
							GSH ng/dL	6.53±1.28	9.29±1.99	0.011	
							CAT ng/dL	4.59±1.088	6.29±1.45	0.006	
							NO ng/dL	35.28±6.58	19.98±3.58	0.0001	
							Vit E ng/dL	7.48±1.44	13.59±4.29	0.041	
							Vit C ng/dL	2.48±0.956	4.58±0.956	0.019	
							Vit A ng/dL	358.98±21.58	652.35±19.65	0.017	

References	Sample size (M+F)		Mean Age/ Age Range in Years		Duration of Disease in Years	Sample	Oxidative stress Marker Analyzed	Results			Main Findings / Outcomes
								RA Patients	Control	*p** Value	
	P	C	P	C							
Sun Y. *et al.*, 2022[26]	45	30	55.98	56.23	6	Blood	HO-1	↑	↓	<0.01	ROS and MDA were remarkably higher whereas TAOC was decreased in the serum RA patient which indicates increase in oxidative stress in patients with RA.
							ROS	↑	↓	<0.01	
							TAOC	↓	↑	<0.01	
Nawaz H. *et al.*, 2021[22]	10	20	_	_	_	Blood	MDA	↑	↓	0.001	MDA content was high and all the free radical scavenging capacity was low in RA patients. FCA was found to be non-significant.
							Ferrous Chelating activity (FCA)	↑	↓	0.375	
							DPPH Scavanging Capacity	↓	↑	0.000	
							Superoxide Scavanging Capacity	↓	↑	0.006	
							Hydroxyl Scavanging Capacity	↓	↑	0.475	
							ABTS radical Scavanging Capacity	↓	↑	0.001	
							LARC-FTCA	↑	↓	0.048	
Das DC. *et al.*, 2021[29]	20	20	36.95	32.20	--	Blood	MDA (nmol/mL)	3.85	1.76	<0.01	MDA was significantly higher wherein Vit C was lower representing a higher oxidative stress in RA patients.
							Vit C (µmol/L)	24	31.51	<0.01	

References	Sample size (M+F)		Mean Age/ Age Range in Years		Duration of Disease in Years	Sample	Oxidative stress Marker Analyzed	Results			Main Findings / Outcomes
								RA Patients	Control	*p** Value	
	P	C	P	C							
Ogul Y. *et al.*, 2021[30]	28	20	44.3	--	--	Blood	MDA (nmol/grHb)	8.84± 0.60	6.54±0.63	0.0001	In comparison to the healthy volunteers, the value of MDA and XO was higher and the value of GPx, SOD and CAT was lower in RA patient which denotes the participation of oxidative stress.
							GPx (U/grHb)	51.23±13.23	63.38±16.97	0.008	
							SOD (U/grHb)	1.41±0.48	1.72±0.24	0.009	
							CAT (U/grHb)	37.45±9.49	42.79±9.32	0.059	
							XO (U/grHb)	3.49±0.52	3.16±0.43	0.023	
Al-Jawadi WA. *et al.*, 2021[31]	95	50	18-74	--	--	Blood	MDA (μ mol/L)	5.543±0.388	1.200±0.043	≤0. 05	MDA content was significantly increased in RA patients. GSH, Ceruplasmin, SOD, Uric acid and Albumin concentration appeared as remarkably low whereas GPx was higher in RA patients than that of Normal volunteers.
							GSH (μ mol/L)	2.560±0.155	4.955±0.198	≤0. 05	
							Ceruloplasmin (μ mol/L)	187.56±1.260	209.03±1.767	≤0. 05	
							SOD (ΔO.D)	0.0343±0.003	0.0917±0.047	≤0. 05	
							GPx (μ mol/L)	5.512±0.390	3.829±0.224	≤0. 05	
							Uric Acid (mg/dL)	4.786±0.297	4.998±0.343	≤0. 05	
							Albumin (g/dL)	3.595±0.109	4.348±0.129	≤0. 05	
Alisik M. *et al.*, 2021[32]	152	89	43-61	43-59	10	Blood	GSH (μmol/L)	758.7 (609.5-987.5)	869.8 (737.8-992.1)	0.005	There was a remarkable decrease in GSH in RA patients as compared to Normal. Thiol Content was also low but Disulfide content was appeared high in RA patients.
							Thiol (SH) (μmol/L)	309.7 (269.2-335.6)	315.9 (296.1-382.4)	<0.001	
							Disulfide (SS) (μmol/L)	21.75 (19.09-24.5)	15.45 (14.05-17.63)	<0.001	

References	Sample size (M+F)		Mean Age/ Age Range in Years		Duration of Disease in Years	Sample	Oxidative stress Marker Analyzed	Results			Main Findings / Outcomes
								RA Patients	Control	*p** Value	
	P	C	P	C							
Mukhopadhyay K. *et al.*, 2021[33]	29	10	43.3	38.3	9.58	Blood	ROS	↑	↓	<0.01	Patients with RA were shown to have greater levels of ROS production.
Chetia P. *et al.*, 2020[24]	15	_	24-58	_	3-30	Blood	Superoxide	↑	↓	<0.01	Superoxide, Nitrite and MDA content was appeared to be high in patients with RA. But SOD and GSH level was low in RA patients.
							Nitrite	↑	↓	<0.01	
							SOD	↓	↑	<0.01	
							MDA	↑	↓	<0.01	
							GSH	↓	↑	<0.01	
Mititelu RR. *et. al.*, 2020[34]	15	10	59.69	56.4		Blood	MDA	↑	↓	<0.05	TAC was observed to be lowered while MDA and Protein Carbonyl levels significantly increased in RA patients.
							TAC	↓	↑	<0.05	
							Protein Carbonyl	↑	↓	<0.05	
Aljoboury BA. *et al.*, 2020[35]	61	127	47.43	48.94		Blood	MDA (µmol/L)	2.35±1.93	0.86±0.52	<0.001	MDA level of the RA patients attained to be significantly higher while TAC was extremely lower in comparison to normal individuals.
							TAC	0.10±0.21	0.53±1.02	<0.001	
Baasu S. *et al.*, 2020[23]	164	101	55	54.9	9.6	Blood	MDA	2.58±0.7	2.52±0.6	0.55	Patients with RA had significantly higher MDA levels than healthy people.
							PON-1	109.73±67.4	128.09±76.2	0.042	
							PSH	3.15±3.7	3.77±0.7	<0.001	
Mateen S *et al.*, 2019[36]	20	10	40	39		Blood	NO	↑	↓	<0.05	Increase in NO, ROS and MDA was observed in RA patients while the level of Reduced Glutathione, SOD, Catalase and GPx was significantly decreased in comparison to normal human volunteers
							ROS	↑	↓	<0.05	
							GSH	↓	↑	<0.05	
							SOD	↓	↑	<0.05	
							CAT	↓	↑	<0.05	
							GPx	↓	↑	<0.05	
							Protein Carbonyl	↑	↓	<0.05	
							MDA	↑	↓	<0.05	

References	Sample size (M+F)		Mean Age/ Age Range in Years		Duration of Disease in Years	Sample	Oxidative stress Marker Analyzed	Results		Main Findings / Outcomes
	P	C	P	C				RA Patients	Control	*p** Value	
Mahdi JK. *et al.*, 2018[37]	42	50	30-50	30-50		Blood	MDA (µmol/L)	1.24±0.12	0.67±0.12	<0.001	Patient with RA contains remarkable increase in the MDA content whereas GPx, SOD and CAT were higher.
							GPx (U/gHb)	36.4±9.8	45.9±15.3	<0.001	
							SOD (U/gHb)	1158±254	1800±313	<0.001	
							CAT (U/gHb)	218±30.3	275±37.7	<0.001	

M: Male, F: Female, P: Case/Patient C: Control/Normal human Volunteer, MDA: Malonaldehyde, TAA: Total antioxidant Activity, SOD: Superoxide dismutase, TOS: Total oxidant status, PON-1: Paraoxonase-1, PSH: Protein-SH, GPx: Glutathione Peroxidase, CAT: Catalase, GSH: Glutathione, NO: Nitric oxide, ROS: Reactive Oxygen Species, XO: Xanthine oxidase, TAC: Total antioxidant capacity, FCA: Ferrous chelating assay.

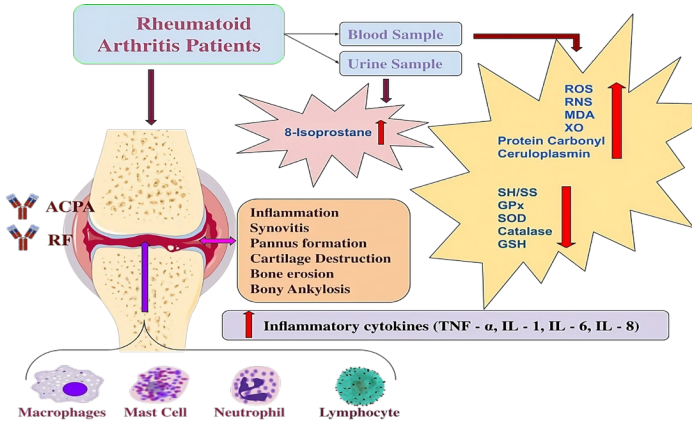

Figure 2: Pathogenesis and involvement of different mediators in Rheumatoid Arthritis.

which is water soluble and helps recycle other antioxidants and vitamins.[46] In both plants and mammals, low molecular weight glutathione, which is composed of cysteine, glycine, glutamic acid are found throughout the cell.[47] Furthermore GSH seems to be a powerful antioxidant and performs a variety of other tasks, including helping the body remove xenobiotics from the body, transporting amino acids, metabolising prostaglandins and leukotrienes and absorbing minerals primarily iron and selenium from the intestine.[48,49]

Antioxidant capacities

Determining the Total Antioxidant Capacity (TAC) or Total Antioxidant Activity (TAA), comprised of different assay protocols, is the most promising method to evaluate the oxidant-antioxidant balance in a wide range of biological and chemical systems, including food, drink and other, as well as plasma or bodily fluid.[50,51] In this systematic review, five researchers used different methods, such as the DPPH radical assay, the ABTS radical assay and Ferrous Chelating Activity (FCA), to evaluate TAC or TAA. Ahmed R *et al.*[27] represented non-significant variation in TAOS between patients with RA and normal individual groups. Sun Y. *et al.*[26] Mititelu RR. *et al.*[34] and Aljoboury BA. *et al.*[35] reported a significant decrease in the antioxidant capacities in the patients suffering from RA than that of normal human volunteers, denoting the possibility of the incorporation of oxidative stress in RA. Nawaz H. *et al.*[22] performed Ferrous Chelating activity (FCA), DPPH and ABTS radical assays and reported significant reductions in DPPH and ABTS scavenging abilities in RA patients, but no significant difference was observed in the case of Ferrous Chelating Activity (FCA).

Reactive Oxygen Species (ROS)/Reactive Nitrogen Species (RNS)

These are the small molecules generated by oxidative physiological mechanisms and have a substantial impact on biological processes and pathological pathways. They are implicated in the damage

and death caused by cellular stress. On the other hand, the biocidal activity that was exhibited by RNS through free radical peroxidation might worsen the total damage.[52] The free radicals, namely superoxide radical, hydroxyl radical and nitric oxide, were analysed in the articles recruited for this systematic review. The major sources of ROS in humans are the mitochondrial respiratory chain and activated phagocytes during infection.[53] Nitric oxide synthase catalyses the generation of potentially damaging RNS and NO.[54] Despite playing a normal function in immunity, homeostasis and cell signaling in low concentrations, excessive ROS and RNS production may contribute to the oxidative destruction of lipids, proteins and nucleoside bases, which can cause necrosis.[55] Therefore, measurement of ROS and RNS is one of the most important biomarkers to get information about oxidative state status in the human body. This systematic review comprised 16 research articles. Of those, 5 were found to evaluate ROS and 3 were found to evaluate RNS. Anwar K. *et al.*[28] reported a significant increase in NO (35.28 ng/dL) in RA patients as compared to normal subjects (19.98 ng/dL) (p=0.000*). Likewise, Sun Y. *et al.*, Nawaz H. *et al.* and Mukhopadhyay K. *et al.* found significantly higher ROS generation in patients with RA while comparing with normal human volunteers (p<0.01). Chetia P. *et al.*[24] and Mateen S. *et al.*[36] estimated both ROS and RNS and reported a significant increase in ROS and RNS levels in RA patients compared to normal individuals (p<0.05). All of these studies highlight the role of oxidative stress caused by free radicals in the pathological process of RA.

Albumin

Serum albumin is found to be synthesised in the liver with the help of a polypeptide chain containing 585 amino acid residues. Under normal and oxidative stress circumstances, serum albumin plays a critical role in antioxidant defence.[56] Al-Jawadi WA *et al.*[31] evaluated albumin as an oxidative stress parameter both in RA patients and in normal individuals. This albumin level was analysed in 95 RA patients and 50 healthy volunteers and the value of the RA patients was discovered to be considerably lower than that of the healthy group. (p≤0. 05). It is well established that Serum Albumin curtails oxidative stress by binding to certain pro-oxidants similar to iron and copper. It also prevents peroxidation of lipids and traps ROS with the help of methionine and cysteine residues.[57] Therefore, a decrease in the serum albumin level in patients with RA may postulate the association of oxidative stress with the pathological process of RA.

Protein Carbonyl

Mititelu RR. *et al.*[34] estimated an effective and promising oxidative stress marker, Protein Carbonyls (PCO), in 15 RA patients and 10 healthy volunteers, which are related to disease state and treatment in a variety of disorders due to the simplicity of the sampling and relatively long half-life.[58] Protein carbonyls are formed through the oxidation of protein side chains, incorporating aldehydes and ketone groups into the protein.[59] Different ROS are responsible for the production of protein carbonyl by direct and indirect oxidative pathways to proteins and amino acids.[60] Therefore, an increase in protein carbonyl levels in the blood directly or indirectly correlates with oxidative stress in our body. This aforementioned study illustrates the escalation of the protein carbonyl level in RA patients while comparing them with the normal individual, representing the contribution of oxidative stress in RA.

Xanthine Oxidase

Xanthine Oxidase (XO) and Xanthine Dehydrogenase (XDH) are the enzymes responsible for purine metabolism to produce uric acid.[61] Both forms are vital biological sources of oxygen-derived free radicals that stimulate NADH oxidation and bring about tissue destruction and other related diseases.[62] The gene for XDH is transcriptionally controlled by hormones, cytokines and growth factors. Later on, it is possible to turn XDH into xanthine oxidase.[63] Ogul Y. *et al.*[30] evaluated Xanthine oxidase along with MDA, GPx, Catalase and SOD, implicating 28 RA patients and 20 normal human volunteers and reported a remarkable elevation of xanthine oxidase in RA patients (p=0.023). As mentioned earlier, XO is a vital biological source of free radicals. Increasing its value in RA patients favours the possibility of oxidative stress in patients with Rheumatoid Arthritis.

Cerruloplasmin

Despite being an important biomarker, out of 16 studies, only one researcher, Al-Jawadi WA. *et al.*,[31] estimated the cerruloplasmin level in 90 RA patients and 100 normal human volunteers. The liver synthesises Ceruloplasmin, a circulating α_2-glycoprotein which promotes the conversion of Fe^{2+} (ferrous iron) into Fe^{3+} (ferric iron), demonstrating an oxidase activity depending on copper.[64] Plasma redox processes are fundamental to ceruloplasmin's physiological function. Iron can be incorporated into transferrin with the help of ceruloplasmin without producing any harmful iron by-products.[65] Ceruloplasmin levels may rise as a protective response to an escalation in the amount of free Fe^{2+}, which may contribute to lipoperoxidation prompted by free radicals. As a result, increased levels of plasma ceruloplasmin may indicate unusually high levels of oxidative stress.[64] But the researcher found a significant decrease in ceruloplasmin level in the patients with RA than that of a normal human individual, questioning the conceptualization of Rheumatoid Arthritis as oxidative stress.

Thiol/Disulphide (SH/SS) Homeostasis

Thiol is classified as a non-enzymatic, vital and potent antioxidant protecting organisms from the harmful consequences of oxidative stress and is made up of the Sulfhydryl (-SH) group.[66] Alisik M. *et al.*[32] analysed the thiol/disulfide homeostasis for 152 RA patients and 89 normal human volunteers. There was a remarkable decrease in SH values (p=0.001), whereas the percentage ratios

of SS and SS/SH were considerably elevated ($p<0.001$) in patients with RA in comparison with normal humans, denoted as the control group. It is known that thiols can either be protein-bound or free as Glutathione (GSH) and cysteine, which are available in both intracellular and extracellular space and form disulfides through oxidation if oxidative stress is increased. So, thiol/disulfide homeostasis can be an excellent biomarker for oxidative stress measurement because, being a reversible process, disulfide bonds tend to reduce into thiol.[67] Detoxification is based on the maintenance of thiol/disulfide equilibrium. Thiol measurements in serum provide an indirect indication of antioxidant defence.[68]

Different researchers considered in this review article employed discrete biomarkers of oxidative stress for evaluation in normal individuals and RA patients. Figure 2 represents the pathogenesis and involvement of different antibodies and oxidative stress markers in the progression of Rheumatoid Arthritis. Blood serum from both patients with RA and normal individuals was used for the assessment of the aforementioned and the results were compared for analysis. Only one biomarker, known as 8-isoprostane, was estimated in urine by Duarte G *et al.*[25] The most extensively evaluated marker was the MDA content, which is a product obtained through the peroxidation of lipids by free radicals. GPx, SOD, catalase and GSH were also estimated by a few researchers, along with ROS, RNS and Antioxidant capacity. These evaluated biomarkers in these selected studies suggest the contribution of free radical-induced oxidative stress in the pathological process of RA, but of course more cross-sectional, case-control studies will be required to support this observation. This systematic review has a number of strengths and limitations. One of the major strengths is the extensive analysis of the selected articles in consort with reviewing the other literature to gather information in terms of oxidative stress biomarkers. However, our ability to quantitatively explore the contribution of oxidative stress in the pathological process of RA is constrained by the relatively smaller number of articles that were chosen as a result of inclusion and exclusion criteria and the assessed parameters' heterogeneity and disparateness in the assessment techniques. Current treatment strategies for RA employ Disease-Modifying Anti-Rheumatic Drugs (DMARDs) that are both synthetic and biological and focus on achieving early and long-lasting low disease activity.[69] Philippou E. *et al.*, in their systematic review, revealed the beneficial effect of dietary intervention in RA. He summarised that dietary factors such as excess consumption of meat and free fructose may increase the risk of RA development, while the Mediterranean diet and fatty fish may lower it.[70] Previous cross-sectional case-control studies demonstrate the association between dietary antioxidant intakes in conjunction with reduction in the risk of RA progression.[71,72] Therefore, piling up all the information analysed from the selected articles in this systematic review and also from the other literature, it can be postulated that free radicals associated with oxidative stress could possibly act as a potential biomarker for RA diagnosis and progression, leaving a scope for further studies involving the usage of antioxidants in its management. Quionez-Flores CM *et al.*[4] in 2016 in their systematic review also support the oxidative stress relevance in the pathological process of RA. Nevertheless, it's still unclear how these potential supportive treatments based on the use of antioxidants will be benefited to control disease activity and to what extent the different biomarkers of oxidative stress may be cooperative for early diagnosis and management of this disease. Therefore, we recommend more number of cross-sectional case-control studies in the future to define the involvement and accuracy of different novel serum/plasma, salivary and urinary oxidative biomarkers such as 8-hydroxy guanosine, modified albumin, advanced oxidation protein products, biopyrins and others, in addition to diverse conventional oxidative biomarkers concerning disease activity, pathological mechanisms and progression of RA.

CONCLUSION

Rheumatoid Arthritis has diverse aetiologies and pathophysiological mechanisms, including autoimmunity affecting cartilage and synovial joints, hampering longevity and standard of living. There are few shreds of corroboration of the contribution of free radical-induced oxidative stress to the pathological mechanism of RA accompanying its concomitant comorbidities and well as the beneficial effect of numerous dietary antioxidants helping to reduce oxidative stress in RA patients. Again, in this systematic review, oxidative stress biomarkers are found to be involved in RA pathological mechanisms and disease progression after critically analysing the 16 aforementioned cross-sectional case-control studies involving RA patients and normal human volunteers. Consequently, these oxidative biomarkers may become a crucial instrument in the early diagnosis of RA, commencing at the preclinical stage, as well as in assessing the course of evolution, thereby providing fresh hope for using these biomarkers as a focus for supportive therapy. Nevertheless, the small number of articles, the different evaluated oxidative markers, the differences in the methodology in the evaluation of these biomarkers and the lack of a specific mechanism of action limit the distinct establishment of this knowledge. Therefore, to demonstrate at which specific phase of RA this oxidative stress comes into play, its accurate mechanism of action and whether the antioxidant consumption would be beneficial or not, future studies would be required.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

RA: Rheumatoid Arthritis; **RF:** Rheumatoid factor; **ACPA:** Anti Citrullinated Protein Antibodies; **RNS:** Reactive nitrogen species; **MDA:** Malonaldehyde; **TAA:** Total antioxidant Activity; **SOD:** Superoxide dismutase; **TOS:** Total oxidant status; **PON-1:** Paraoxonase-1; **PSH:** Protein-SH; **GPx:** Glutathione Peroxidase; **CAT:** Catalase; **GSH:** Glutathione; **NO:** Nitric oxide; **ROS:** Reactive Oxygen Species; **XO:** Xanthine oxidase; **TAC:** Total antioxidant capacity; **FCA:** Ferrous chelating assay; **TR:** Thioredoxin reductase.

SUMMARY

The main purpose of this review paper is to find out whether oxidative stress biomarkers play any role in the pathogenesis of Rheumatoid Arthritis (RA). It is a chronic systemic autoimmune illness that has devastating effects on human health, mainly in the joints. To meet the goal, several pieces of literature were searched systematically in scientific databases like PubMed, Google Scholar, Science Direct and Web of Science by putting in the required phrases of words and finally, 16 research articles were selected for final review after final screening. The results of all the selected articles were documented in tabular form. All the selected articles in this systematic review reported an increase in oxidative markers in the blood of patients with RA compared to that of a normal human individual. These oxidative biomarkers may therefore become an important tool in the early diagnosis of RA starting at the preclinical stage as well as in determining the course of evolution, offering new promise for employing these biomarkers as a focal point for supportive therapy. Nevertheless, the authors recommend further studies to demonstrate at which specific phase of RA this oxidative stress comes into play, its accurate mechanism of action and the beneficial effect of antioxidants.

AUTHOR CONTRIBUTIONS

Conceptualization: Abdul Baquee Ahmed, Purbajit Chetia; Data Collection: Purbajit Chetia, Hemen Kalita; Design of Study: Abdul Baquee Ahmed; Validation: Abdul Baquee Ahmed, Purbajit Chetia, Heman Kalita; Drafting and editing: Purbajit Chetia.

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