Uluslararası Fen Araştırmalarında Yenilikçi Yaklaşımlar Dergisi
International Journal of Innovative Approaches in Science Research 2018, Vol. 2 (4), 140-151
https://doi.org/10.29329/ijiasr.2018.173.3

Original article

Impaired Dynamic Thiol/disulfide Homeostasis and Pro-inflammatory Parameters in Hand Osteoarthritis

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Abstract

Background: Reactive oxygen species have a role in pathogenesis of osteoarthritis.

The main objective of this study was to determine other oxidant/antioxidant substances and inflammatory markers in hand osteoarthritis patients.

Methods: Thirty healthy controls and 50 patients with hand osteoarthritis (HOA) were included in the study. All patients were questioned about age, sex, history of the symptoms, presence of sensitive and swollen joints, smoking habits, other systemic diseases and medications. Serum thiol-disulfide homeostasis tests (TDHT), catalase (CAT), ceruloplasmin (Cp), arylesterase (ARES), paraoxonase (PON), stimulated paraoxonase (SPON), total antioxidant status (TAS), total oxidant status (TOS), malondialdehyde (MDA), myeloperoxidase (MPO), routine biochemistry tests and inflammatory markers: Interleukin-1β (IL-1β), interleukin-6 (IL-6), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured.

Results: MPO, TDHT, MDA, MPO and inflammatory markers (IL-6, CRP and ESR) were significantly different in HOA patients from those in control group (p=0.005; p=0.001; p=0.014; p=0.005; p=0.012; p=0.003 and p<0.001, respectively).

Conclusion: Our results support that oxidative stress increases in HOA and with the severity of the disease, suggesting that oxidative stress might be involved in pathogenesis of HOA.

Keywords: Oxidative stress, Thiol disulfide homeosthasis, Osteoarthritis, Erosive hand osteoarthritis, Non-erosive hand osteoarthritis, Inflammatory markers, Cytokines.

Received: 22 November 2018 * **Accepted**: 12 December 2018 * **DOI**: https://doi.org/10.29329/ijiasr.2018.173.3

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INTRODUCTION

Hand osteoarthritis (HOA) is a common degenerative joint disease mainly affecting proximal (PIPs) and distal interphalangeal joints (DIPs), and first carpometacarpal joints (CMCs) (1-3). HOA occur mostly in women rather than men, lead to pain and restricts daily activities.

Erosive hand osteoarthritis (EHOA) is a subset of HOA characterized by an abrupt onset, with the presence of erythema, inflammatory flares of the interphalangeal joints, and swollen joints. Limited evidence shows different pathogenesis between EHOA and non-erosive HOA (NHOA) (4, 5). The role of systemic inflammation in erosive and non-erosive HOA is contradictory (6); studies have shown high prevalence of synovitis or the presence of intra-articular low-grade inflammation in both forms of HOA (3-7). Due to the low-grade elevation of the classical acute-phase response parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), laboratory investigations were found to be unsatisfactory in EHOA patients.

In osteoarthritis (OA) patients, inflammatory compounds and cytokines in joint tissues and synovial membrane are up-regulated. Inflammatory mediators and markers such as interleukin-1β (IL-1β), CRP and interleukin-6 (IL-6), prostaglandin E2, nitric oxide (NO) and reactive oxygen species (ROS) are released in response to the matrix degradation and chondrocyte apoptosis. Thus, homeostasis between anabolic and catabolic pathways cannot be maintained by chondrocytes anymore. Moreover, one catabolic factor, IL-1β was shown to have a predominant role in the pathogenesis of EHOA ROS generation (8, 9).

Previous in vitro studies reported the role of ROS in the pathogenesis of HOA using malondialdehyde (MDA) and myeloperoxidase (MPO) as markers of oxidants/antioxidants (10, 11). This is the first study assessing oxidant/antioxidant status HOA patients by using multiple oxidative stress markers other than MDA and MPO.

The primary aim of this study is to evaluate the role of various oxidant/ antioxidant parameters; thiol-disulphide homeostasis tests (TDHT), MPO, catalase (CAT), ceruloplasmin (Cp), arylesterase (ARES), paraoxonase (PON), stimulated paraoxonase (SPON), total antioxidant status (TAS), total oxidant status (TOS) activities and lipid peroxidation product MDA in HOA ethiopathogenesis, and to compare the HOA results with the control group and within erosive and non-erosive subgroups. The secondary aim of the study is to investigate inflammatory molecules (IL-6, IL-1β etc.) and markers (CRP and ESR) in the same groups.

MATERIALS AND METHODS

Patient selection

Fifty (39 female, 11 male) patients with hand osteoarthritis, aged between 39 and 79 (59.96 ± 1.36) years, who applied to Adnan Menderes University Medical Faculty Training and Research Hospital Physical Therapy and Rehabilitation Polyclinic included in this study. The control group consisted of 30 (18 female, 12 male) healthy individuals aged between 20 and 52 (32.37 ± 1.17) years. All patients were questioned about the age, sex, history of the symptoms, presence of sensitive and swollen joints, smoking habits, other systemic diseases and medications. Changes in wrist-hand radiographs of patients were scored using the Larsen method (12). The subjects with history of malignancies and usage of antioxidant supplement such as vitamin C, E or N- acetylcysteine, and other chronic or systemic diseases were not included. HOA patients were categorized in 2 subgroups as Erosive (E; n=8) and Non-erosive (NE; n=42), according to their clinical and radiological findings. All participants were informed about the procedure, signed the informed consent form and the study was approved by the Institutional Ethical Committee.

Blood sampling and laboratory analysis

The 8 hour fasting blood samples of the subjects were collected and serums were obtained by centrifugation. Samples were stored at −80°C until the analysis day.

Serum TDHT, Cp, MPO, CAT, MDA, TAS, TOS, PON, SPON, ARES and routine biochemistry analyses were performed spectrophotometrically (Cobas 501, Roche, Mannheim, Germany), CRP levels were analyzed by using turbidimetric method (Prestige 24i, Chema Diagnostica, Tokyo, Japan), and complete blood count (hemoglobin, hematocrit) were measured (ADVIA 2120 Hematology System, Siemens, Erlangen, Germany) in whole blood samples.

TDHT analyses were performed with an automated method described by Erel & Neselioglu (13). Half of the difference between total and native thiol concentrations gave the disulfide amounts. The disulfide/native thiol ([–SS–] / [–SH]), disulfide/total thiol ([–SS–] / [–SH + –SS–]), and native thiol/total thiol ([–SH] / [–SH + –SS–]) ratios were also indicated as Index 1, Index 2 and Index 3, respectively. A colorimetric method, based on enzymatic oxidation of ferrous ion to ferric ion, described by Erel O (14) was used for the Cp concentration measurements. Results were expressed in units per liter serum. Goth's method (15) was used for the measurement of CAT activity and results were stated in kU/L. MPO activity was measured by a modification of the o-dianisidine method (16), activity was expressed in units per liter serum. TAS concentrations were analyzed for determination of anti-oxidative effect of the sample against the potent free radical reactions by using colorimetric kits (Rel Assay Diagnostic, Gaziantep, Turkey) developed by Erel O (17). The results were expressed as mmol Trolox equivalent/L. TOS levels were measured with commercially available kits (Rel Assay Diagnostic,

Gaziantep, Turkey) developed by Erel O (18). Results were expressed as micro molar hydrogen peroxide equivalent per liter (μmol H_2O_2 equivalent/L). PON activity was measured in the absence (basal activity) and presence of NaCl (salt-stimulated activity-SPON) with commercial kits (Rel Assay Diagnostic, Gaziantep, Turkey) and its activity was shown in U/L (19). ARES activity was measured with commercially available kits (Rel Assay Diagnostic, Gaziantep, Turkey) and its activity expressed as kU/L serum (20). MDA levels were determined by using Asakawa and Matsushita method and given as nmol/ml (21).

Serum levels of TIMP-1, IL-1β and IL-6 were determined using commercial enzyme-linked immunosorbent assays (ELISA) (eBioscience, Bender MedSystems, Vienna, Austria). All measurements were carried out in accordance with the manufacturer's instructions and implemented using a microplate reader. The results were expressed as pg/ml. The intra-assay coefficient of variation of IL-1β was 5.1%; the inter-assay coefficient of variation was 8.6%. The intra-assay coefficient of variation of IL-6 was 3.4%; the inter-assay coefficient of variation was 5.2%. The intra-assay coefficient of variation of TIMP-1 was 10%; the inter-assay coefficient of variation was 12%. The minimum detection doses for IL-1β, IL-6 and TIMP-1 were 0.3 pg/ml, 0.92 pg/ml and 2 pg/ml, respectively.

Statistical analysis

The data analysis were performed by using the statistics software SPSS 22 (SPSS version 22, Chicago, IL, USA). The mean ± standard error of the mean (SEM) was used for the variables. In addition, the homogeneity of variance was checked with Levene's test. The normality hypothesis was evaluated with the Shapiro–Wilk test. The one-way analysis of variance (ANOVA) test and independent t test were used for parametric conditions. The relationship between two variables was evaluated with the Pearson's test. *p* values less than 0.05 were considered statistically significant with a 95% confidence interval.

RESULTS

Patients admitted to the out-patients clinic, were diagnosed by means of clinical and radiological evaluation as having HOA. Subjects with physical evidence of hard tissue enlargement and/or deformity in three or more index hand joints and hand radiographs were then sub-grouped as non-erosive and erosive. Patients with radiographic central gull-wing erosions and/or erosions in the interphalangeal joints (DIP and PIP) were described as EOA, while patients with joint-space narrowing, osteophytes in the interphalangeal joints were categorized as non-erosive (Figure 1).

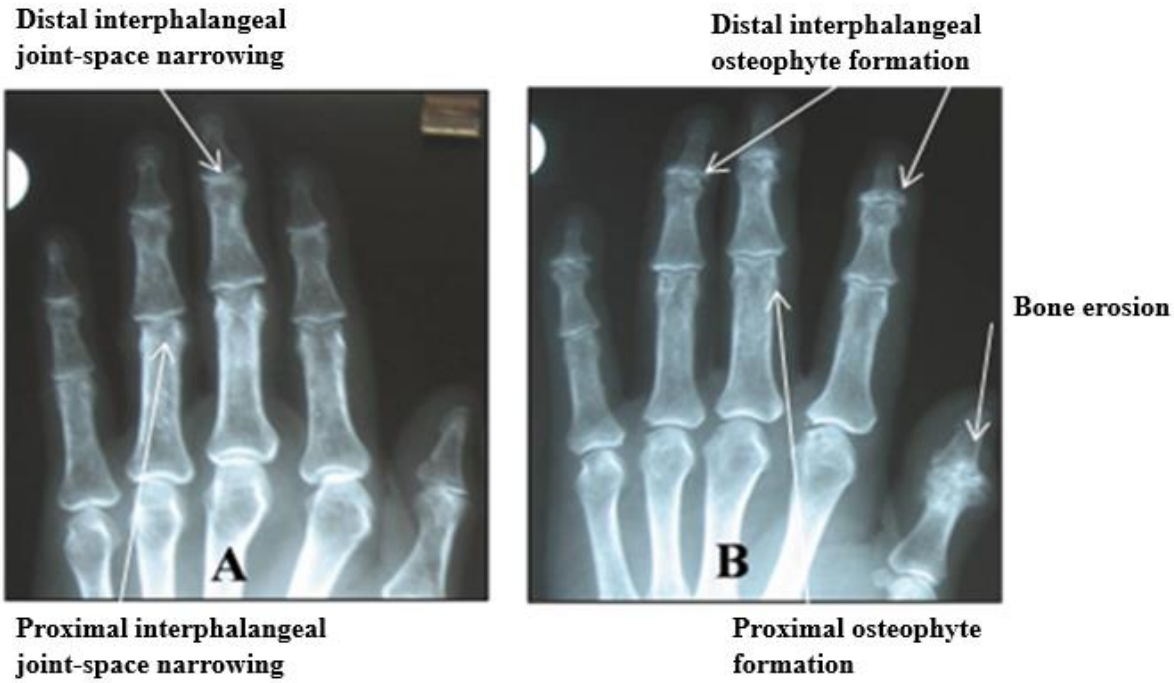

Figure 1. Examples of diagnostic radiographs of patients. (A) Stenosis in distal and proximal interphalangeal joints. (B) Distal and proximal interphalangial osteophyte formation. Metacarpophalangeal joints were relatively preserved.

The mean number of retained joints in patients with hand osteoarthritis in erosive form (7.75 ± 0.70) was significantly higher than those in non-erosive form patients (4.67 ± 0.39) (p= 0.004). Biochemistry tests, inflammatory and oxidative stress marker mean values of OA patients and control group were given in Tables 1 and 2. ESR concentrations of OA patients were significantly higher (p<0.001) than the control group. A positive correlation between the CRP values of the OA patients and the number of retained joints (r = 0.430, p=0.002) was found yet, this correlation was only significant for NEOA patients (r = 0.321, p=0.038). In addition, EOA patients had the highest fasting blood glucose concentrations and mean values of two OA groups were significantly higher than control group (p< 0.001 for both). Although, IL-6 levels of EOA group was highest compared to the others, this difference was only significant in between EOA patients and control group (p= 0.042). On the other hand, IL-1β concentrations did not show any significant difference among three groups.

Interestingly, when MPO levels of the participants were examined, there were significant differences among all groups (Tables 2 and 3). Mean MPO concentrations of HOA patients were significantly higher than those in control group (p=0.005) and patients with EHOA had higher MPO levels than NEHOA (p=0.009). Vice versa, native and total thiol levels of HOA patients were significantly lower than those in control group (p= 0.012; p<0.001, respectively). However, there were no significant difference in the native and total thiol concentrations between HOA groups (p=1.000 for both parameter). Furthermore, there were no significant difference between EHOA and NEHOA mean MDA concentrations, HOA patients had higher MDA levels than control group (p=0.014). MDA and

disulfide concentrations had significant correlations in both control and HOA groups (r = 0.400, p=0.007; r = 0.402, p=0.014 respectively).

Table 1. Characteristics and measured parameters of control and hand osteoarthritis groups

	Control (n=30)	**Osteoarthritis (n=50)**	
			***p* Values**
Number of joints retained		5.16 ± 0.38	
Sex (Women %)	60	78	0.003
Age	32.37 ± 1.17	59.96 ± 1.36	0.018
MDA (nmol/mL)	2.18 ± 0.13	3.75 ± 0.07	0.014
IL-1 β (pg/mL)	3.01± 0.11	3.14 ± 0.13	0.097
IL-6 (pg/mL)	0.99 ± 0.09	1.30 ± 0.09	0.012
Hemoglobin (g/dL)	13.65 ± 0.25	13.32 ± 0.18	0.479
Hematocrit (%)	36.75 ± 1.94	38.75 ± 0.42	0.004
ESR (mm/hr)	16.63 ± 2.00	33.62 ± 1.91	<0.001
CRP (µg/mL)	3.00 ± 0.01	3.32 ± 0.16	0.003
Fasting Glucose (mg/dL)	61.90 ± 8.28	105.88 ± 3.46	<0.001
TAS (µmol/EqL)	0.97 ± 0.04	1.05 ± 0.02	0.156
TOS (µmol/EqL)	44.97 ± 5.20	35.85 ± 3.94	0.592
PON (U/L)	79.43 ± 10.58	82.49 ± 9.48	0.528
SPON (U/L)	310.50 ± 48.25	292.69 ± 39.93	0.687
ARES (U/L)	65.91 ± 7.06	64.19 ± 5.46	0.511
Ceruloplasmin (U/L)	84.50 ± 4.71	83.63 ± 3.52	0.863
Catalase (kU/L)	58.79 ± 7.84	52.19 ± 4.81	0.342
Myeloperoxidase (U/L)	134.86 ± 12.60	197.79 ± 8.79	0.005
Native Thiol (SH) (µmol/L)	218.58 ± 12.48	149.50 ± 6.18	0.012
Total Thiol (TT) (µmol/L)	271.37 ± 14.10	199.00 ± 7.04	0.001
Disulphide (SS) (µmol/L)	26.40 ± 1.79	22.47 ± 1.20	0.526
SS/SH % (Index 1)	12.71 ± 0.88	16.88 ± 1.41	0.002
SS/TT % (Index 2)	9.94 ± 0.56	11.82 ± 0.74	0.003
SH/TT % (Index 3)	80.13 ± 1.12	75.11 ± 1.72	0.004

MDA: Malondialdehyde; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; TAS: Total antioxidant status; TOS: Total oxidant status; PON: Paraoxonase; SPON: Stimulated paraoxonase; ARES: Arylesterase.

Descriptive statistics were given in mean ± SEM (standard error of mean)

p values were obtained from independent samples t test

Table 2. Characteristics and measured parameters of control, erosive and non-erosive hand osteoarthritis groups

	Control (n=30)	**Non-Erosive (n=42)**	**Erosive (n=8)**	***p* Values**
Number of joints retained		4.67 ± 0.39	7.75 ± 0.70	*0.003
Sex (Women %)	60	73.81	100	0.075
Age	32.37 ± 1.17	59.17 ± 1.49	64.13 ± 3.14	<0.001
MDA (nmol/mL)	2.18 ± 0.13	3.75 ± 0.07	3.74 ± 0.25	<0.001
IL-1β (pg/mL)	3.01± 0.11	3.16 ± 0.15	2.98 ± 0.32	0.703
IL-6 (pg/mL)	0.99 ± 0.09	1.26 ± 0.10	1.49 ± 0.21	0.019
Hemoglobin (g/dL)	13.65 ± 0.25	13.31 ± 0.21	13.39 ± 0.25	0.567
Hematocrit (%)	36.75 ± 1.94	38.78 ± 0.48	38.63 ± 0.81	0.459
ESR (mm/hr)	16.63 ± 2.00	32.21 ± 1.81	41.00 ± 7.08	<0.001
CRP (µg/mL)	3.00 ± 0.01	3.20 ± 0.18	2.87 ± 0.48	0.001
Fasting Glucose (mg/dL)	61.90 ± 8.28	100.74 ± 1.56	132.88 ± 18.00	<0.001
TAS (µmol/EqL)	0.97 ± 0.04	1.06 ± 0.02	0.97 ± 0.06	0.099
TOS (µmol/EqL)	44.97 ± 5.20	37.17 ± 4.43	28.93 ± 8.17	0.287
PON (U/L)	79.43 ± 10.58	90.70 ± 11.00	44.55 ± 7.12	0.139
SPON (U/L)	310.50 ± 48.25	324.94 ± 46.50	143.54 ± 32.88	0.192
ARES (U/L)	65.91 ± 7.06	68.62 ± 6.23	43.69 ± 7.44	0.207
Ceruloplasmin (U/L)	84.50 ± 4.71	80.51 ± 3.52	98.06 ± 10.32	0.161
Catalase (kU/L)	58.79 ± 7.84	47.44 ± 4.98	62.9 ± 14.15	0.330
Myeloperoxidase (U/L)	134.86 ± 12.60	193.72 ± 7.08	206.65 ± 6.46	<0.001
Native Thiol (SH) (µmol/L)	218.58 ± 12.48	151.07 ± 7.30	142.23 ± 8.68	<0.001
Total Thiol (TT) (µmol/L)	271.37 ± 14.10	195.92 ± 7.13	213.24 ± 22.62	<0.001
Disulphide (SS) (µmol/L)	26.40 ± 1.79	22.42 ± 1.42	22.69 ± 1.69	0.180
SS/SH % (Index 1)	12.71 ± 0.88	16.93 ± 1.68	16.63 ± 1.92	0.119
SS/TT % (Index 2)	9.94 ± 0.56	11.89 ± 0.85	11.48 ± 1.42	0.212
SH/TT % (Index 3)	80.13 ± 1.12	76.21 ±1.70	70.02 ± 5.57	0.034

MDA: Malondialdehyde; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; TAS: Total antioxidant status; TOS: Total oxidant status; PON: Paraoxonase; SPON: Stimulated paraoxonase; ARES: Arylesterase.

Descriptive statistics were given in mean ± SEM (standard error of mean)

p values were obtained from one way ANOVA test, * *p* value was obtained from independent samples t test

Table 3. Comparison of study groups

	Control vs. Non-Erosive	Non-Erosive vs. Erosive	Control vs. Erosive
Age	<0.001	0.402	<0.001
MDA (nmol/mL)	<0.001	1.000	<0.001
IL-6 (pg/mL)	0.099	0.648	0.042
ESR (mm/hr)	<0.001	0.213	<0.001
CRP (µg/mL)	<0.001	0.012	<0.001
Fasting Glucose (mg/dL)	<0.001	0.038	<0.001
Myeloperoxidase (U/L)	0.006	0.009	0.002
Native Thiol (SH) (µmol/L)	<0.001	1.000	0.001
Total Thiol (TT) (µmol/L)	<0.001	1.000	0.045
SH/TT % (Index 3)	0.358	0.318	0.036

MDA: Malondialdehyde; IL-6: Interleukin-6; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

p values were obtained from one-way ANOVA test.

DISCUSSION

Osteoarthritis is a degenerative disorder resulting from the imbalance between anabolic and catabolic reactions occur in joints. HOA is a frequent form of the osteoarthritis affecting proximal and distal interphalangeal joints. One form of HOA is erosive type which is distinguished by inflammatory episodes and an aggressive course.

Previous studies reported significant increases in diagnostic markers of cartilage catabolism such as CTX-I and II (22), markers of activity, CRP and ESR (2, 23-25). In accordance with these studies, the increase in ESR values observed in our study was somewhat more prominent in the patients with EHOA (41.00 ± 7.08 mm/s) than with the NE group (32.21 ± 1.81mm / s) yet, this difference was statistically insignificant. While we did not see statistically significant difference in CRP values among groups, we observed a positive correlation (r= 0.430; p= 0.002) between CRP values of the OA patients and the number of retained joints.

Among several other biomarkers, we also examined MPO and major pro-inflammatory cytokines in patients with hand OA. Cytokines, IL-1β, TNF-α and IL-6 were shown to be effective on chondrocyte activities. Increased levels of IL-1β and IL-6 have been shown in synovial fluid of joints in OA patients (26). IL-1β was responsible from elevation of matrix metalloproteinases (MMPs) and reduction of type II collagen synthesis (27). IL-6 has been reported to contribute to IL-1β-induced inflammation, cartilage degeneration, OA pathogenesis and many other pathologies with bone resorption (25, 28). There are, however, studies suggesting that higher IL-6 doses might suppress inflammatory findings, reduce the synthesis of other pro-inflammatory cytokines or inhibit MMP activity and acute phase proteins such as CRP, initiate IL-1 receptor antagonists (IL-1Ra) and tissue inhibitors of metalloperoxidase-1 (TIMP) production (24, 29). Other investigators also has questioned the potential roles of inflammatory cytokines such as IL-1 and IL-6 in the pathogenesis of hand OA, especially for EHOA. Stern et al

showed an association between EHOA and one certain type of IL-1β polymorphism, while Roux et al reported negative correlation between loss of function, and positive correlation with radiologic erosions with serum levels of IL-1β (30). In our study, unlike the literature, IL-1β serum levels were not statistically significant when OA patients were compared with those in control group (31, 32). Whereas, similar with Ramonda et al., the IL-6 concentration was higher in patients with osteoarthritis, especially those with erosive osteoarthritis compared to the control group. This difference was statistically significant (Table 3) (2). MPO, on the other hand, is an activated neutrophil product which reflects the proteolytic activity of leukocytes during inflammation and serves as an oxidative stress marker. Some investigations manifested the diagnostic role of MPO concentrations in early OA. In contrast to Ramonda et. al, our mean MPO concentrations of three groups were increased with the severity of disease and inflammation (2).

Oxidative stress caused by increased levels of free radicals or ROS and decreased antioxidant capacity is another factor in the ethiopathogenesis of cartilage degradation and osteoarthritis (33, 34). Continuous elevated levels of those oxidants lead to oxidation of lipid compounds such as cell membranes and impair their functions (34). The MDA molecule, which is not directly related to oxidative stress but arises as a result of lipid peroxidation, is one of the markers used to show oxidative stress (10, 11). Supporting the Zhuang et al. study, MDA results in our control group were significantly lower than OA patients, however there were no significant difference between patients with EHOA and NEHOA (11). Thiols are antioxidant organic molecules which possess sulfhydryl groups (35, 36). They are components of essential antioxidants and proteins in the body like glutathione or albumin. Native thiol has an antioxidant property and is the reductive form of thiols which donates one hydrogen atom to oxidant species. After, two oxidized native thiol combine, reversible reaction, with a disulfide bond and form one disulfide molecule. Total thiol is the sum of native thiol and disulfide. ROS lead to disruption of the thiol–disulfide homeostasis by consuming plasma thiol pool (albumin, ascysteine, glutathione, thioredoxin and homocysteine, etc.). Imbalance between thiol-disulphide homeostasis have been shown to be involved in the pathogenesis of several diseases (13, 35, 36). To our knowlegde this is the first report to analyze oxidative stress markers in HOA patients. In our study, we found that native thiol levels of OA patients were significantly lower than the control group, and even if not statistically significant, EHOA patients had lower native thiol concentrations than NEHOA. This can be explained by, faster depletion of antioxidant agents while attempting to remove oxidant molecules in high amounts resulting from severe inflammation in osteoarthritis.

Another interesting point that we faced in our study was fasting serum glucose levels of osteoarthritic patients were higher than those in control group. As a consequence of elevated blood glucose concentrations, diffusion of glucose through the cartilage tissue and binding with matrix proteins, especially collagen, increases and results increment of advanced glycation end products

(AGEs) formation due to collagen glycation. AGEs are oxidative molecules which results increased oxidative stress on chondrocytes which distorts normal cell function and eases degradation of cartilage (37).

In conclusion, markers of disruption of balance between oxidative/anti-oxidative mechanisms together with elevation of inflammatory markers may have diagnostic and/or prognostic value in managing hand OA patients.

Acknowledgements

Part of this project is funded by The Scientific and Technological Research Council of Turkey (SBAG 106S355).

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