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ORIGINAL ARTICLE

Paraoxonase-1 activity and oxidative status in patients with knee osteoarthritis and their relationship with radiological and clinical parameters

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Abstract

Background. The aim of this study was to investigate serum paraoxonase-1 (PON1) activity and oxidative/anti-oxidative status in knee osteoarthritis (OA), and evaluate their relationship using radiological and clinical parameters. ***Materials and methods.*** The study population comprised 127 patients with knee OA and 107 healthy volunteers. Patients with knee OA were divided into four subgroups according to the Kellgren–Lawrence (K&L) grading scale. In addition, each patient was clinically evaluated by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Serum PON1 activity was measured spectrophotometrically. Oxidative status was assessed by measuring serum lipid hydroperoxide (LOOH) and total oxidant status (TOS). Anti-oxidative status was assessed by measuring serum free sulfydryl groups (–SH = total thiol) and total antioxidant capacity (TAC). Oxidative stress index (OSI) was calculated. Lipid parameters were determined by routine laboratory methods. ***Results.*** Serum PON1 activity was significantly lower in the knee OA group compared to the control group ($p < 0.001$), whereas serum LOOH, TOS, and OSI levels of the knee OA group were significantly higher than those of the controls ($p < 0.001$ for all). However, TAC and –SH levels did not differ between the two groups ($p > 0.05$). The lowest and highest mean serum PON1 activities were detected in patients with grades 4 and 1, respectively (ANOVA $p < 0.001$). In multiple regression analysis, WOMAC score was independently associated with serum PON1 activity ($\beta = -0.248$, $p = 0.027$). ***Conclusions.*** Decreased serum PON1 activity and elevated LOOH, TOS, and OSI levels may be associated with knee OA, and serum PON1 activity may be a useful adjunctive indicator of the severity of knee OA for follow-up.

Key Words: *Paraoxonase, oxidative status, knee osteoarthritis, WOMAC score, X-ray grading*

Introduction

Osteoarthritis (OA) is the most common joint disorder of the locomotor system, and the knee is one of the most frequent joints involved. It is slowly progressive and results in severe instability over the long term. OA is a disease of cartilage degeneration, and morphological changes occur in the cartilage, subchondral bone, and synovial membrane. However, the etiology of OA is not fully understood, although mechanical, biochemical, and genetic factors are accepted as playing a role [1,2]. One possible explanation for OA is oxidative damage that promotes cartilage degradation, and levels of pro-inflammatory mediators, such as reactive oxygen species (ROS), are elevated in OA [3–5]. Oxidative stress-induced lipid peroxidation products may play an important role in the pathogenesis of OA [5–7] because lipid peroxides can induce severe damage to nucleic acids and proteins, altering their function and causing a loss of both the structural and metabolic function of cells. Recent studies have shown that oxidized low-density lipoprotein (LDL) plays a role in the pathogenesis of OA by inducing chondrocyte senescence [5,8,9].

Human serum paraoxonase-1 (PON1) is a 45-kDa glycoprotein synthesized mainly in the liver and secreted to the bloodstream, where it circulates and attaches to high-density lipoprotein (HDL) [10]. PON1 is an enzyme and a Ca^{2+}-dependent serum

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esterase with paraoxonase, arylesterase, and dyazoxonase activities [11]. PON1 has been shown to catalyze the hydrolysis of many organophosphates and aromatic carboxylic acid esters [12–14]. Also, PON1 hydrolyzes lipid peroxidation products and decreases their accumulation [15,16]. Thus, PON1 plays a role in an organism's anti-oxidative and anti-inflammatory properties [14]. Reduced PON1 activity and increased oxidative stress were closely related to atherosclerotic heart disease [17], likely because PON1 protects LDL and HDL from oxidation by hydrolyzing activated phospholipids and lipid peroxide products [15,16]. Also, serum PON1 activity has been demonstrated to be lower in patients with some renal, neurologic, gynecologic, and connective tissue disorders [18]. In several studies, serum PON1 activities were shown to be lowered in patients with rheumatoid arthritis [19,20]. However, knowledge of the relationship between serum PON1 activity and OA severity is limited.

Therefore, we investigated PON1 activity, oxidative status (lipid hydroperoxide [LOOH], total oxidant status [TOS], and the oxidative stress index [OSI]), anti-oxidative status (free sulfhydryl groups (–SH = total thiol), and total anti-oxidative capacity [TAC]) in knee OA and evaluated their relationship applying radiological and clinical parameters.

Materials and methods

Study population

In this study, 127 patients with OA (83 females and 44 males) and 107 healthy controls (68 females, 39 males) were enrolled. Diagnosis of OA was made according to the American College of Rheumatology Criteria [21]. Exclusion criteria included use of supplemental vitamins, smoking, diabetes mellitus, hypertension, coronary artery disease, acute/chronic liver diseases, inflammatory rheumatic disease, clinically unstable medical illness, or the use of any medication within 4 weeks prior to initiation of the study. These controls were matched with regard to patient age, body mass index (BMI), and gender. For inclusion into the control group, subjects must have had no known knee OA symptoms. Knee radiographs of the control group were not obtained. Members of the control group were free of any medication for at least 4 weeks prior to blood sampling. Written informed consent was obtained from all subjects, and approval to use their medical records was given by the Local Research Ethics Committee.

Radiological assessment

All radiographs (weight-bearing anteroposterior and weight-bearing lateral and Merchant's X-rays of both knees) were evaluated. Additionally, clinical baseline parameters such as weight, height, BMI, age, gender, side of involvement (left or right), or both knees were recorded. The severity of OA was assessed and classified according to the Kellgren–Lawrence (K&L) grading scale [22]. Grade 0 was regarded as normal; grade 1 as possible osteophytes only; grade 2 as definite osteophytes and possible joint space narrowing; grade 3 as moderate osteophytes and/or definite joint space narrowing; and grade 4 as large osteophytes, severe joint space narrowing, and/or bony sclerosis. The grade used was the highest grade of either the right or left knee. Patients with knee OA were divided into four subgroups according to the K&L grading scale.

Clinical assessment

Clinical assessments included the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The WOMAC questionnaire consisted of three items: pain, stiffness, and physical function. The WOMAC scores were recorded on a Likert scale of 0 to 4 (0 = no pain/limitation, 1 = mild pain/limitation, 2 = moderate pain/limitation, 3 = severe pain/limitation, and 4 = very severe pain/limitation). Maximum scores for pain, stiffness, and physical function were 20, 8, and 68, respectively, with a total score of 96 (0–96 scale with 0 as the best and 96 as the worst) [23].

Blood sample collection

Blood samples were collected into empty tubes and immediately stored on ice at 4°C. Serum samples were then separated from cells by centrifugation at 3000 rpm for 10 min. Lipid parameters were then measured. The remaining serum portions were stored at –80°C until analysis.

Measurement of PON1 activity

Measurement of serum PON1 activity was performed in the absence of basal activity. The rate of paraoxon hydrolysis (diethyl-*p*-nitrophenylphosphate) was measured by monitoring the increase in absorbance at 412 nm and 37°C. The amount of generated *p*-nitrophenol was calculated from the molar absorptivity coefficient at pH 8, which was 17,000 M^{-1} cm^{-1} [24]. PON1 activity was expressed as U/L serum. The coefficient of variation (CV) for the measurement of serum PON1 activity was 2%.

Measurement of lipid hydroperoxide levels

Serum LOOH levels were measured by a ferrous ion oxidation–xylenol orange (FOX-2) assay, which involves the oxidation of ferrous ion to ferric ion via the effect of various oxidants. The ferric ion level is then measured with xylenol orange. LOOH levels are

reduced by the application of triphenyl phosphine (TPP), a reductant specific for lipids. LOOH levels are then calculated as the difference between the absence or presence of TPP [25]. The CV for the determination of the LOOH level was 5%.

Measurement of total free sulfhydryl groups of serum samples

Free sulfhydryl groups (–SH) in serum samples were assayed according to the method of Ellman [26] as modified by Hu et al. [27]. Briefly, 1 mL of buffer containing 0.1 M Tris, 10 mM EDTA (pH 8.2), and 50 µL serum was added to cuvettes, followed by 50 µL of 10 mM DTNB in methanol. Blanks were run for each sample as a test, but without DTNB. Following incubation for 15 min at room temperature (RT), sample absorbance was read at 412 nm on a Cecil 3000 spectrophotometer (Cecil Instruments, Cambridge, UK). Sample and reagent blanks comprised the substrate. The concentration of sulfhydryl groups was calculated using reduced glutathione as the free sulfhydryl group standard, and the results are expressed as millimoles. The CV for the measurement of the serum –SH level was 3.6%.

Measurement of the activity of total oxidant status

The TOS of serum was determined using an automated measurement method (Rel® assay diagnostics kits; Mega Tip, Gaziantep, Turkey) developed by Erel [28]. Oxidants present in the sample oxidized the ferrous ion–*o*-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundant in the reaction medium. The ferric ion produces a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide (H_2O_2), and the results are expressed as micromoles of H_2O_2 equivalents per liter (µmol H_2O_2 equiv/L). The CV for the measurement of the serum TOS level was $<3\%$.

Measurement of the total anti-oxidative capacity

TAC of serum was determined using an automated measurement method (Rel® assay diagnostic kits) of Erel [29], in which the hydroxyl radical, the most potent biological radical, is produced. Ferrous ion solution in reagent-1 is mixed with H_2O_2, which is present in reagent-2. Sequentially produced radicals include the brownish-colored dianisidinyl radical cation, produced by the hydroxyl radical. Using this method, the anti-oxidative effect of the sample against the potent free radical reactions, which was initiated by the produced hydroxyl radical, was measured. The data are expressed as mmol Trolox equiv/L. The CV for the measurement of the serum TAC level was $<3\%$.

Oxidative stress index (OSI)

The ratio of TOS to TAC yielded the OSI, an indicator of the percent degree of oxidative stress [28,29]. For calculations, the unit of TAC was changed to µmol/L and the OSI value was calculated according to the following formula: OSI (arbitrary unit): TOS (µmol H_2O_2 equiv/L)/TAC (µmol Trolox equiv/L) $\times 10$.

Measurement of other biochemical parameters

The levels of triglycerides (TG), total cholesterol (TC), HDL cholesterol (HDL-C), and LDL-cholesterol (LDL-C) were determined using commercially available assay kits (Abbott, Wiesbaden-Delkenheim, Germany) with an autoanalyzer (Aeroset®; Abbott).

Statistical analysis

All analyses were conducted using SPSS ver. 16 (SPSS Inc., Chicago, Il, USA). Continuous variables were expressed as the mean $\pm$ SD. The normality of distributions was evaluated using the one-sample Kolmogorov–Smirnov test, revealing a uniform distribution. Comparison of categorical and continuous variables between the knee OA and control groups was performed using the χ^2 test and independent-samples *t*-test, respectively. Comparison of laboratory variables between groups categorized according to the grade of knee OA was performed using one-way analysis of variance (ANOVA) with the least significant difference post hoc test. The correlation between serum PON1 activity and clinical and laboratory parameters was evaluated using Pearson's correlation test. Standardized β-regression coefficients and their significance in a multiple linear regression analysis were reported. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Demographic characteristics of patients with knee OA and control groups are shown in Table I. No significant differences were observed in age, BMI, or female/male ratio between patients and controls. No significant difference existed between the groups in terms of fasting blood triglyceride, total cholesterol, and LDL and HDL levels ($p > 0.05$). PON1 activity was significantly lower in patients with knee OA compared to controls ($p < 0.001$), whereas oxidant parameters (LOOH, TOS, and OSI) were significantly higher in knee OA patients ($p < 0.001$ for all). However, antioxidant parameters (TAC and –SH) did not differ between the two groups ($p > 0.05$).

Table I. Demographic characteristics of the knee osteoarthritis and control groups.

	Patients* ($n = 127$)	Controls* ($n = 107$)	p-value
Age (years)	57.6 ± 9.9	56.6 ± 9.5	> 0.05
Gender (M:F)	44/83	39/68	> 0.05
BMI (kg/m^2)	30.6 ± 4.1	31.0 ± 4.4	> 0.05
TG (mmol/L)	1.86 ± 0.62	1.87 ± 0.65	> 0.05
TC (mmol/L)	5.20 ± 1.09	5.26 ± 1.18	> 0.05
HDL (mmol/L)	1.20 ± 0.36	1.22 ± 0.46	> 0.05
LDL (mmol/L)	3.14 ± 0.97	3.18 ± 0.99	> 0.05
Paraoxanase activity (U/L)	114.2 ± 52.0	175.2 ± 67.9	< 0.001
LOOH (μmol/L)	7.71 ± 0.82	6.01 ± 0.43	< 0.001
TOS (μmol H_2O_2 equiv/L)	16.09 ± 2.30	10.9 ± 1.49	< 0.001
OSI (Arbitrary unit)	1.72 ± 0.44	1.14 ± 0.29	< 0.001
Total –SH (mmol/L)	0.38 ± 0.11	0.39 ± 0.12	> 0.05
TAC (mmol Trolox equiv/L)	0.97 ± 0.19	0.99 ± 0.20	> 0.05

BMI, body mass index; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LOOH, lipid hydroperoxide; TOS, total oxidant status; OSI, oxidative stress index; SH, free sulfhydryl groups (total thiol); TAC, total antioxidant capacity.
*Measurements are given as the mean ± SD.

The comparison included 127 patients with OA in four subgroups according to the K&L grading scale; grade 1 ($n = 29$), grade 2 ($n = 31$), grade 3 ($n = 36$), and grade 4 ($n = 31$), along with 107 controls. Comparison of serum PON1 activity according to the K&L grading in the knee OA groups is shown in Figure 1. The lowest and highest mean serum PON1 activities were detected in patients with grades 4 and 1, respectively (ANOVA, $p < 0.001$).

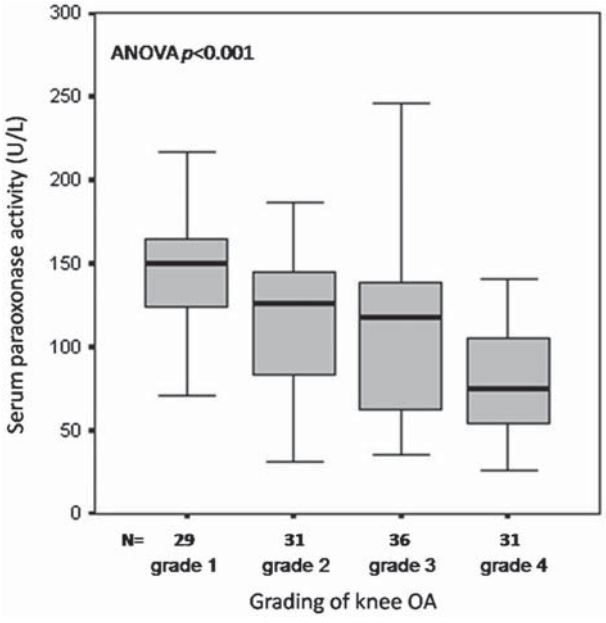

Figure 1. Graph demonstrating that the lowest and highest mean serum paraoxonase activities were detected in patients with grade 4 and grade 1, respectively (ANOVA, $p < 0.001$).

The relationship between serum PON1 activity and clinical characteristics and laboratory parameters is presented in Table II. Serum PON1 activity was inversely correlated with knee OA grading and LOOH levels, TOS, OSI, and WOMAC score in a bivariate analysis ($p < 0.001$ for all; Table II). The correlation between serum PON1 activity and WOMAC score is shown in Figure 2. In a multiple regression analysis, we found that the knee OA grading ($\beta = -0.251$, $p = 0.025$) and WOMAC score ($\beta = -0.248$, $p = 0.027$) were independently associated with serum PON1 activity (Table II).

We also investigated the correlation between LOOH and TOS and OSI parameters. LOOH level was positively correlated with TOS ($r = 0.631$, $p < 0.001$) and OSI ($r = 0.840$, $p < 0.001$) in patients with OA of the knee.

The relationship between WOMAC score and clinical characteristics and laboratory parameters is presented in Table III. The WOMAC score was positively correlated with age ($r = 0.194$, $p < 0.05$), BMI ($r = 0.192$, $p < 0.05$), and knee OA grading ($r = 0.515$, $p < 0.001$), but inversely correlated with serum PON1 activity ($r = -0.392$, $p < 0.001$) in a bivariate analysis. In a multiple regression analysis, we found that age ($\beta = 0.189$, $p = 0.013$), BMI ($\beta = 0.197$, $p = 0.007$), knee OA grading ($\beta = 0.380$, $p < 0.001$), and serum PON1 activity ($\beta = -0.271$, $p = 0.001$) were independently associated with the WOMAC score (Table III).

Discussion

The main findings of this study are as follows. First, PON1 activity was low in the OA group compared to the control group. Second, the oxidative stress parameters (LOOH, TOS, and OSI) of the OA group were significantly greater than those of the control group, whereas the anti-oxidative stress parameters (–SH groups and TAC) remained unchanged. Third, the lowest and highest mean serum PON1 activities

Table II. Relationship between serum paraoxonase activity and clinical characteristics and laboratory parameters.

	Pearson's correlation coefficient	p value	β regression coefficient*	p value
Grading of knee OA	–0.381	< 0.001	–0.251	$p = 0.025$
LOOH (μmol/L)	–0.337	< 0.001		
TOS (μmol H_2O_2 equiv/L)	–0.323	< 0.001		
OSI (arbitrary units)	–0.255	< 0.001		
WOMAC score	–0.392	< 0.001	–0.248	$p = 0.027$

OA, osteoarthritis; LOOH, lipid hydroperoxide; TOS, total oxidant status; OSI, oxidative stress index; WOMAC, Western Ontario and McMaster University Osteoarthritis Index.
*From multiple linear regression.

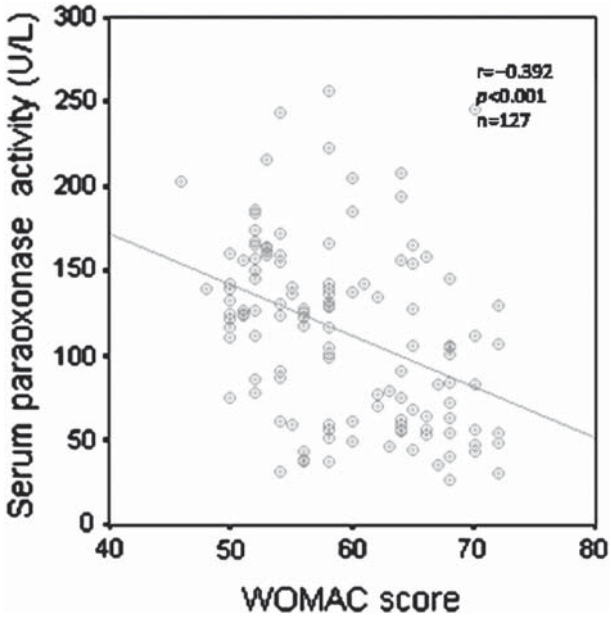

Figure 2. The correlation of serum paraoxonase activity with the grading of knee osteoarthritis.

were detected in patients with grades 4 and 1, respectively. Fourth, serum PON1 activity was inversely correlated with knee OA grading, LOOH, TOS, OSI levels, and WOMAC score. Fifth, the WOMAC score was independently correlated with PON1 activity and knee OA grading.

We observed a significant decrease in serum PON1 activity in patients with OA compared to controls. The pathogenetic mechanisms underlying this decrease in serum PON1 activity in patients with OA are unclear. In this study, we observed significantly elevated oxidant parameters in patients with OA compared to controls. Oxidative stress is associated with OA, as increased lipid and protein oxidation products and decreased antioxidant enzymes have been found in such patients [3–5,30]. Thus, decreased serum PON1 activity may be due to the consumption of PON1 to prevent oxidation [13,14].

Various studies have reported that LDL was protected against oxidative modification by HDL [13,16] and is known to be central to the initiation and progression of atherosclerosis [12,17]. Additionally, studies have indicated that PON1 can prevent lipid peroxide accumulation on LDL *in vitro* and *in vivo* [15]. Another study [17] reported that reduced PON1 activity may play a role in the severity of coronary atherosclerosis. Therefore, PON1 enzyme is a significant antioxidant and prevents the induction of inflammatory responses in arterial wall cells [12]. On the other hand, the increase in LDL oxidation arises from the low HDL and PON1 levels, possibly indicating an acceleration of the progress of atherosclerosis in patients with OA. Therefore, OA and atherosclerosis have some pathologic similarities. In a recent review, an important interconnection between OA and atherosclerosis was reported [31]. In this study, serum PON1 activity was inversely correlated with LOOH levels and TOS. Therefore, we believe that the decreased PON1 activity and increased oxidative stress play roles in the development of atherosclerosis through increasing the susceptibility to lipid peroxidation of patients with OA. Many studies have reported on an association between OA and increased cardiovascular comorbidity. Indeed, the management of patients with OA includes effective treatment of cardiovascular risk factors and comorbidities [32]. Thus, the propensity of patients with OA of the knee to develop atherosclerosis may be a significant problem for these individuals, in parallel with their increasing quality of life expectations.

We used LOOH as a marker of oxidative stress. LOOH is an important indicator of oxidative stress that results from oxidation of unsaturated phospholipids, glycolipids, and cholesterol under oxidative stress [33]. Furthermore, oxidized LDL is the essential form of LOOH responsible for the development of oxidative stress-related atherosclerosis and adverse cardiovascular events [33]. On the other hand, lipid peroxidation is a well-established mechanism of cellular injury that operates in the pathogenesis of cartilage aging and OA. Tiku et al. [6] reported a link between chondrocyte lipid peroxidation and cartilage matrix protein oxidation and degradation in OA. Moreover, another study indicated that lipoxidation plays a role in the pathogenesis of OA [7]. In our study, LOOH, TOS, and OSI levels were significantly elevated in subjects with OA compared to the control group. Our findings concurred with those of our previous studies [34,35]. Notably, the –SH groups of proteins are an important component of the antioxidant mechanism [29]. The decreased PON1 activity during oxidative stress has been primarily attributed to changes in the redox status of the free sulfhydryl groups, since sulfhydryl compounds prevented the inhibition of PON1 activity caused by ROS [36]. In a previous study performed in our laboratory, Soran et al. [37] reported that serum –SH group levels, PON1, and arylesterase activities were lower in the OA group than those of the controls, whereas LOOH levels were higher in

Table III. Relationship between the WOMAC score and clinical characteristics and laboratory parameters.

	Pearson's correlation coefficient	*p* value	β regression coefficient*	*p* value
Age (years)	0.194	$p<0.05$	0.189	$p=0.13$
BMI (kg/m^2)	0.192	$p<0.05$	0.197	$p=0.007$
Grading of knee OA	0.515	<0.001	0.380	<0.001
Paraoxonase activity (U/L)	–0.392	<0.001	–0.271	$p=0.001$

BMI, body mass index; OA, osteoarthritis.
*From multiple linear regression.

36 patients with knee OA than in 30 healthy individuals. However, we detected no difference in the serum levels of the –SH groups and TAC in patients with knee OA compared to controls. Therefore, the cause of the unchanged anti-oxidative stress parameters (–SH groups and TAC) may be due to an increased oxidative stress compensator mechanism in patients with OA of the knee.

We found a relationship between the grading of radiographic knee OA and serum PON1 activity. Furthermore, the major decrease in PON1 activity was observed in grade 4, a more advanced OA stage. The cause of the decreased serum PON1 activity with advancing OA stage is unclear, but note that grade 4 is the terminal stage of OA, in which most of the cartilage is degenerated and morphological changes are marked. On the other hand, we found no association between the grade of radiographic knee OA and serum LOOH and TOS levels.

In the present study, the WOMAC score was positively correlated with the grade of radiographic knee OA. The WOMAC scale allows detailed analysis of pain and dysfunction [38]. The cartilage tissue is aneural and cannot directly generate pain. However, the changes in articulation caused by structural and associated degenerative changes in articular cartilage may result in the manifestation of pain in joint tissues [39].

The inverse correlation of PON1 with oxidative stress and its ability to protect against oxidation suggest that increasing PON1 expression could be a potential therapeutic target for treating OA. A previous study demonstrated that PON1 activity is positively correlated with the quantity of vitamins C and E in the diet [40]. Also, pomegranate extract consumption (10 mL/day for 12 weeks) was shown to decrease oxidative stress and increase serum PON1 activity in patients with active rheumatic arthritis [41]. Therefore, reducing oxidative stress through the use of antioxidant medications may be a novel future treatment strategy for OA.

Several limitations of this study should be noted. First, it had a cross-sectional design. Second, the PON1 gene polymorphism was not examined, since we did not have the opportunity to perform genotype analysis. Third, radiographically visualized degeneration is only part of the total of knee OA and so X-ray grading should be confirmed with magnetic resonance imaging or arthroscopy, as we did not have the opportunity to perform the procedures. Further studies are needed to explain the molecular mechanisms of the association of PON1 activity with OA.

Conclusions

In conclusion, we found significantly lower levels of PON1 activity and significantly higher LOOH and TOS levels in patients with knee OA. Additionally, serum PON1 activity was closely related to the radiographic severity of OA and showed a marked increase in advanced compared to early OA stages. Furthermore, the WOMAC was correlated with serum PON1 activity in patients with knee OA. The findings of this study demonstrate for the first time the relationship between serum PON1 activity and the extent of OA.

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