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# Relationship between oxidative balance score and quality of life in patients with osteoarthritis
## Data from the Korea National Health and Nutrition Examination Survey (2014–2015)

Joo-Hyun Lee, MD, PhD[a], Young Bin Joo, MD, PhD[b], Minkyung Han, PhD[c], Seong Ryul Kwon, MD, PhD[d], Won Park, MD, PhD[d], Kyung-Su Park, MD, PhD[b], Bo Young Yoon, MD, PhD[a], Kyong-Hee Jung, MD, PhD[d,*]

**Abstract**

Osteoarthritis (OA) has a multifactorial etiology that includes oxidative stress. Oxidative balance score (OBS) is a well-known indicator of oxidative stress. However, the association between OBS and OA has not been assessed. Thus, this study aimed to investigate the associations of OBS with OA and quality of life (QOL) in patients with OA.

By using data from the Korea National Health and Nutrition Examination Survey VI, patients previously diagnosed and/or treated by a physician were considered to have OA regardless of the affected joints. The control group was defined as participants without any form of chronic arthritis. OBS was calculated by combining 10 pro-oxidant and antioxidant factors through a baseline nutritional and lifestyle assessment. Higher OBS scores indicated a predominance of antioxidant exposure. Multivariable logistic regression was used to estimate the adjusted odds ratios (ORs) for OA, and the EuroQoL five-dimensional questionnaire (EQ5D) was used in patients with OA after adjusting for demographic factors and comorbidities.

Among the 14,930 participants, 296 patients with OA, and 1,309 controls were included in the analysis. In the age- and sex-adjusted model, the OR of the total OBS for OA was significant. In the full model adjusted for age, sex, education, income, and comorbidities, the total OBS for OA was not significant. Only the non-dietary pro-oxidant OBS had a significant inverse association with OA. The patients with OA who had a high EQ5D score had a higher total OBS than those with a low EQ5D score. The OR of the total OBS for a high EQ5D score was 1.14 in the multivariable logistic regression model. As we analyzed the OBS as a categorical variable (reference = Q1), the ORs of the Q2, Q3, and Q4 (highest) total OBS were 1.43, 2.71, and 2.22, respectively.

In the fully adjusted model, the total OBS was not associated with OA. However, a positive association was observed between the total OBS and QOL in the patients with OA, indicating that antioxidative status was associated with better QOL in patients with OA.

**Abbreviations:** BMI = body mass index, CI = confidence interval, EQ5D = EuroQoL five-dimensional questionnaire, IRB = institutional review board, KCDC = Korea Centers for Disease Control and Prevention, KNHANES = Korea National Health and Nutrition Examination Survey, OA = osteoarthritis, OBS = oxidative balance score, OR = odds ratio, PUFA = n-6 polyunsaturated fatty acid, QOL = quality of life, ROS = reactive oxygen species, SE = standard error, SFA = saturated fatty acids.

**Keywords:** osteoarthritis, oxidative stress, quality of life

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[a] Department of Rheumatology, Inje University Ilsan Paik Hospital, Goyang, [b] Department of Rheumatology, St. Vincent's Hospital, The Catholic University of Korea, [c] Department of Biomedical Systems Informatics, College of Medicine, Yonsei University, Seoul, [d] Division of Rheumatology, Department of Internal Medicine, College of Medicine, Inha University, Incheon, Republic of Korea.

* Correspondence: Kyong-Hee Jung, Division of Rheumatology, Department of Internal Medicine, College of Medicine, Inha University, Incheon 22332, Republic of Korea (e-mail: khjung@inha.ac.kr).

## 1. Introduction

Osteoarthritis (OA) is the most prevalent type of arthritis and is characterized by inflammation, chronic pain, and reduced functional ability. In particular, pain and functional impairments are the primary burden of patients, and taken together, they often cause a significant decrease in quality of life (QOL). QOL is considered a vital component of the Outcome Measures in Rheumatology core domain set for OA.[1]

OA could be reclassified as a systemic heterogeneous disorder rather than a focal joint disease,[2,3] and the multifactorial etiology of OA includes increased oxidative stress and reactive oxygen species (ROS) levels. The role of ROS in the pathogenesis of OA has been described in several basic and animal studies.[4–6] ROS cause cartilage destruction and synovial inflammation, thereby promoting disease progression. However, the degree to which ROS has a significant effect on the individual level is not fully elucidated owing to the complex and multifactorial mechanism of OA.[7] Various pro-oxidative and antioxidative factors were proposed in previous studies. High intakes of certain dietary nutrients, including vitamin C, vitamin E, and carotenoids (e.g., lycopene, β-carotene, and lutein), may have protective effects against oxidative stress, whereas pro-oxidant factors such

as smoking and iron intake can produce ROS and accelerate oxidative stress-related cellular damage.[8–10] Furthermore, the different types of fatty acids have remarkable effects on inflammation. Saturated fatty acids (SFAs) and n-6 polyunsaturated fatty acids (PUFAs) have a more pro-inflammatory effect, whereas n-3 PUFAs have anti-inflammatory effects.[11] Therefore, the balance between these components, rather than each component alone, may play a specific role in metabolic OA.

Oxidative balance score (OBS) reflects an individual's overall balance of exposure to pro-oxidants and antioxidants.[12,13] A higher OBS indicates a predominance of antioxidant over pro-oxidant exposure. Several studies have investigated the associations between OBS and various chronic diseases.[14–16] Inverse associations between OBS and colon adenoma or colon cancer were identified in recent studies.[16] Furthermore, a higher OBS (i.e., a greater balance of antioxidants vs pro-oxidants) was associated with lower all-cause mortality in a large population-based cohort study.[7] Several OBS components such as obesity, physical activity, and dietary exposure (PUFA consumption) are correlated with the modifiable risk factors of OA. However, data regarding the benefits of antioxidant vitamins in OA are insufficient and conflicting.[17]

At present, the association between OBS and OA has not been assessed despite the great interest of both physicians and patients in the possible impacts of antioxidant nutrients and physical activities on OA. Identifying the association between OBS and OA would provide important data for future patient education and therapeutic strategies. The aims of this study were to assess the relationship of OBS with OA and to investigate the association between OBS and QOL in OA patients.

## 2. Methods

### 2.1. Study participants

Data were obtained from the sixth Korean National Health and Nutrition Examination Survey (KNHANES VI) conducted between 2014 and 2015. The KNHANES is a nationwide survey conducted annually by the Korea Centers for Disease Control and Prevention (KCDC) to investigate the health and nutritional statuses of the Korean population.[18] The participants were selected using the proportional allocation-systematic sampling method with multistage stratification to obtain a representative sample of the Korean population. Among the 14,930 participants in the KNHANES VI (2014–2015), we selected healthy controls and those with chronic arthritis (Fig. 1). Patients previously diagnosed and/or treated by a physician were considered to have OA regardless of the affected joints. The control group was defined as participants without any form of chronic arthritis. We excluded participants from each group aged <50 years, those with missing data required to calculate the OBS, and those who took dietary supplements. The KNHANES was approved by the institutional review board (IRB) of the KCDC, and all the participants provided a written informed consent. The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the IRB of the KCDC (2013-12EXP-03-5C). The study was approved by the ethics committee of Inha University Hospital.

### 2.2. Demographic variables and data collection

A professional researcher visited the investigation site after completing 1 month of education and practice. A standardized interview was performed in the participants' houses, and an established questionnaire was used to collect information about demographic variables and socioeconomic characteristics. Data about age, sex, educational level, and income were collected. Smoking history was classified on the basis of current smokers' self-reported smoking status and the number of cigarettes consumed per day. Alcohol consumption was classified into four categories based on how frequently participants consumed any type of alcoholic drinks. The short form of the International Physical Activity Questionnaire was used to evaluate physical activity.[19] Height and weight were measured by a skilled health technician, in accordance with the standardized procedures for all the participants, to calculate body mass index (BMI). Information about comorbidities such as diabetes mellitus, hypertension, dyslipidemia, and cancer were also obtained. The EuroQoL five-dimensional questionnaire (EQ5D) score was calculated to measure QOL. The EQ5D score was dichotomized as high or low, with the top three quartiles considered high and the bottom quartile considered low.[20]
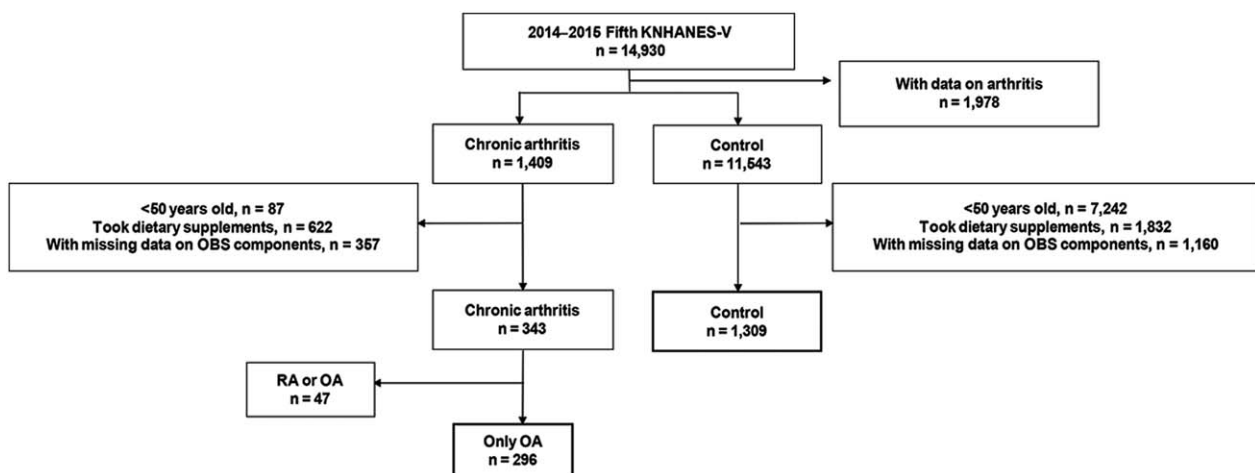


Figure 1. Flowchart showing the inclusion and exclusion criteria of the participants in this study.

**Oxidative balance score components.**

| Component | Scoring assignment | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| Pro-oxidants | | | | |
| Dietary factors | | | | |
| PUFA | 4th quartile | 3rd quartile | 2nd quartile | 1st quartile |
| n-6 fatty acid | 4th quartile | 3rd quartile | 2nd quartile | 1st quartile |
| Non-dietary lifestyle factors | | | | |
| Smoking | Current (≥1 pack/day) | Current (<1 pack/day) | Former | Never |
| Alcohol intake | ≥4 drinks/week | 2–3 drinks/week | 1–4 drinks/month | Never or <1 drink/month |
| BMI* | Severe obesity | Obesity | Overweight | Normal |
| Antioxidants | | | | |
| Dietary factors | | | | |
| β-carotene | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile |
| Retinol | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile |
| Vitamin C | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile |
| n-3 fatty acid | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile |
| Non-dietary lifestyle factors | | | | |
| Physical activity | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile |

BMI = body mass index, PUFA = polyunsaturated fatty acid.

* BMI: severe obesity, ≥30 kg/m$^2$; obesity, 25–29.9 kg/m$^2$; overweight, 23–24.9 kg/m$^2$; normal, <23 kg/m$^2$.

### 2.3. Oxidative balance score

OBS was calculated by combining 10 *a priori*-defined pro-oxidant and antioxidant exposure factors (Table 1). These included pro-oxidant factors (PUFA, n-6 fatty acid, smoking, alcohol, and BMI) and antioxidant factors (carotene, retinol, vitamin C, n-3 fatty acid, and physical activity) obtained through baseline nutritional and lifestyle assessment. Among the OBS components reported by Goodman et al,[13] information about several nutrients such as vitamin E and the use of medications such as aspirin and non-steroidal anti-inflammatory drugs was not included as data on these variables that were not available in the KNHANES VI. The OBS components were divided into quartiles (Q1–Q4), with Q1 being the lowest quartile (predominance of pro-oxidants) and reference. With respect to dietary antioxidants, the first to fourth quartiles were assigned 0–3 points, whereas the pro-oxidants were assigned 0 points for the highest quartile and 3 points for the lowest quartile. The participants were categorized according to their smoking history, namely as non-smokers, former smokers, and current smokers (<1 and >1 pack/day), and each category was assigned a score from 3 to 0. With respect to alcohol intake, the consumption of <1 drink/month, 1–4 drinks/month, 2–3 drinks/week, and ≥4 drinks/week received 3, 2, 1, and 0 points, respectively. BMI was categorized as normal weight (<23 kg/m$^2$), overweight (23–24.9 kg/m$^2$), obesity (25–29.9 kg/m$^2$), and severe obesity (≥30 kg/m$^2$). The overall OBS was calculated using the sum of the points for each component, and higher OBS scores indicated a predominance of antioxidant exposure.

### 2.4. Statistical analysis

We conducted our analyses using survey weighting that accounted for the complex survey design, which consisted of multistage, stratified, and clustered samples. The baseline characteristics of the patients with OA were compared with those of the control group by using the PROC SURVEYREG procedure for continuous variables and PROC SURVEYFREQ (Rao-Scott chi-square test) for categorical variables. The OBS quartiles were analyzed as ordinal variables in the crude and adjusted models. Weighted multivariable logistic regression was used to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for OA and EQ5D score in the patients with OA after adjusting for the demographic factors and comorbidities. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, the USA). All reported *P* values are two-sided, with an alpha value of .05.

## 3. Results

### 3.1. Baseline characteristics of the patients with OA

Among the 14,930 participants in the KNHANES 2014–2015, 296 patients with OA and 1,309 controls were included in the analysis. The patients with OA were older and had lower education and income statuses than those without OA (Table 2).

### 3.2. Associations between OBS and OA

The total OBS of the patients with OA and the control group were 17.04 ± 0.22 and 17.08 ± 0.12, respectively. In the univariate model, pro-oxidant OBS was associated with an increased risk of OA (Table 3). Both dietary and non-dietary pro-oxidants were considered significant factors. In addition, antioxidant OBS was associated with a low risk of OA. Both dietary and non-dietary antioxidants were considered significant factors. In the multivariate analysis adjusted for age and sex, the OR of the total OBS for OA remained significant (OR: 0.94, 95% confidence interval [CI]: 0.9–0.99, *P* = .026; data not shown). Among the OBS components, dietary pro-oxidants were not considered significant. However, non-dietary pro-oxidants remained significant. A significant relationship between antioxidant OBS and OA was not observed. We further analyzed the association between OBS and OA by using a model adjusted for age, sex, education, income, and comorbidities (diabetes mellitus, hypertension, dyslipidemia, and cancer) that were significant in the univariate analysis. In the multivariable regression model, no significant differences were observed between the groups (Table 3). Among the OBS components, non-dietary pro-oxidant OBS showed a significant inverse association with OA, that is, the odds of OA

**Baseline characteristics of the patients with and without osteoarthritis.**

|  | Osteoarthritis (n=296) | Control (n=1,309) | P |
|---|---|---|---|
| Age, years, mean ± SE | 66.0±0.7 | 61.2±0.3 | <.001 |
| Sex, female, n (%) | 222 (75.0) | 560 (42.8) | <.001 |
| Education, n (%) |  |  |  |
| <Primary school | 187 (63.2) | 468 (35.8) | <.001 |
| Middle school | 45 (15.2) | 223 (17.0) |  |
| High school | 41 (13.9) | 364 (27.8) |  |
| ≥College | 23 (7.8) | 254 (19.4) |  |
| Income, n (%) |  |  |  |
| Low | 129 (43.7) | 331 (25.4) | <.001 |
| Middle | 74 (25.1) | 387 (29.7) |  |
| Upper middle | 55 (18.6) | 292 (22.4) |  |
| High | 37 (12.6) | 294 (22.6) |  |

OBS = oxidative balance score, SE = standard error.

decreased by approximately 12% with every 1-point increase in the non-dietary pro-oxidant OBS. Compared with the Q1 of the non-dietary pro-oxidant OBS, the odds of OA in Q4 (the highest) was 0.36 (95% CI: 0.18–0.72), indicating a decreased risk of developing OA in individuals with a low pro-oxidant status. Antioxidant OBS was not significantly associated with OA (data not shown).

### 3.3. Association between OBS and QOL in patients with OA

We investigated the association between OBS and QOL, as represented by EQ5D score, in patients with OA. Our study showed a positive association between OBS and EQ5D score.

Patients with OA who presented with a high EQ5D score had a higher OBS than those with a low EQ5D score. The OR of the OBS for a high EQ5D score in our multivariable logistic regression model is presented in Table 4. Dietary antioxidants had a significant relationship with a high EQ5D score in patients with OA. We used the OBS as a categorical variable, and it showed a dose-dependent positive association with the EQ5D score. In the multivariable analysis, the odds for obtaining a high EQ5D score with Q4 total OBS were more than twice the odds with Q1 total OBS, and the odds for obtaining a high EQ5D score with Q4 antioxidant OBS were almost three times higher than those with the Q1 antioxidant OBS (Fig. 2).

## 4. Discussion

The roles of oxidative stress in the pathogenesis of OA and pain have been a topic of interest. In this study, we represented the degree of oxidative stress in terms of OBS and investigated the associations of OBS with OA and QOL in patients with OA. In the fully adjusted model, the total OBS was not associated with OA. Only the non-dietary pro-oxidant OBS was inversely associated with OA. Notably, OBS showed a dose-dependent positive association with QOL in the patients with OA, indicating that antioxidative status was associated with higher QOL in patients with OA.

OA is closely linked to the aging process and inflammation. Age- and inflammation-related mitochondrial dysfunction has been proposed as a possible mechanism underlying the development of OA. The mitochondria is an important source of ROS.[21] As compared with the healthy controls, the patients with OA had decreased mitochondrial mass in the chondrocytes, and the protein expressions correlated to the regulation of antioxidant genes also

**Associations between oxidative balance score and osteoarthritis.**

|  | Osteoarthritis (n=296) | Control (n=1,309) | Univariate analysis | | Multivariable analysis[*] | |
|---|---|---|---|---|---|---|
|  |  |  | Crude OR (95% CI) | P | Adjusted OR (95% CI) | P |
| Total OBS | 17.04±0.22 | 17.08±0.12 | 0.99 (0.95–1.04) | 0.87 | 0.96 (0.91–1.01) | .14 |
| Pro-oxidants | 10.22±0.20 | 9.19±0.10 | 1.12 (1.07–1.18) | <0.001 | 0.94 (0.87–1.01) | .07 |
| Dietary | 3.66±0.15 | 2.91±0.07 | 1.18 (1.09–1.27) | <0.001 | 1.01 (0.92–1.09) | .92 |
| Non-dietary | 6.56±0.11 | 6.28±0.06 | 1.09 (1.01–1.17) | 0.04 | 0.82 (0.73–0.91) | <.001 |
| Antioxidants | 6.82±0.26 | 7.89±0.13 | 0.91 (0.87–0.96) | 0.001 | 1.01 (0.95–1.06) | .92 |
| Dietary | 5.51±0.24 | 6.33±0.11 | 0.92 (0.87–0.97) | 0.001 | 1.01 (0.95–1.07) | .83 |
| Non-dietary | 1.31±0.07 | 1.55±0.04 | 0.82 (0.71–0.94) | 0.004 | 0.98 (0.84–1.14) | .77 |

OBS = oxidative balance score.
[*] Adjusted for age, sex, education, income, and comorbid diseases (diabetes mellitus, hypertension, dyslipidemia, and cancer), which were significant factors in the univariate analysis.

**Associations between oxidative balance score and EuroQoL five-dimensional questionnaire score in the patients with osteoarthritis.**

|  | Low EQ5D (n=74) | High EQ5D (n=222) | Univariate analysis | | Multivariable analysis[*] | |
|---|---|---|---|---|---|---|
|  |  |  | Crude OR (95% CI) | P | Adjusted OR (95% CI) | P |
| Total OBS | 16.01±0.44 | 17.30±0.25 | 1.14 (1.03–1.25) | 0.008 | 1.14 (1.04–1.25) | .008 |
| Pro-oxidants | 10.69±0.41 | 10.10±0.23 | 0.93 (0.82–1.05) | 0.22 | 1.01 (0.88–1.14) | .99 |
| Dietary | 4.20±0.26 | 3.53±0.18 | 0.85 (0.72–0.99) | 0.05 | 0.93 (0.78–1.11) | .41 |
| Non-dietary | 6.49±0.24 | 6.57±0.12 | 1.03 (0.84–1.27) | 0.76 | 1.15 (0.92–1.45) | .21 |
| Antioxidants | 5.32±0.37 | 7.19±0.30 | 1.18 (1.08–1.29) | 0.001 | 1.14 (1.03–1.25) | .01 |
| Dietary | 4.31±0.34 | 5.81±0.27 | 1.17 (1.07–1.29) | 0.001 | 1.12 (1.02–1.24) | .02 |
| Non-dietary | 1.01±0.13 | 1.38±0.09 | 1.41 (1.06–1.89) | 0.02 | 1.31 (0.95–1.80) | .10 |

EQ5D = EuroQoL five-dimension questionnaire.
[*] Adjusted for age, sex, education, income, and comorbid diseases (asthma), which were significant factors in the univariate analysis.
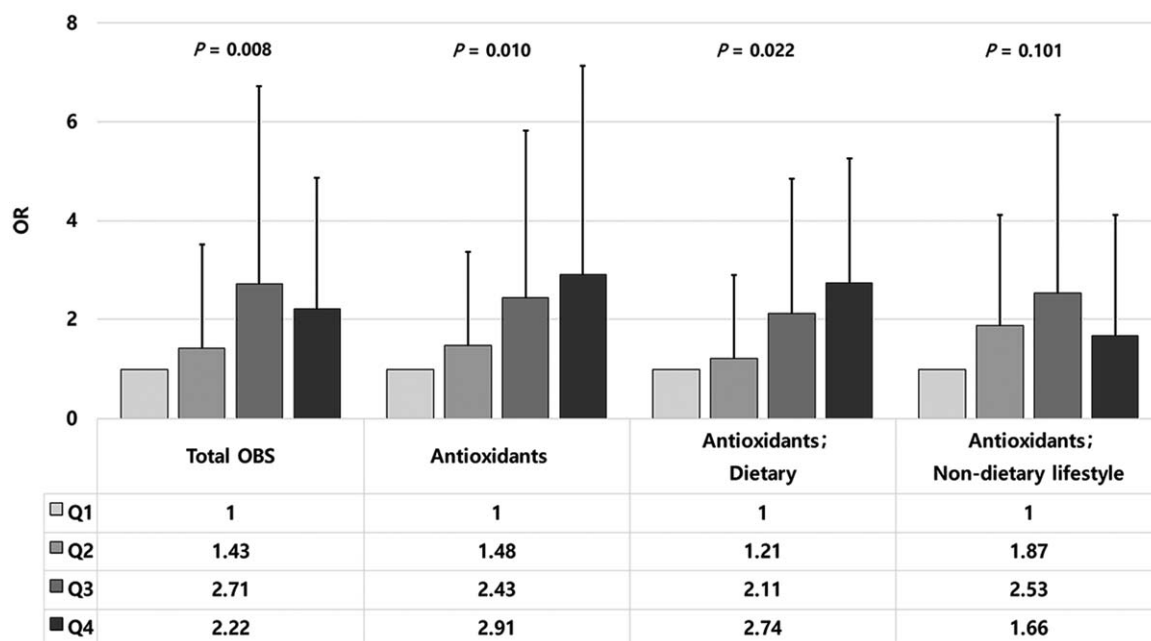
**Figure 2.** Associations between the oxidative balance score and EuroQoL five-dimensional questionnaire score in the patients with osteoarthritis. The multivariable model was adjusted for age, sex, education, income, and comorbidities (asthma).

decreased.[22] These factors cause an imbalance between ROS and antioxidants, and regulate cell signaling through oxidative post-translational modifications of special proteins, thereby contributing to cartilage degeneration.[23–28]

In this study, we focused on more modifiable factors that correlated with oxidative stress in the development of OA. OBS is inversely associated with the levels of γ-glutamyltransferase, which is a biomarker of oxidative stress, and has been validated to show a relationship with various diseases and conditions.[7,19,29–32] The association between OBS and OA in the present study was significant after adjusting for age and sex. However, the association was not significant after adjusting for comorbidities, including diabetes mellitus, hypertension, dyslipidemia, and cancer. OA was associated with low intakes of dietary and non-dietary antioxidants. However, pro-oxidants showed a weaker relationship with OA than expected. Therefore, OBS, which is the sum of pro-oxidants and antioxidants, showed no statistical significance. The better scores for smoking and alcohol use in the patients with OA than in the healthy controls may reflect the patients' will to improve their health after diagnosis. Nonetheless, the patients with OA had lower scores for antioxidants than the healthy controls.

Our study showed that a higher OBS was significantly associated with a high EQ5D score. That is, an antioxidant-predominant status was associated with higher QOL in the patients with OA. Alleviation of joint pain and increases in physical activity in patients with OA are closely related with QOL.[33–35] Recently, an increasing number of studies have reported that antioxidant-rich foods or supplements can decrease joint pain in patients with OA. For example, the natural antioxidants, quercetin, and resveratrol, improved OA pain and physical function in a monoiodoacetate-induced OA model.[36] Clinical trials have reported evidence for the similar effects of antioxidants. Antioxidant-rich pomegranate juice decreased joint pain and improved physical function.[37] Spearmint tea with high

levels of rosmarinic acid also improved physical disability and decreased pain.[38] Improvement in QOL in participants with a higher antioxidative status correlated with reduced pain and increased physical activity in patients with OA based in a previous study. These results support the concept that the consumption of dietary antioxidants and lifestyle modifications must be considered as treatment options for patients with OA.

Our study had several limitations. First, complete information about the presence of OA in each patient, which includes the affected joints, severity, disease duration, radiological and clinical information, and treatment information, was not obtained. Furthermore, patients with severe OA and poor health conditions were not included in this study because they did not participate in the nationwide survey. Second, the 24-h dietary recall method used in our study may not obtain day-to-day variability in dietary pro-oxidant and antioxidant consumption.[39] Third, this study used a cross-sectional design, with possible selection bias arising from missing data and residual confounding. Thus, to confirm our results, more studies with a prospective design must be conducted.

Regardless, to the best of our knowledge, this study is the first to investigate the association between OBS and OA using a representative sample of the entire Korean population. Furthermore, our findings indicated the importance of modifiable antioxidants in patients with OA. So far, no proven disease-modifying drug has been developed for OA treatment. However, recent clinical trials of therapeutic agents targeting oxidative stress in patients with OA have begun.[40–42] These studies can identify the therapeutic effects of dietary antioxidants and physical activity, in addition to the use of therapeutic agents.

In conclusion, we did not observe a significant association between OA and OBS. However, a higher OBS was associated with a high EQ5D score in the patients with OA. This study showed the importance of modifiable antioxidants in patients with OA and the correlation of OBS with OA and QOL,

reflecting the balance between antioxidants and pro-oxidants. Further prospective studies with a long follow-up period must be conducted to evaluate the causal relationship between oxidative stress and OA.

## Author contributions

**Conceptualization:** Joo-Hyun Lee, Young Bin Joo, Kyong-Hee Jung.

**Data curation:** Joo-Hyun Lee, Young Bin Joo, Minkyung Han, Kyong-Hee Jung.

**Formal analysis:** Joo-Hyun Lee, Young Bin Joo, Minkyung Han, Kyong-Hee Jung.

**Funding acquisition:** Kyong-Hee Jung.

**Methodology:** Joo-Hyun Lee, Young Bin Joo, Kyong-Hee Jung.

**Resources:** Joo-Hyun Lee, Young Bin Joo, Kyong-Hee Jung.

**Supervision:** Seong Ryul Kwon, Won Park, Kyung-Su Park, Bo Young Yoon.

**Writing – original draft:** Joo-Hyun Lee, Young Bin Joo, Kyong-Hee Jung.

**Writing – review & editing:** Joo-Hyun Lee, Young Bin Joo, Minkyung Han, Seong Ryul Kwon, Won Park, Kyung-Su Park, Bo Young Yoon, Kyong-Hee Jung.

Kyong-Hee Jung orcid: 0000-0002-5757-5775.

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