

Serum oxidative stress test and the progression of knee osteoarthritis: A 5-year longitudinal cohort in the Yakumo Study

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INTRODUCTION:

Knee osteoarthritis (KOA) is a chronic degenerative disease characterized by a reduction in joint cartilage in the knee joint. However, few reports have investigated the relationship between serum reactive oxygen species (ROS) and KOA. We aimed to investigate whether oxidative stress, assessed using d-ROMs and biological antioxidant potential (BAP), is associated with the severity and progression of KOA in community-dwelling individuals.

METHODS:

Since 1982, we have been conducting a health examination program for healthy elderly residents in Yakumo, a rural area in southern Hokkaido, Japan. In the present study, 424 participants with knee anteroposterior radiographs that could be evaluated using the knee osteoarthritis computer-aided diagnostic (KOACAD) system in 2017 and 2018 were selected as participants for analysis. From the initial cohort, a total of 95 participants (190 knees) underwent prospective examinations in 2022 and 2023, five years after the health checkups conducted in 2017 and 2018 (Fig. 1). The blood samples were collected at the annual physical examinations and stored at -80°C until d-ROMs and BAP levels were measured in our laboratory. Both tests were conducted using a REDOXLIBRA (Wismar Co., Ltd. Tokyo, Japan).

All participants underwent radiographic examination of both knees using the Rosenberg method. KOACAD automatically measures the average joint space width (aJSW), mJSW, joint space area (JSA) in the medial and lateral compartments, and the femorotibial angle (FTA) using digitized knee radiographs (Supplemental Fig. 1). We calculated the difference between the JSW and JSA at 5 years and at baseline, and the progression of KOA was defined as a reduction of >1 mm in the mJSW.

The study population was divided into two groups based on the median values of d-ROMs and BAP, and a statistical analysis was conducted between the two groups. Differences between groups were assessed using Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for group comparisons of continuous variables that did not follow a normal distribution. The Chi-squared test was used to compare categorical variables. Logistic regression analysis was performed to investigate risk factors for the progression of medial mJSW narrowing. All statistical analyses were performed using EZR software version 1.38 (64-bit). $P < 0.05$ was considered indicative of statistical significance.

RESULTS:

We identified 95 participants (190 knees) from the Yakumo Study who met the inclusion criteria between 2017 and 2018. The cohort comprised 52 females (54.7%) ranging in age from 41 to 85 years at baseline (mean age, 64.2 ± 9.3 years). The mean BMI was 23.4 ± 3.3 kg/m². The median values for lateral and medial mJSW at baseline was 4.20 mm and 2.89 mm, respectively, and median progression of medial mJSW narrowing was 0.17 mm in 5 years ranging from 0 to 3.91 mm. The participants were classified into two groups according to the median d-ROMs and BAP and followed up for 5 years (Tables 1 and 2). In the high d-ROMs and BAP level group, there was a significantly higher proportion of females compared to the group with lower levels (32 females [68.1%] and 31 females [66.0%]; $P = 0.013$ and 0.04 , respectively). The mean BMI was significantly higher in the HD group than in the LD group; however, no significant differences were observed between the two groups in terms of age, GLFS-25 score, smoking status, alcohol consumption, VAS score, FTA, or medical history with respect to d-ROMs and BAP. The median values for lateral and medial mJSW, aJSW, and JSA differed significantly between the d-ROMs groups ($P \leq 0.01$). In contrast, there were no significant differences in these values among the BAP groups. Knee radiographic parameters measured using the KOACAD system at 5-year follow-up are shown in Table 2. In the HD group, the medial mJSW, aJSW, and JSA at the 5-year follow-up were significantly narrower than those in the LD group (0.09 mm, 0.53 mm, and 3.8 mm² in LD group vs. 0.70 mm, 0.90 mm, and 10.9 mm² in HD group; $P = 0.004$, 0.03 , and 0.049 , respectively). In contrast, there were no significant differences in these values among the BAP groups.

To investigate the risk factors for progression of medial mJSW narrowing >1 mm after 5 years, variables including age, sex, BMI, VAS, d-ROMs ($320 \leq$), BAP (≤ 2280), FTA, and medial mJSW at baseline were entered into a multivariate logistic regression analysis model; BMI (odds ratio [OR], 1.15; 95% confidence interval [CI], 1.02–1.29; $P = 0.03$), d-ROMs ($320 \leq$) (OR, 2.39; 95% CI, 1.12–5.09; $P = 0.02$), and medial mJSW (OR, 4.17; 95% CI, 1.57–11.00; $P = 0.004$), were identified as independent risk factors for the progression of medial mJSW narrowing (Table 3).

DISCUSSION AND CONCLUSION:

Previous studies have reported the involvement of both oxidative stress levels and antioxidant capacity in the deterioration of cartilage quality or the incidence of KOA. Furthermore, studies using animal models have reported that an age-related

imbalance in ROS production against the antioxidant capacity of chondrocytes is associated with cartilage degradation and chondrocyte cell death. However, no clinical studies have investigated the relationship between oxidative stress and KOA progression. To our knowledge, this is the first longitudinal study to explore the relationship between KOA progression and oxidative stress in a longitudinal study. The oxidative stress level, which reflects ROS production, is associated with narrowing of the joint space. The same relationship was observed in the progression of joint space narrowing over the course of 5 years. Our findings suggest that increased oxidative stress may play a more critical role in the progression of KOA than a decrease in antioxidant defense, emphasizing its significance as a contributing factor in the progression of KOA.