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Original Article

Dehydroepiandrosterone sulfate level and knee osteoarthritis in older adults: preliminary data for the possible link

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ABSTRACT

Background: Dehydroepiandrosterone (DHEA) is believed to be protective against articular cartilage injury and it is widely used as one of the natural remedies for inflammatory and degenerative arthritis. Yet, information about the association between DHEA level and knee OA is lacking.

Objectives: To explore the link between serum dehydroepiandrosterone sulfate (DHEAs) levels and knee OA among elderly patients.

Methods: A case control study was conducted on 80 elderly subjects (40 males, 40 females) aged 60 years and older attending the outpatient clinics in Ain Shams University Hospital. Participants underwent a standard clinical examination of the knee, assessment of physical difficulty and pain severity using WOMAC OA index. Weight-bearing anteroposterior radiographs of the knees in the semi-flexed position were performed. Serum levels of DHEAs were examined.

Results: The serum level of DHEAs in males with knee OA was 0.29 ± 0.17 $\mu\text{g/mL}$ compared to those without knee OA 0.59 ± 0.51 $\mu\text{g/mL}$ ($p=0.006$), small but significant difference existed between the serum level of DHEAs in females with knee OA 0.25 ± 0.11 $\mu\text{g/mL}$ compared to those without knee OA 0.39 ± 0.26 $\mu\text{g/mL}$ ($p=0.044^*$). Additionally, the serum DHEAs level negatively correlated with the severity of knee OA in both sexes.

Conclusions: There was a sex difference in serum DHEAs level and occurrence of knee OA. Lower levels of DHEAs were reported in elderly with knee OA and the serum DHEAs level negatively correlated with the severity of knee OA.

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INTRODUCTION

Dehydroepiandrosterone (DHEA) and its sulfated form (DHEAs) are the most abundant circulating adrenal steroids that convert to androgen and estrogen in the peripheral tissues.¹ Adrenal production of DHEA begins during puberty, peaks at the age of 20 years and then declines with aging.² This decline is called adrenopause in which a gradual progressive decline of DHEA and its sulfated form occurs throughout life.³

Previous researches linked low DHEA levels to a number of common diseases in elderly e.g. dementia,⁴ depression,⁵ osteoporosis in elderly women,⁵ frailty,⁶ and ischemic heart disease in elderly men.⁷ However, the exact biological role of DHEA is still unknown. It is considered a biomarker of successful ageing.³ and is viewed by many researchers as a potential fountain of youth. That is why, DHEA supplementation has been recommended to prevent many of age related clinical disorders and to enhance wellbeing.¹

Osteoarthritis (OA) particularly at the knee, is the most common form of arthritis associated with increased morbidity and disability in elderly people.⁸ It is a debilitating condition characterized by pain, joint inflammation and stiffness.⁹

Both the rapid rise in the elderly population worldwide and the rising obesity epidemic are paralleled by an increase in the prevalence of knee OA. By 2025, the prevalence of knee OA is expected to increase by 40% leading to a public health crisis.¹⁰ Thus, early diagnosis and the development of preventive or therapeutic interventions could enhance the quality of life for the elderly and minimize health care costs.¹¹

Although, the link between DHEA levels and inflammatory arthritis, including rheumatoid arthritis (RA), is increasingly recognized^{12,13} there is little information about the association of DHEA levels with OA.

It was reported that, exogenously administered DHEA in animal models had positive effects on the maintenance of

the articular cartilage matrix integrity during experimentally induced OA.¹⁴

Moreover, there are some observations that suggest a possible link between knee OA and low levels of DHEA, the occurrence of knee OA increases with age and is more common in women compared with men.¹⁵ Similarly, age related decline and gender difference are well documented in serum DHEA levels, with higher levels in men than in women.³

The current study was designed to explore the relationship between knee OA and serum DHEAs levels.

METHODS

Study Sample

A case control study was conducted on 80 elderly subjects (40 males, and 40 females) aged 60 years and older attending the outpatient clinics in Ain Shams University Hospital, Cairo, Egypt. OA of the knee was defined using the American College of Rheumatology (ACR) diagnostic criteria.¹⁶

Patients with a history of rheumatoid or other inflammatory arthritis, periarticular fractures, previous knee injuries, and the use of exogenous androgen, estrogen, DHEA or glucocorticoids therapy in the preceding year were excluded from the study.

All participants were subjected to a detailed clinical assessment including:

Anthropometric Data

Weight and height were measured at the time of assessment and body mass index (BMI) was calculated.

A standard clinical examination of the knee

It included the assessment for bony and soft tissue swelling, pain on passive movement, joint line tenderness, and tenderness on patellofemoral compression, crepitus (patellofemoral or tibiofemoral), fixed flexion deformity and range of movement (degrees).

Functional assessment was done using the activities of daily living (ADL).¹⁷

Self-reported difficulty with different tasks using the function subscale of the Western Ontario and McMaster Universities (WOMAC) OA index.¹⁸ This is a validated scale designed to assess functional difficulties associated with lower limb OA. Patients rate their difficulty with 17 different tasks using a scale from 0 to 4, with higher scores indicating more difficulty. The total response to these 17 tasks was calculated as an overall disability score.

Pain severity was measured for the worse knee (index knee) using the pain section of the WOMAC OA index.¹⁸

Radiographic assessment

Weight-bearing anteroposterior radiographs of the knees in the semi-flexed position were performed in all subjects. Radiographs were obtained using General Electric radiograph equipment (Shimadzu RadSpeed MF. model UD

150 L 40, Tokyo, Japan). Knees were scored by a single trained observer using the Kellgren and Lawrence (K-L) grading system of the Atlas of Standard Radiographs of Arthritis¹⁹ where grade 0=normal; 1=doubtful OA; 2=minimal OA; 3=moderate OA; 4=severe OA. Radiographic knee osteoarthritis was defined as at least one knee with a K-L score ≥ 2 .

Laboratory assessment

Serum samples after overnight fasting was used for the assessment of DHEAs concentration. Samples were stored at -70° for 6 months Serum DHEA-S measurement by ELISA using The DRG DHEAs ELISA which is a solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding for the quantitative in vitro diagnostic measurement of DHEAs in serum and plasma. ([DRG Diagnostics](#), Germany).

The expected normal values using the DRG DHEA-S ELISA are:

Men >50 years mean: 1.01 $\mu\text{g}/\text{mL}$

Women >50 years mean: 0.63 $\mu\text{g}/\text{mL}$

Ethical considerations

Informed consent was obtained from all the participants in this study. The study methodology was reviewed and approved by the Research Review Board of the Geriatrics and Gerontology Department, Faculty of medicine, Ain Shams University.

Statistical methods

The collected data were coded, tabulated, revised and statistical analyzed using SPSS program (version 16). Quantitative variables were presented in the form of means and standard deviation. Qualitative variables were presented in form of frequency tables (number and percent). The comparison between quantitative variables was done using student t test or ANOVA. Comparison between qualitative variables was done using Pearson's Chi square test. Spearsman's correlation coefficient was used for non-parametric correlations. Receiver operating characteristic (ROC) curves were constructed. The area under each ROC curve was calculated to assess the discriminatory ability of the serum DHEAs to distinguish patients with knee OA. P value is considered significant if equal to or less than 0.05.

RESULTS

The characteristics of the two study groups are shown in Table 1. The group with knee OA was more obese as indicated by higher BMI (34.25 ± 6.51) vs. (27.16 ± 3.6) in those without knee OA. Moreover, knee OA was more common among females (25/ 41 [60.98%]; $p=0.03^*$). Cases with knee OA were more functionally dependent as measured by ADL. There was no significant difference between both groups regarding age.

In Table 2, there was no significant difference between both sexes regarding age, BMI, or presence of obesity. Knee OA was more common among the female group (25/40 cases; 62.5%) compared to the male group (16/40 cases; 40%). This difference was statistically significant ($p=0.03$). The mean

serum DHEAs level was significantly higher among males (p=0.03).

Table 1. Demographic data of the studied sample

| Characteristics | Knee OA | | P value |
|-------------------------------------|--------------|-------------|---------|
| | Yes, 41 (%) | No, 39 (%) | |
| Age (y), mean ± SD | 68.51 ± 6.48 | 66.38±6.7 | 0.15 |
| BMI (kg/m ²), mean ± SD | 34.25 ± 6.51 | 27.16 ± 3.6 | 0.000* |
| Obese % | 18 (72%) | 4 (26.7%) | 0.007* |
| Male % | 16(39.02%) | 24(61.54%) | 0.03* |
| Female % | 25(60.98%) | 15(38.46%) | |
| ADL % | | | 0.000* |
| Independent | 17 (41.5%) | 33 (84.6%) | |
| Assisted | 16 (39%) | 4 (10.3%) | |
| Dependent | 8 (19.5%) | 2 (5.1%) | |
| DHEAs level (µg/mL) | 0.29 ± 0.15 | 0.49 ± 0.44 | 0.007* |
| Smoker% | 7(17.07%) | 11(28.20%) | |
| WOMAC physical | 32.9 ± 24.00 | -- | -- |
| WOMAC pain | 7.12 ± 2.9 | -- | -- |

Table 2. Clinical characteristics of the studied groups

| | Female | Male | P value |
|--------------------------|--------------|--------------|---------|
| Symptomatic knee OA (%) | 25 (62.5%) | 16 (40%) | 0.03* |
| Age (years) | 66.52 ± 6.14 | 68.42 ± 7.04 | 0.2 |
| BMI (kg/m ²) | 31.88 ± 6.43 | 29.71 ± 6.21 | 0.12 |
| Obesity (%) | 22 (55%) | 15 (37.5%) | 0.08 |
| DHEAs (µg/mL) | 0.31 ± 0.19 | 0.47 ± 0.43 | 0.03* |

*Statistically significant. OA, osteoarthritis; BMI, body mass index; DHEAs, Dehydroepiandrosterone sulfate.

Table 3 showed that there was a significant difference between patients with and without knee OA in both genders in regard to BMI, serum DHEAs, and functional dependency assessed by ADL. The serum level of DHEAs was lower in males with knee OA 0.29 ± 0.17 µg/mL compared to those without knee OA 0.59 ± 0.51 µg/mL (p=0.006), and the serum level of DHEAs was lower in females with knee OA 0.25 ± 0.11µg/mL compared to those without knee OA 0.39 ± 0.26 µg/mL (p=0.044*), yet, the difference in serum DHEAs level among females with and without knee OA was small. The serum DHEAs level was 0.25 ± 0.11 µg/mL among females with knee OA while it was 0.29 ± 0.17 µg/mL among males with knee OA (p=0.09). Women tended to report more physical difficulty than men in WOMAC OA index (39.60 ± 23.53 vs. 22.50 ± 21.44; P=0.02).

Table 3. The differences between cases with and without Knee OA in both sexes

| Characteristics | Females Knee OA | | P value | Males Knee OA | | P value | P value [†] |
|-------------------------------------|--------------------|----------------|---------|------------------|--------------|---------|----------------------|
| | Yes, 25 (62.5%) | No, 15 (37.5%) | | Yes, 16 (40%) | No, 24 (60%) | | |
| Age (y), mean ± SD | 67.76 ± 6.22 | 64.46 (5.61) | 0.12 | 69.68 ± 6.90 | 67.58 ± 7.15 | 0.32 | 0.36 |
| BMI (kg/m ²), mean ± SD | 33.93 ± 7.00 | 28.46 ± 3.35 | 0.02* | 34.75 ± 5.85 | 26.35 ± 3.68 | 0.000* | 0.63 |
| Obese % | 18 (72%) | 4 (26.7%) | 0.007* | 13 (81.25%) | 2 (8.33%) | 0.000* | 0.38 |
| ADL % | | | 0.026* | | | 0.031* | 0.33 |
| Independent | 9 (36%) | 12 (80%) | | 8 (50%) | 21 (87.5%) | | |
| Assisted | 12 (48%) | 2 (13.3%) | | 4 (25%) | 2 (8.33%) | | |
| Dependent | 4 (16%) | 1 (6.7%) | | 4 (25%) | 1 (4.17%) | | |
| DHEAs level (µg/mL) | 0.25 ± 0.11 | 0.39 ± 0.26 | 0.044* | 0.29 ± 0.17 | 0.59 ± 0.51 | 0.006* | 0.09 |
| Smoker% | 0 | 0 | -- | 7 (43.75%) | 11 (45.83%) | 0.36 | 0.004* |
| WOMAC physical | 39.60 ± 23.53 | -- | -- | 22.50 ± 21.44 | -- | -- | 0.02* |
| WOMAC pain | 6.92 ± 3.4 | -- | -- | 7.25 ± 3.3 | -- | -- | 0.7 |

*Statistically significant; [†]P value comparing males and females with OA. BMI, Body Mass Index; WOMAC, the Western Ontario and McMaster Universities OA index.

Among females with knee OA, there was no statistical significance difference between the different radiographic grades of knee OA regarding age, pain severity, or physical disability assessed by WOMAC OA index. Those with advanced radiographic grades were more functionally dependent in performing ADL. They had a higher BMI and a lower serum DHEAs level (Table 4).

Among males with knee OA, there was no statistical significance difference between the different radiographic grades of knee OA regarding BMI, or pain severity. Those with advanced radiographic grades were older, functionally dependent in performing ADL and had lower serum DHEAs level. The physical disability score of WOMAC OA index was higher in patients with advanced radiographic grades of knee OA (Table 4).

The serum DHEAs level negatively correlated with the severity of knee OA in both sexes, but it did not correlate with age, BMI or functional status in patients with knee OA of both sexes (Table 5).

Among males, the Roc curve analysis demonstrated that the probability of predicting knee OA by measuring serum DHEAs was 68%. Serum DHEAs level of 0.4 µg/mL had 75% sensitivity and 60% specificity to predict knee OA (figure 1).

While among females, the Roc curve analysis, although not reaching statistical significance (p=0.6), demonstrated that the probability of predicting knee OA by measuring serum DHEAs was 54%. Serum DHEAs level of 0.3 µg/mL had 60% sensitivity and 50% specificity to predict knee OA (figure 1).

The Area under the curve for females is 0.54, 95% CI (0.32-0.75), p=0.6, while the area under the curve for males is 0.68, 95% CI (0.51-0.85), p=0.04* (figure 1).

DISCUSSION

The presence OA is a common disease among older adults and is one of the leading causes of disability in this age group.⁸ Therefore, identifying new preventive measures should be a public health priority. This was a small single site study performed in the outpatient setting designed to study the prevalence of knee OA in elderly and to study the relationship between serum DHEAs level and knee OA among elderly participants at the outpatient setting.

Table 4. Comparison between different radiographic grades of knee OA and different variables among both sexes

| | | Grade 2 KL score 5 (20%) | Grade 3 KL score 12 (48%) | Grade 4 KL score 8 (32%) | P value |
|-----------|----------------|-------------------------------|------------------------------|--------------------------------|---------|
| Females | Age | 66.80 ± 6.53 | 68.16 ± 7.04 | 76.75 ± 5.41 | 0.9 |
| | BMI | 27.86 ± 1.89 | 33.33 ± 7.27 | 38.62 ± 5.55 | 0.017* |
| | DHEAs level | 0.44 ± 0.12 | 0.34 ± 0.09 | 0.25 ± 0.14 | 0.014* |
| | WOMAC physical | 20.00 ± 18.7 | 41.66 ± 26.22 | 48.75 ± 15.52 | 0.08 |
| | WOMAC pain | 4.8 ± 3.6 | 8.50 ± 3.71 | 5.87 ± 1.72 | 0.07 |
| | ADL | | | | |
| | Independent | 3 (60%) | 6 (50%) | 0 | |
| Assisted | 1 (20%) | 6 (50%) | 5 (62.5%) | 0.044* | |
| Dependent | 1 (20%) | 0 | 3 (37.5%) | | |
| | | Grade 2 KL score 6 (37.5%) | Grade 3KL score 7(43.75%) | Grade 4 KL score 3 (18.75%) | P value |
| Males | Age | 68.66 ± 5.35 | 66.42 ± 5.02 | 79.33 ± 5.50 | 0.011* |
| | BMI | 35.50 ± 7.25 | 34.71 ± 6.21 | 33.33 ± 2.30 | 0.88 |
| | DHEAs level | 0.42 ± 0.17 | 0.24 ± 0.19 | 0.14 ± 0.09 | 0.031* |
| | WOMAC physical | 11.66 ± 24.01 | 25.14 ± 17.18 | 50.00 ± 0.00 | 0.04* |
| | WOMAC pain | 6.50 ± 4.18 | 8.71 ± 2.21 | 11.33 ± 1.51 | 0.11 |
| | ADL | | | | |
| | Independent | 4 (66.67%) | 4 (57.14%) | 0 | |
| Assisted | 2(33.33%) | 2 (28.58%) | 0 | 0.02* | |
| Dependent | 0 | 1(14.28%) | 3 (100%) | | |

*Statistically significant. OA, osteoarthritis; BMI, body mass index; DHEAs, Dehydroepiandrosterone sulfate.

The prevalence of knee OA in this study was 51.25% (41/80 participants). While, the prevalence of knee OA was 24.2% among elderly Korean, it was higher in women than in men.²⁰

In another study of Chinese population, the knee OA occurred in 15.0% of women and 5.6% of men.²¹ These differences among populations could be attributed to the age distribution of the population in study, genetic differences, differences in obesity prevalence, or the level of physical activity.

Epidemiologic studies have proved the presence of sex differences in the incidence and severity of knee OA. In the current study, the prevalence of knee OA was significantly higher among females. This female predominance was well documented. Meta-analytic evidence reported a greater risk in females for prevalent knee OA.²²

Although many studies suggested that the prevalence of knee OA increased with age,^{23,24} our findings demonstrated that there was no significant difference between subjects with and without knee OA in regard to age in both genders. This may be due to studying only elderly participants. However, there was a statistical significant difference between the different radiographic grades of knee OA regarding age only in male group.

The Framingham osteoarthritis study, however, reported that among the elderly, age may not affect new disease occurrence or progression.²³

Obesity is the most frequent modifiable risk factor of knee OA. A strong positive correlation was shown between BMI (over 30 kg/m²) and radiographic knee OA in longitudinal Framingham and Baltimore studies.^{25,26}

Similarly, in the current study, there was a significant difference between those with and without knee OA in both genders regarding BMI.

Dehydroepiandrosterone (DHEA) is believed to be protective against articular cartilage injury and it is widely used as one of the natural remedies for inflammatory and degenerative arthritis. Yet, the researches about the

association between DHEA level and knee OA are lacking. Previous studies showed a significant relationship between DHEA levels and inflammatory arthritis, including rheumatoid arthritis.^{12,13} Recent investigations have demonstrated that patients with rheumatoid arthritis had low serum levels of DHEAs many years prior to the onset of disease.²⁷ However, comparative data regarding knee OA is lacking.

In this study, serum DHEAs levels were higher among male participants (0.47 ± 0.43 µg/mL vs. 0.31 ± 0.19 µg/mL; p=0.03). The effect of sex on DHEAs levels in adults has previously been described. The mean levels of DHEAs were significantly higher in males in all age groups.²⁸

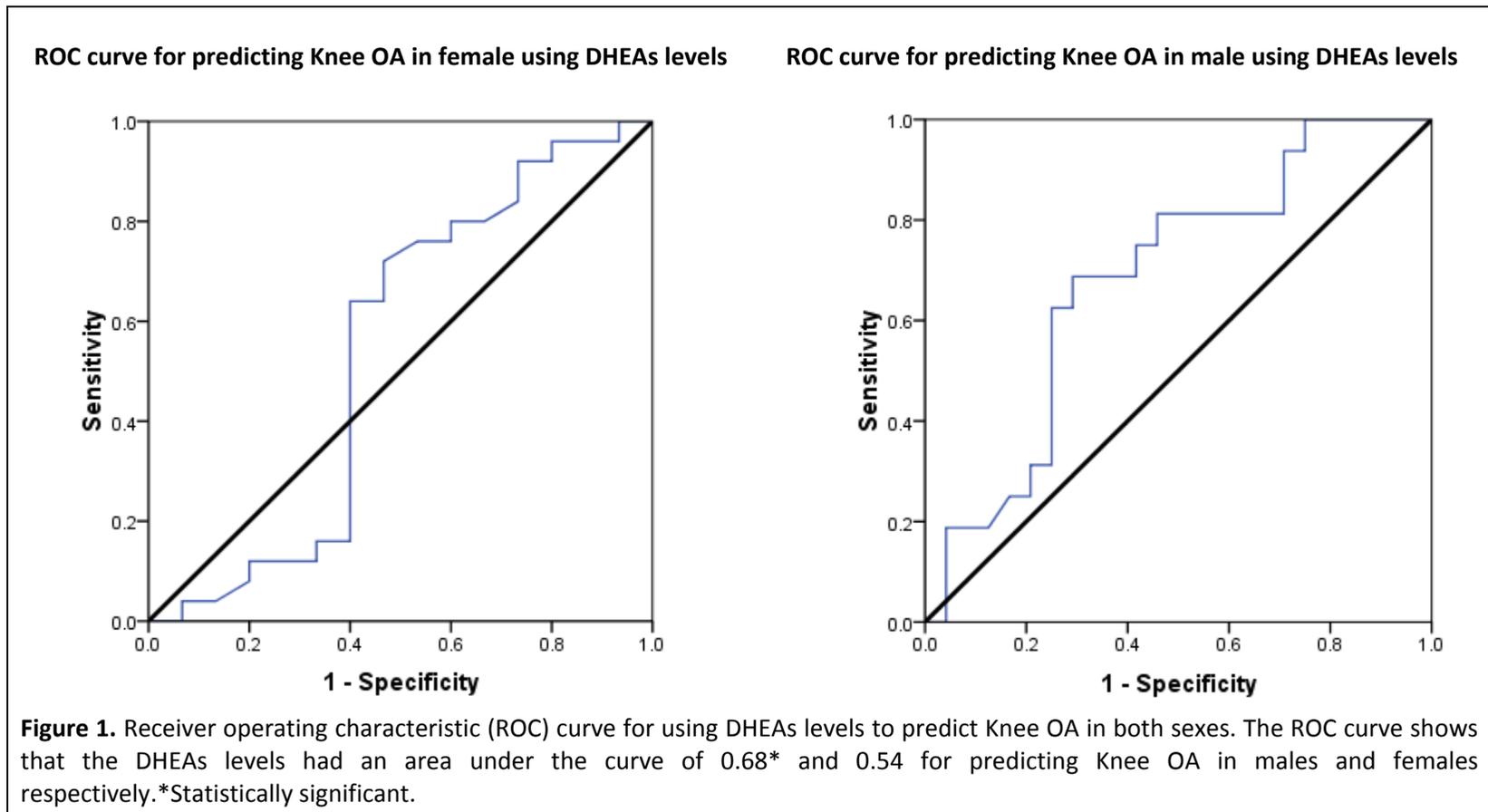
Those with knee OA had lower serum level of DHEAs, the serum level of DHEAs was lower in males with knee OA 0.29 ± 0.17 µg/mL compared to those without knee OA 0.59 ± 0.51 µg/mL (p=0.006), and a less significant difference in the serum level of DHEAs was observed in females. The women with knee OA had serum DHEAs level of 0.25 ± 0.11 µg/mL compared to those without knee OA 0.39 ± 0.26 µg/mL (p=0.044*).

Moreover, the advanced radiographic grades of knee OA were associated with lower DHEAs levels in both sexes. These results supported the previous in vitro data suggesting that DHEA had a protective role against articular cartilage loss.²⁹

Table 5. Correlation between studied variables and DHEAs level in both genders

| | Males | | Females | |
|----------------|---------|-------|---------|-------|
| | P value | r | P value | r |
| Age | 0.69 | -0.11 | 0.57 | -0.11 |
| BMI | 0.88 | 0.03 | 0.12 | -0.31 |
| OA severity | 0.007* | -0.64 | 0.05* | -0.39 |
| WOMAC physical | 0.46 | 0.19 | 0.37 | -0.18 |
| WOMAC pain | 0.54 | 0.16 | 0.49 | 0.14 |

*Statistically significant. BMI, Body Mass Index; WOMAC, the Western Ontario and McMaster Universities OA index.



Regarding possible protective mechanism of DHEA, Jo et al.,²⁹ demonstrated that in OA, DHEA modulated the imbalance between matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases 1 (TIMP-1) at the transcription level. Additionally, DHEA exerted a cartilage-protecting effect during the development of OA following anterior cruciate ligament transection in a rabbit model.¹⁴

This study has several limitations first, small sample size; its statistical power might be insufficient. Second, only antero-posterior knee radiographs were used, thus, patellofemoral compartment OA was not evaluated. Longitudinal studies will be required to confirm causal relationship. Third, the sex hormone profile was not available for our participants and it should be evaluated in the future studies because it is closely associated with both DHEAs level and the occurrence of OA. Fourth, future larger studies are needed for the general population living in the community.

In conclusion, Knee OA is a common condition among older adults. This preliminary study reported lower levels of DHEAs in elderly with knee OA. There is a significant relationship between low serum levels of DHEAs and the knee OA among elderly males. Small but significant difference existed between the serum level of DHEAs in females with and without knee OA. However, longitudinal studies will be required to confirm causal relationship.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest with respect to the authorship and publication of this article. 9.

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Informed consent was taken from each participant. The study methodology was reviewed and approved by the Research Review Board of the Geriatrics and Gerontology Department, Faculty of medicine, Ain Shams University.

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