

**PREVALENCE AND EFFECTS OF PROGRESSIVE OSTEOARTHRITIS ON SEX STEROIDS IN MALE AND FEMALE PATIENTS OF DISTRICT BUNER, KPK PAKISTAN**

**KHAN L<sup>\*1</sup>, SHAMAS S<sup>\*2</sup>, TABASSUM S<sup>3</sup>, ALAM M<sup>1</sup>, KHAN BT<sup>1</sup>, QURESHI IZ<sup>4</sup>**

<sup>1</sup>Department of Zoology, University of Buner, Khyber Pakhtunkhwa/ Quaid-i-Azam University, Islamabad, Pakistan

<sup>2</sup>Department of Zoology, Rawalpindi Women's University, Rawalpindi, Pakistan

<sup>3</sup>Department of Zoology, University of the Punjab, Lahore, Pakistan

<sup>4</sup>Laboratory of Animal and Human Physiology, Department of Zoology, Quaid-i-Azam University, Islamabad, Pakistan

\*Corresponding author email address: [lubnazologist@gmail.com](mailto:lubnazologist@gmail.com) [shazia.shamas@f.rwu.edu.pk](mailto:shazia.shamas@f.rwu.edu.pk),

(Received, 18<sup>th</sup> October 2023, Revised 29<sup>th</sup> December 2023, Published 13<sup>th</sup> January 2024)

**Abstract:** Osteoarthritis is a major cause of disability in older people; pain is considered one of the most important signs of osteoarthritis, which normally affects the weight-bearing joint, especially the knee joint. The objective of the present study was to find out the prevalence and effects of progressive Osteoarthritis (OA) on sex steroids in male patients of district Buner KP, Pakistan. Data was collected from 294 OA patients (Male, 46.18%; Female, 54.76%) at different hospitals through questionnaires, face-to-face interviews and blood sampling in district Buner. Results showed that the 50 to 60-year age group was mostly affected by OA (29.81%). In the case of females, OA was common in the plain areas, while male patients were in hilly areas. Among 294 patients, housewives (23.46%) and agriculture (18.7%) are more affected by Osteoarthritis. Blood samples were collected from 18 male patients of different age groups and analysed through the ELISA (enzyme-linked immunosorbent Assay) Test. The results obtained from ELISA showed that most of the OA patients have normal testosterone levels, but the two age groups, i.e., 50 to 60 and 60 to 70, have abnormal results of 0.251 ng/ml and 1.89 ng/ml. After analysis of all testosterone test results at different age groups, analysis of variance (ONE WAY ANOVA) results show that SS, MS and F values were 36.30, 7.26 and 9.3, respectively. We concluded that people over 40 are more likely to get OA. Osteoarthritis is more common in women than males, and it is more common in overweight people. Mountainous locations have a higher incidence of males with OA than females. Additionally, there are more females than males in plain terrain. According to our findings, bilateral OA is more typical than unilateral OA. Our research indicates a tenuous connection between OA and male patients' testosterone levels.

**Keywords:** Testosterone; Osteoarthritis, Male, Female

## Introduction

Osteoarthritis is one of the most common musculoskeletal disorders worldwide (Yapar et al., 2019). The most dangerous symptoms of osteoarthritis were stable and intense pain. It has been linked to increasing the risk of mental health conditions such as depression, anxiety, and mood swings (Vancampfort et al., 2019). OA, a whole-joint disease affecting the cartilage, subchondral bone, and synovium, was once solely associated with ageing. (Bijlsma et al., 2011). 2004, the OA caused moderate to severe impairment in 43.4 million people globally (Cuesta and Meneses, 2021). Osteoarthritis is a condition influenced principally by older adults. In 2010, about 250 million people had knee osteoarthritis worldwide; it was 3.6% of the population (Wijesinghe et al., 2021). Individuals with knee OA further limit mobility to avoid pain during activity (Walter et al., 2018). Around 9.6% of males and 18% of women over 60 have symptomatic OA, respectively. The total incidence in Asian countries ranges from 20.5 to 68.0%, but it is significantly greater there with wide variances. Because ageing is a big risk factor for developing OA and the elderly population has been growing considerably in Asian nations, the prevalence of the disease has increased rapidly (Zamri et al., 2019).

The prevalence of OA in males and females is similar up to the age of 50, after which the prevalence for females increases more quickly than men, with estimates of 18.0%

of women and 9.6% of men above 60 worldwide (WHO, 2020) the prevalence of bilateral KOA (both knees are affected) is considerably higher than the unilateral form (Jhun et al., 2013). The prevalence of OA is predicted to rise due to several unavoidable variables, including population expansion, ageing brought on by longer life expectancies, an increase in the frequency of overweight and obesity, and a lack of OA medications that can slow the disease's course (Nemes et al., 2014). Reduced physical activity and a rise in the demand for nursing homes among the elderly due to OA incidence could indirectly increase cardiovascular morbidity (Bahler et al., 2015). Compared to knee and hand OA, hip OA is less frequent. (Peat et al., 2001). About 50% of OA patients with knee pain will have radiographic alterations consistent with OA and are categorised as having symptoms of OA (Jordan et al., 2004). Numerous studies have examined how OA develops differently in men and women, and interest in this subject is growing as new information is continuously brought to researchers' attention. (Yan et al., 2021; Tschon et al., 2021; Li and Zheng, 2021). The main male sex hormone, testosterone, declines after age 40 by an average of 0.8–2% per year (Çayan et al., 2020). The strongest naturally released steroid androgenic hormone is testosterone. It is necessary for muscle growth, neuromuscular adaptation, and the promotion of secondary male-sex traits (Vingren et al., 2018).

[Citation: Khan, L., Shamas, S., Tabassum, S., Alam, M., Khan, B.T., Qureshi I.Z. (2024). Prevalence and effects of progressive osteoarthritis on sex steroids in male and female patients of district Buner, KPK Pakistan. *Biol. Clin. Sci. Res. J.*, 2024: 656. doi: <https://doi.org/10.54112/bcsrj.v2024i1.656>]

Serum testosterone levels are known physiologically to decrease with increasing age, body mass index, poor diet, stress, sleep deprivation, and alcohol use (Diver, 2006; Hisaue, 2015). Within 24 to 48 hours of the commencement of a critical disease, such as surgery, severe burns, numerous injuries, and a catastrophic medical condition requiring ventilator dependence, the serum testosterone level drops by about 90%. (WOOLF et al., 1985; Dong et al., 1992). Therefore, chronic diseases that are linked to mortality are connected with low testosterone levels. It is unclear how gender differences in knee OA severity and prevalence in later life affect different populations (Hame and Alexander, 2013; O'Connor, 2006). However, given that testosterone receptors are expressed in the articular cartilage, underlying bone, and surrounding muscles of the male knee (Koelling and Miosge, 2010; Ushiyama et al., 1999).

In studies linking testosterone levels to OA, lower blood testosterone levels were linked to a higher prevalence of hand OA but not knee OA. (Sowers et al., 1996). Beginning at age 40, men's testosterone levels have been shown to decline by about 1% annually (Feldman et al., 2002). Testosterone levels had an adverse relationship with the severity of knee pain in a study looking at chronic knee pain from all causes. (Jin et al., 2017). Less well-known is the relationship between physiological testosterone levels and the health of cartilage tissue (Daigle et al., 2012). Particularly, those with the lowest risks for total knee replacement and hip arthroplasty also have the greatest amounts of androstenedione, a precursor to testosterone. Accelerated knee cartilage loss was reported in those with the lowest testosterone levels (Hanna et al., 2005).

Human patients with degenerative joint disease have even successfully undergone intra-articular testosterone injections to increase chondrocyte activity and immunological mechanisms necessary to treat the osteoarthritis process (Ravin, 2010). The research suggests that healthy testosterone levels are essential for osteoarthritis prevention and correction. Recently, a positive causal link between the concentration of circulating sex hormone-binding globulin (SHBG) In overweight men, low plasma androstenedione concentration has been linked to an increased risk of knee and hip arthroplasty (Hussain et al., 2016). According to the available data, sex steroids are a significant factor in the emergence of OA. However, there is a connection between sex and calcium level (Qu et al., 2020) and the risk of OA. Thus, the study aims to investigate the prevalence and ratio of osteoarthritis in District Buner KP and its relationship with decreased sex hormones in males. Additionally, the study seeks to explore the relevance of osteoarthritis in both plain and hilly areas.

**Methodology**

The current study was conducted in the district of Buner, located in the Malakand Division of Khyber Pakhtunkhwa province of Pakistan, over nine months in 2022. The study aimed to investigate the serum testosterone levels in adult and older patients (>20 years) with osteoarthritis. Patients under 19 years of age were excluded from the study. The study design was a prospective observational study approved by the research ethics board at DHQ Hospital Dagggar Buner and the University of Buner research committee. Data was collected through self-structured questionnaires and face-to-face interviews from DHQ

Hospital Dagggar. Details related to patients with osteoarthritis were provided by the Department of Statistics at DHQ Hospital Dagggar Buner. Face-to-face interviews were arranged with orthopaedic surgeons to confirm the data provided by the local participants. Blood collection was carried out in the health institutes of Buner, where 3 mL of venous blood was collected in an EDTA (Ethylene diamine Tetra Acetic acid) tube. Samples were stored in an ice container for up to 17 hours and then centrifuged at 3500 rpm at four °C for 15 minutes. Blood plasma was separated and held at -20 °C until hormone analysis.

The collected serum was put into an Elisa kit, with one Elisa kit used for one hundred tests. The Elisa kit was further treated by Maglumi 1000 CLIA Analyzer (Lotus Global Co., Ltd; 15 Alexandra Road, London, UK, NWB ODP), which is an automatic machine that uses the methods of (ECLIA) Electrochemiluminescent Immunoassay. After 21 minutes, the result for serum testosterone level was obtained.

Before data collection, data collectors briefly introduced the participants, explained the aims and benefits of the study, and obtained written consent from all participants. Secrecy and privacy of data were maintained throughout the study, and there was no conflict of interest.

**Results**

The present study is based on the prevalence of osteoarthritis and its impact on the level of sex steroids in OA male patients. In this study, data from 294 people was collected, of which 133 were male and 161 were female. We concluded that females were more prone to osteoarthritis than males, which is much more prevalent in females than males (Table 1).

**Table 1. Percentage values of OA in males and females.**

| Gender | Patients | (%)   |
|--------|----------|-------|
| Male   | 133      | 46.18 |
| Female | 161      | 54.76 |

Our study shows that the prevalence of osteoarthritis is different based on geographical distribution. In plain areas, OA affects males and females more than in hilly areas. Out of the total cases, 31% of male patients belong to hilly areas, and 69% belong to plain areas. 79% of females belong to bare areas, while 21% of hilly regions (table 2.).

**Table 2. Percentage values of OA based on locality.**

| Area  | Male | (%)   | Female | (%)   |
|-------|------|-------|--------|-------|
| Hilly | 41   | 30.82 | 34     | 21.11 |
| plain | 92   | 69.17 | 127    | 78.88 |

In terms of age below 30 years, the OA prevalence is low; in the case of males, 4.51% of patients are observed, while in the case of females, 3.1% of patients are followed. Figure 1 shows that between the ages 40 to 50 years, the OA prevalence rate in males is 21.05%, while in the case of females, the prevalence of OA is 19.81%. In ages 50 to 60 years, the ratio of prevalence of OA in the case of males is 27.06%, and in the case of females, the prevalence of OA is 29.81%.

[Citation: Khan, L., Shamas, S., Tabassum, S., Alam, M., Khan, B.T., Qureshi I.Z. (2024). Prevalence and effects of progressive osteoarthritis on sex steroids in male and female patients of district Buner, KPK Pakistan. *Biol. Clin. Sci. Res. J.*, 2024: 656. doi: <https://doi.org/10.54112/bcsrj.v2024i1.656>]

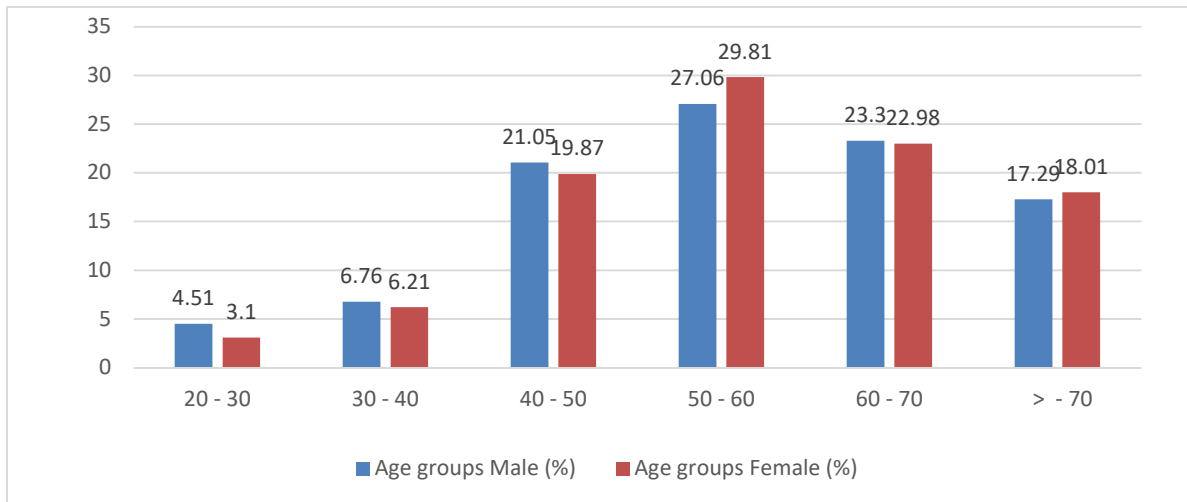


Figure 1. Percentage of OA in different age groups.

Table 3 shows the demographics of the study population. The provided table presents a comprehensive overview of the prevalence of osteoarthritis (OA) based on different variables and subgroups. Regarding the stages of the disease, it is observed that 28.23% of patients fall into the mild category, 41.49% into the moderate category, and 30.27% into the severe category, highlighting the distribution of OA severity among the study population. The data also delves into the association between OA and body weight. Notably, 49.31% of patients are classified as overweight, 35.03% as having a normal weight, and 15.64% as underweight. This categorisation sheds light on the potential relationship between body weight and the prevalence of OA.

Occupational factors are considered in the next section, revealing varied percentages across different professions. Former occupations account for 18.7% of patients, with drivers and homemakers contributing 3.06% and 23.46%, respectively. Labor-related occupations make up 9.86%, while tailors and those involved in climbing represent 4.42% and 7.48%, respectively. The category labelled "Other" encompasses 32.99% of the patient population, emphasising the diversity of occupations within the study. Lastly, the table explores the prevalence of unilateral and bilateral OA. Specifically, 23.93% of patient’s exhibit left OA, 28.63% display right OA, and 47.44% manifest bilateral OA. This breakdown provides insights into the distribution of OA regarding lateral involvement

Table 3 Demographics of study population:

| Variable             | subgroups    | Patients | %     |
|----------------------|--------------|----------|-------|
| <b>Stages</b>        | Mild         | 83       | 28.23 |
|                      | Moderate     | 122      | 41.49 |
|                      | Severe       | 89       | 30.27 |
| <b>Body weight</b>   | Overweight   | 145      | 49.31 |
|                      | Normal       | 103      | 35.03 |
|                      | Underweight  | 46       | 15.64 |
| <b>Occupations</b>   | Former       | 55       | 18.7  |
|                      | Driver       | 9        | 3.06  |
|                      | Housewife    | 69       | 23.46 |
|                      | Housewife    | 69       | 23.46 |
|                      | Labour       | 29       | 9.86  |
|                      | Tailor       | 13       | 4.42  |
|                      | Climbing     | 22       | 7.48  |
|                      | Other        | 97       | 32.99 |
| <b>Unilateral OA</b> | Left OA      | 56       | 23.93 |
|                      | Right OA     | 67       | 28.63 |
|                      | Bilateral OA | 111      | 47.44 |

The results obtained from the ELISA (enzyme-linked immunoassay) test showed that the majority of the OA patients have normal testosterone levels, but at the two age groups, i.e., 50 to 60 and 60 to 70, have abnormal results of 0.251 and 1.89, respectively (Table 4). The findings showed that OA has no clear association with the testosterone level

of male OA patients. After analysis of all testosterone test results at different age groups through STATISTIX 10, analysis of variance (ANOVA) results shows that SS, MS and F values were 36.30, 7.26 and 9.3, respectively (Table 5)

[Citation: Khan, L., Shamas, S., Tabassum, S., Alam, M., Khan, B.T., Qureshi I.Z. (2024). Prevalence and effects of progressive osteoarthritis on sex steroids in male and female patients of district Buner, KPK Pakistan. *Biol. Clin. Sci. Res. J.*, 2024: 656. doi: <https://doi.org/10.54112/bcsrj.v2024i1.656>]

**Table 5. Analysis of variance (ANOVA) among different age groups of male patients and their testosterone levels.**

| Source | DF | SS      | MS      | F | P      |
|--------|----|---------|---------|---|--------|
| Age    | 5  | 36.301  | 7.2613  | 3 | 0.0008 |
| Error  | 12 | 9.3703  | 0.78086 |   |        |
| Total  | 17 | 45.6754 |         |   |        |

DF; Degree of Freedom, SS; Sum-of-Squares, MS; Mean squares, F; Variation between sample means, P; Probability.

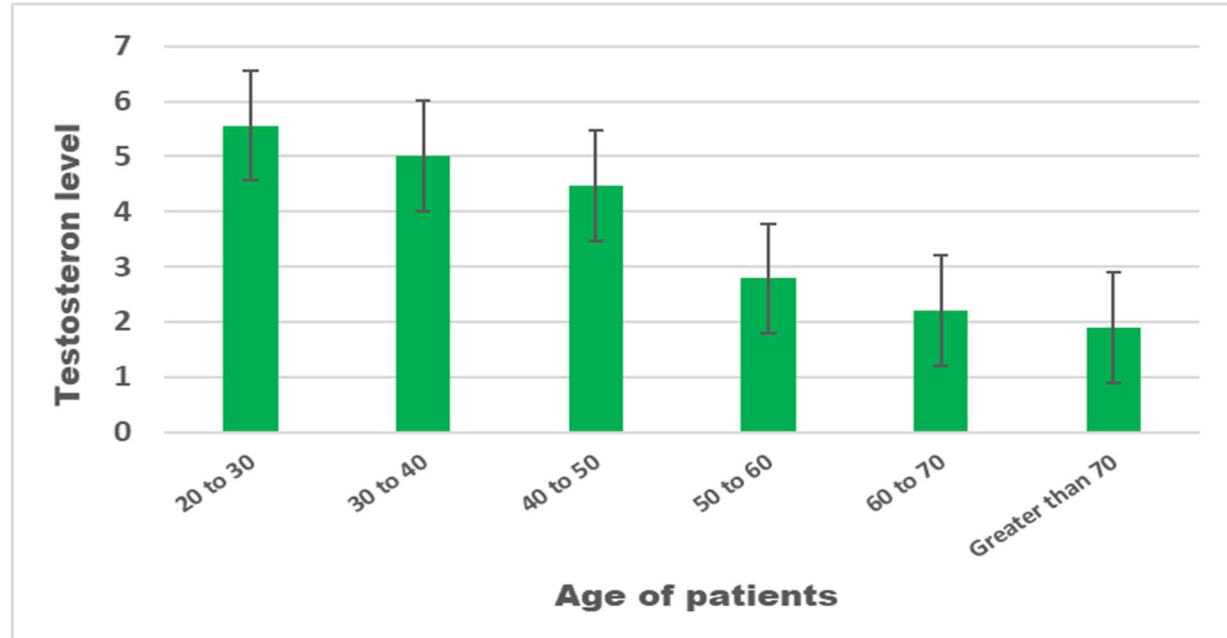


Figure 2 shows testosterone levels in different age groups.

**Discussion**

Al-Arfaj, 2002 conducted a study that women were more likely than men to have osteoarthritis and that this difference could be explained by women's greater rates of obesity, lack of mobility, and social problems, particularly in our region. (Al-Arfaj, 2002). Badshah *et al.*, 2021, also reported that compared to the male population, women are more likely than men to have OA. (Badshah *et al.*, 2021).

Our study shows that the prevalence of osteoarthritis is different based on geographical distribution. Of male patients, 30.82% belong to hilly areas, and 69.17% belong to plain areas. Regarding females, 78.88% belong to bare areas while 21.11% belong to hilly regions. Moghimi *et al.*, 2019 reported that the likelihood of developing knee OA is higher in people who live in highlands than in plain areas. This study revealed that persons who reside in highland regions experienced greater knee OA (Moghimi *et al.*, 2019).

In our study, we took six age groups, the smallest being from 20 to 30. and the largest age group is from 60 to 70. The prevalence of osteoarthritis showed different frequencies. In our results, we observed that OA is more prevalent in people between 50 and 60 in the case of males (27.06%) and in the case of females (29.81%). In our result, we also see that OA is less common in people whose age is between the 20 to 30 age group in the case of males (6.76%) and in the case of females (6.21%). The present data describe that the prevalence of OA in overweighted patients is 49.31%, normal is 35.03%, and underweight is 16.64%.

It indicates that the OA prevalence is higher in overweight patients as compared to normal and underweight. Zheng and Chen, in 2015, listed that obesity and overweight were strongly linked to greater knee OA. With every 5 kg/m<sup>2</sup> increase in BMI, the risk of knee OA rises by 35%. Our results presented that (18%) patients belong to Farmers, (23%) Hose wives, (10%) Labor, (7%) Climbers (4%) Tailor, (3%) Driver. Srilekha., & Kumar 2019; studied that a major area of attention for this investigation was the occupation of people with osteoarthritis. Twenty-three of the patients in this study were homemakers, demonstrating that they are the group most affected by knee pain (Srilekha., & Kumar, 2019).

Present data shows the stages of osteoarthritis patients: out of 294 patients, 42% are moderate OA, 28% are mild OA, and 30% are severe OA. We determined that the patients are more in the intermediate stage than the soft and severe stages. Srilekha and Kumar, 2019 Show the stages of knee osteoarthritis of patients: 43 patients have a soft knee stage, 54 patients have a moderate knee stage, and 47 patients have a severe knee stage. These indicate that the participants are likelier to be in the middle stage of osteoarthritis than in the mild or severe stages (Srilekha and Kumar, 2019).

Out of the total data, 23.93% are affected by the left knee, 28.63% are affected by the right knee, and 47.44% have both knees affected by OA. It shows that bilateral OA is more common than unilateral OA. In our study, we measure the testosterone levels of OA patients of 18 individuals. Out of this, we observed only two abnormal cases. The results were obtained from the ELISA (enzyme-linked

[Citation: Khan, L., Shamas, S., Tabassum, S., Alam, M., Khan, B.T., Qureshi I.Z. (2024). Prevalence and effects of progressive osteoarthritis on sex steroids in male and female patients of district Buner, KPK Pakistan. *Biol. Clin. Sci. Res. J.*, 2024: 656. doi: <https://doi.org/10.54112/bcsrj.v2024i1.656>]

immunoassay) test. This shows that the majority of the OA patients have normal testosterone levels, but the two age groups, i.e., 50 to 60 and 60 to 70, have abnormal results of 0.251 and 1.89, respectively. Qu et al., 2020 studied the evidence to date, showing that sex steroids play a significant role in the development of OA. However, there is a causal association between sex, calcium level and risk of OA (Qu et al., 2020). Sowers et al., 1996 also studied that Lower serum testosterone levels have been linked to a higher prevalence of hand OA but not knee OA in studies that connect testosterone levels to OA (Sowers et al., 1996).

## Conclusion

In this study, we observed that osteoarthritis is common in patients aged above 40 years of age, and women are more affected than men. The study indicated that overweight individuals are the risk of knee osteoarthritis (KOA) development. Other demographic studies show that agriculture, housewife, walking and prolonged sitting are also related to increased risk of KOA. In this study, we find that the ratio of prevalence of OA in males as compared to females is more in hilly areas. In the case of the plain regions females are more prevalent than males. We conclude that bilateral OA is more common than unilateral OA. According to our findings, OA does not have a clear relation with the testosterone level of male patients. Due to the small sample size, resources and unawareness of people, we found a small number of patients in whom we checked testosterone levels. Out of these patients, two showed low testosterone levels.

## Declarations

### Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

### Ethics approval and consent to participate

Approved by the department concerned.

### Consent for publication

Approved

### Funding

Not applicable

## Conflict of interest

The authors declared the absence of a conflict of interest.

## Author Contribution

### LUBNA KHAN

*Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, final approval of manuscript  
Data entry and Data analysis, drafting article.  
Data acquisition and analysis.*

### SHAZIA SHAMAS

*Coordination of collaborative efforts.  
Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, final approval of manuscript*

### SAADIA TABASSUM

*Coordination of collaborative efforts.  
Data acquisition and analysis.*

### MASOOD ALAM

*Data entry and Data analysis, drafting article.*

### BAKHT T. KHAN

*Coordination of collaborative efforts. Manuscript revisions, critical input.*

### IRFAN ZIA QURESHI (Professor)

*Coordination of collaborative efforts.  
Manuscript revisions, critical input.*

## References

- Al-Arfaj AS. (2002) Radiographic osteoarthritis and obesity. Saudi Med J 2002; 23: 938-42.
- Badshah, Y., Shabbir, M., Hayat, H., Fatima, Z., Burki, A., & Khan, S. (2021). Genetic markers of osteoarthritis: early diagnosis in susceptible Pakistani population. Journal of Orthopaedic Surgery and Research, 16(1), 1-8.
- Bähler, C., Huber, C. A., Brüngger, B., & Reich, O. (2015). Multimorbidity, health care utilisation and costs in an elderly community-dwelling population: a claims data based observational study. BMC Health Services Research, 15(1), 1-12.
- Bijlsma, J. W., Berenbaum, F., & Lafeber, F. P. (2011). Osteoarthritis: an update with relevance for clinical practice. The Lancet, 377(9783), 2115-2126.
- Çayan, S., Uğuz, M., Saylam, B., & Akbay, E. (2020). Effect of serum total testosterone and its relationship with other laboratory parameters on the prognosis of coronavirus disease 2019 (COVID-19) in SARS-CoV-2 infected male patients: a cohort study. The Aging Male, 23(5), 1493-1503.
- Cuesta, S. A., & Meneses, L. (2021). The role of organic small molecules in pain management. Molecules, 26(13), 4029.
- Daigle M E, Weinstein AM, Katz JN, Losina E. (2012) The cost-effectiveness of total joint arthroplasty: a systematic review of published literature. Best Pract Res Clin Rheumatol. ;26(5):649-658.
- Diver, M. J. (2006). Analytical and physiological factors affecting the interpretation of serum testosterone concentration in men. Annals of clinical biochemistry, 43(1), 3-12.
- Dong, Q., Hawker, F., McWilliam, D., Bangah, M., Burger, H., & Handelsman, D. J. (1992). Circulating immunoreactive inhibin and testosterone
- Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD (2012) Age trends in serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male ageing study. J Clin Endocrinol Metab ;87:589-98.
- Hame SL, Alexander RA. Knee osteoarthritis in women. (2013) Curr Rev Musculoskelet Med 6:182-7
- Hanna F, Ebeling PR, Wang Y, et al.(2005) Factors influencing longitudinal change in knee cartilage volume measured from magnetic resonance imaging in healthy men. Ann Rheum Dis.;64(7):1038-1042.
- Hisasue, S.-I.(2015) Contemporary perspective and management of testosterone deficiency: Modifiable factors and variable management. Int. J. Urol. 2015, 22, 1084-1095.
- Hussain SM, Cicuttini FM, Giles GG, et al. (2016) Relationship between circulating sex steroid hormone concentrations and incidence of total knee and hip arthroplasty due to osteoarthritis in men. Osteoarthritis Cartilage. ;24(8):1408-1412.
- Jhun, H. J., Sung, N. J., & Kim, S. Y. (2013). Knee pain and its severity in elderly Koreans: prevalence, risk factors and impact on quality of life. Journal of Korean Medical Science, 28(12), 1807-1813.
- Jin X, Wang BH, Wang X, et al.(2017) Associations between endogenous sex hormones and MRI structural changes in patients with symptomatic knee osteoarthritis. Osteoarthritis Cartilage. ;25(7):1100-1106.

- Jordan, K. M., Sawyer, S., Coakley, P., Smith, H. E., Cooper, C., & Arden, N. K. (2004). The use of conventional and complementary treatments for knee osteoarthritis in the community. *Rheumatology*, 43(3), 381-384.
- Koelling S, Miosge N. (2010) Sex differences in chondrogenic progenitor cells in late stages of osteoarthritis. *Arthritis Rheum.*;62(4):1077-1087.
- Li, C.; Zheng, Z. (2021) Males and Females Have Distinct Molecular Events in the Articular Cartilage during Knee Osteoarthritis. *Int. J. Mol. Sci.*, 22, 7876.
- Nemes, S., Gordon, M., Rogmark, C., & Rolfson, O. (2014). Projections of total hip replacement in Sweden from 2013 to 2030. *Acta orthopaedica*, 85(3), 238-243.
- O'Connor MI (2006) Osteoarthritis of the hip and knee: sex and gender differences. *Orthop Clin North Am*; 37:559-68.
- Peat G, Mc Carney R & Croft P.(2001) Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Annals of the Rheumatic Diseases*; 60(2): 91-97.
- Qu Z, Huang J, Yang F, Hong J, Wang W, Yan S. (2020) Sex Hormone-Binding Globulin and Arthritis: A Mendelian Randomization Study. *Arthritis Res Ther* 22:118. Doi: 10.1186/s13075-020-02202-2.
- Ravin T. (2010) The use of testosterone and growth hormone for prolotherapy. *J Prolotherapy*.;2(4):495-503.
- Sowers MF, Hochberg M, Crabbe JP, Muhich A, Crutchfield M, Updike S. (1996) Association of bone mineral density and sex hormone levels with osteoarthritis of the hand and knee in premenopausal women. *Am J Epidemiol*;143:38-47.
- Srilekha, C., & Kumar, C. P. (2019). The study on prevalence and management of osteoarthritis in South India. *International Journal of Orthopaedics Sciences*, 5(4), 112-7.
- Tschon, M.; Contartese, D.; Pagani, S.; Borsari, V.; Fini, M. (2021) Gender and Sex Are Key Determinants in Osteoarthritis Not Only Confounding Variables. A Systematic Review of Clinical Data. *J. Clin. Med.*, 10, 3178.
- Ushiyama T, Ueyama H, Inoue K, Ohkubo I, Hukuda S. (1999) Expression of genes for estrogen receptors alpha and beta in human articular chondrocytes. *Osteoarthritis Cartilage*; 7:560-6.
- Vancampfort, D., Stubbs, B., Smith, L., Gardner, B., Herring, M. P., Firth, J., & Koyanagi, A. (2019). Correlates of sedentary behaviour among community-dwelling adults with anxiety in six low-and middle-income countries. *Psychiatry Research*, 273, 501-508.
- Vingren, J.; Kraemer, W.J.; Ratamess, N.A.; Anderson, J.M.; Volek, J.S.; Maresh, C.M. Testosterone physiology in resistance exercise and Walter MJM, Kuijper TM, Hazes JMW, Weel AE, Luime JJ.(2018) Fatigue in early, intensively treated and tight-controlled rheumatoid arthritis patients is frequent and persistent: a prospective study. *Rheumatol Int.* ;38(9):1643-1650.
- Walter, M. J., Kuijper, T. M., Hazes, J. M. W., Weel, A. E., & Luime, J. J. (2018). Fatigue in early, intensively treated and tight-controlled rheumatoid arthritis patients are frequent: a prospective study. *Rheumatology International*, 38(9), 1643-1650.
- WHO World Health Organization: The WHO (WHO,2020) register.
- Wijesinghe SN, Lindsay MA, Jones SW.(2021) Oligonucleotide Therapies in the Treatment of Arthritis: A narrative Review. *Biomed*; 9(8):902. doi: 10.3390/biomedicines9080902.
- WOOLF, P. D., HAMILL, R. W., McDONALD, J. V., LEE, L. A., & KELLY, M. (1985). Transient hypogonadotropic hypogonadism is caused by critical illness. *The Journal of Clinical Endocrinology & Metabolism*, 60(3), 444-450.
- Yan, Y.S.; Qu, Z.; Yu, D.-Q.; Wang, W.; Yan, S.; Huang, H.-F.(2021) Sex Steroids and Osteoarthritis: A Mendelian Randomization Study. *Front. Endocrinol.*, 12, 683226.
- Yapar, N., Akan, M., Avkan-Oguz, V., Ergon, C. M., Hancer, M., & Doluca, M. (2019). Risk factors, incidence and outcome of candidemia in a Turkish intensive care unit: a five-year retrospective cohort study. *Anaesthesia, Pain & Intensive Care*, 265-271.
- Zamri, N. A. A., Harith, S., Yusoff, N. A. M., Hassan, N. M., & Qian Ong, Y. (2019). Prevalence, risk factors and primary prevention of osteoarthritis in Asia: A scoping review. *Elderly Health Journal*, 5(1), 19-31



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. © The Author(s) 2024