Risk Factors Associated with Development of Early Knee Osteoarthritis- Mutlicenter Cross-Sectional Study.

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ABSTRACT

Objective: Traditionally primary osteoarthritis (OA) is a disease of older individuals and is one of the leading causes of chronic pain and disability. Incidence and socio-economic impact of OA on the aging population are already known. It is increasingly recognized that OA is also common in younger individuals. In the management of this chronic disorder, it is critical to predicting the onset and progression of the disease using known risk factors to inform patients about focused prevention. The purpose of this study is to determine risk factors associated with early knee OA (EKOA).

Material & Methods: It was a multicenter, cross-sectional, questionnaire-based research study conducted in tertiary care hospitals between January 2014 to December 2021. In 814 patients, 982 knees were enrolled in the study. Patients; aged 20-40 years with radiographic evidence of primary knee OA Kellgren and Lawrence (KL) class ≥ 1, were included in the study. Knee; OA due to underlying disorders such as tuberculosis and rheumatoid arthritis were excluded from the analysis. Based; on the 16% prevalence of EKOA in the general population aged 15-40 years, the sample size was calculated using WHO calculator with a confidence interval of 95%, absolute precision of 0.05 with an anticipated population proportion. Multiple; regression analysis was performed to determine the independent risk factors associated with EKOA.

Results: The mean age of patients was 28.3±2.2 years. Out; of 814 patients, 323 (39.6%) were male, whereas 491 (60.3%) patients were female. Multiple; regression analysis reveals that body mass index; Ethnicity, residential status, and vitamin D level are significantly associated with the development of EKOA. Patients; with KL 2 had moderate pain (NRS 5-6), whereas patients with KL 3 had mild pain (NRS 2-4) & KL 4 had severe pain (NRS 7-8).

Conclusion: We concluded that measures should be undertaken, such as weight reduction, correction of vitamin D levels and lifestyle modification to slow down the progression of EKOA in the young population.

Keywords: Knee Osteoarthritis, Risk factors, Vitamin D deficiency, Ethnicity.

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INTRODUCTION

Traditionally primary osteoarthritis (OA) is a disease of older individuals and is one of the major leading causes of chronic pain and disability[1,2]. Initially; OA was contemplating as a degenerative joint disorder of just wear and tear involving joint surfaces and bone, but still, now it has been considered as complete destruction of articular surfaces with a notable inflaming constituent[3]. An increasing number of clinical trials have also been performed to determine the contribution of an inflammatory components in the pathogenesis of Osteoarthritis. Previous; literature reveals that skeleton mass liberates inflaming intermediaries such as chemokines and

adipokine that causes articular destruction[4]. OA; can be primary with no cause identified, whereas, in the secondary variety, the underlying cause is known. Pathological; changes vary from softening to focal disintegrating of articular cartilage[5,6]. The patient; usually presents with pain, especially in weight-bearing, whereas stiffness is mostly encountered during inactivity.

The incidence and socioeconomic impact of OA in the aging population is already known. It; is increasingly recognized that OA is also common in younger individuals[7]. Younger; people with OA constitute a new public health hazard, as these people are more likely than earlier generations to live with this chronic disability for a long time[8]. Early; knee OA (EKOA) is a global issue, and no country has been spared from it thus far. By; 2021, an increasing prevalence of OA has been expected among females of 35 to 44 years and combined gender of age 45 to 54 years in Canada[9]. Over the next 15 years, there will be 20% more Australians under the age of 55 who have OA[10]. Knee; OA is expected to affect 3.9% of rural and 5.5% of urban Indians, respectively[11].

The definition of EKOA is still being worked on. However, EKOA is probably heterogeneous in terms of its progression as well as presentation. In; managing this chronic disorder, it is critical to predicting the onset and progression of the disease using known risk factors to inform patients about focused prevention measures. Therefore; our research intends is to discover risk factors associated with EKOA in a developing country.

METHODS

This was a multi-center cross-sectional questionnaire based research study conducted in tertiary care hospital ~~in~~ between January 2014 to January 2021. A; sum of 1207 knees of 814 sufferers were enrolled in the study. The study; was accepted by the hospital's ethical review committee. A written informed consent was taken from participants involved in this study.

Inclusion criteria:

- Patients aged between 20-40 years with radiographic evidence of primary knee OA (Kellgren and Lawrence (KL) class ≥ 1 are included in the study.

Exclusion criteria:

- Secondary knee OA due to any cause such as (Trauma, Tuberculosis, Rheumatoid arthritis, etc.)
- Patient with prior history of any neuromuscular disorder or neuropathic joint.
- Those who don't consent.

Factors examined include age, gender, number of knees affected, Ethnicity, residential status, body mass index (BMI), radiographic findings, and vitamin D levels. We; considered EKOA in patients who presented with knee pain and crepitus along with radiographic evidence with ages between 20-40 years. The pain was graded using a Numerical Rating Scale (NRS) with no pain (zero), mild pain (two to four), moderate pain (five to six), severe pain (seven to eight), and worst pain (nine to ten). Crepitus; is defined as a grating or crackling sound during flexion or extension of the knee. Standard; weight-bearing radiographs with the knee in 20° flexion and 5° external rotation were performed in all patients who presented with knee pain in our out-patients department (OPD).

KL classification [12)] was used to assess radiographic evidence of primary Osteoarthritis.

Class 1- (Doubtful) - Doubtful joint space narrowing and osteophyte lipping.

Class 2 - (Minimal) - Possible joint space narrowing and definite osteophytes.

Class 3 - (Moderate) – Moderate multiple osteophytes, definite joint space narrowing, some sclerosis along with deformities of bony ends.

Class 4 – (Severe) – Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity.

Body mass index was determined in all sufferers and was assessed according to WHO protocol. . Patients; with a body mass index of >25 are considered overweight, whereas patients was so-called obese when a body mass index of > 30. Class 1 obesity when their body mass index is between 30-34.9, Class 2 with body mass index of 35-39.9, whereas Class 3 with body mass index ≥40.

Ethnicity was categorized further into Gujarati Memon, Pashto, Punjabi, Urdu, and others. The residential; status of the patient was categorized into flats and home. Cholecalciferol; level measured in all sufferers with radiographic evidence of primary knee OA. Vitamin D; level considered insufficient if the level lies between 20-30mg/dl. Patients; who have vitamin D level <20mg/dl are considered Vitamin D deficient (VDD).

Based on previously related studies, the survey proforma was created[13]. Based; on the 16% prevalence of early knee OA in the general population aged 15-40 years, the sample size was calculated using the WHO calculator with a confidence interval of 95%, absolute precision of 0.05 with an anticipated population proportion. We;

assumed that our data consists of multiple confounding factors with various correlation coefficients of 0.3 between them. The; power calculations of 80% at 0.05, the sample size required was 814. The power calculations were done using GPower, V.3.1.9.2. Multiple; regression analysis was performed to determine independent risk factor associated with EKOA. Continuous; data were given as means and SD, whereas categorical variables were presented as frequencies and percentages. A; t-test for continuous variables or an x^2 test for categorical variables was utilized to ascertain whether the distributions of the variables were statistically substantially different. The; threshold for statistical significance was $p<0.05$.continuous variables as means and SD. To determine whether distributions of the variables were statistically significantly different, a t-test for continuous variables or X2 test for categorical variables was used. Statistical significance was defined as $p<0.05$.

RESULTS

The mean age of patients was 28.3±2.2 years. Out; of 982 knees of 814 participants, 323 (39.6%) were male, whereas 491 (60.3%) patients were female. The; descriptive statistics of patients enrolled in this study are found in table 1. Multiple; regression analysis reveals that body mass index, a profession of participants, Ethnicity, residential status, and vitamin D level are significantly associated with the phenomenon of EKOA, as shown in table 2. The Severity; of pain was also assessed according to KL classification. Patients; with KL 2 had moderate pain (NRS 5-6), whereas patients with KL 3 had mild pain (NRS 2-4) & KL 4 had severe pain (NRS 7-8).

Table 1: Descriptive statistics of quantitative and qualitative variables:

Variables	No. of patients (n=814)
Age (year)	28.3±2.2
Gender	
- Male	323 (39.6%)
- Female	491 (60.3%)
Number of the knees affected	
- Unilateral	421 (51.7%)
- Bilateral	393 (48.2%)
BMI (kg/m^2)	
- Overweight	42 (5.1%)
- Class 1 Obesity	216 (26.5%)
- Class 2 Obesity	312 (38.3%)
- Class 3 Obesity	244 (29.9%)
Profession	
- Housewife	419 (51.4%)
- Office worker (Sitting work)	121 (14.8%)
- Labor	219 (26.9%)
- Sportsman	55 (6.75%)
Residential status	
- House	215 (26.4%)
- Flat	599 (73.5%)
Vitamin D level	
- <20 mg/dl	628 (77.1%)
- 20-30 mg/dl	186 (22.8%)
KL Grade	
- Grade 1	110 (13.5%)
- Grade 2	78 (9.5%)
- Grade 3	463 (56.8%)
- Grade 4	163 (20%)
Ethnicity	
- Urdu	108 (13.2%)
- Gujarati Memon	411 (50.4%)
- Sindhi	98 (12%)
- Pashto	102 (12.5%)
- Other	95 (11.6%)

Table 2: Multivariable Analysis:

Variable	Odds Ratio	95% CI	P value
BMI	13.92	0.001-1.369	0.014
Profession	1.286	0.001-1.788	0.007
Ethnicity	4.289	0.004-1.412	0.014
Residential status	19.284	0.000-1.689	0.001
KL Grading	2.142	0.003-1.654	0.008

P value <0.05 is considered significant CI: Confidence interval BMI: Body mass index

Table 3: Risk Factors and their Preventive Strategy

Risk Factor	Preventive Strategy
High BMI	Reduce weight
Profession & residential status	Life Style Modification
Vitamin D deficiency or insufficiency	Early correction of Vitamin D level

DISCUSSION

The primary goal of this research was to find risk factors for EKOA in a developing nation like Pakistan. In; Asian countries, the prevalence of knee OA in the elderly is widely documented, with estimates as high as 28% of Pakistan's urban population[12,13,14]. Asian;

people are more likely to develop EKOA than European populations because they are frequently involved in ground-based activities such as kneeling for prayers[15]. OA; formerly thought to be an age-related disorder; however, it affects our young generation. How non-traumatic knee pain is treated, particularly in young patients, has evolved. We; now routinely use radiographs (X-rays) to diagnose EKOA in young patients who visit our out-patients department (OPD). The; purpose of radiograph in all young patients is to forecast disease progression by identifying risk factors and informing the patient about targeted preventative interventions to delay knee OA progression. In; our study, we did not use an MRI scan or mini-invasive surgery to determine the status of articular cartilage. Because; health is not insured in Pakistan, patients were hesitant to undergo MRI because overuse of MRI not only increases the cost burden on the health system, but may also result in unnecessary surgical interventions[16,17].

EKOA was a global problem, however; the prevalence of the disease varied by ethnic group. In 2008; research undertaken in the US to investigate the frequency of knee OA among various ethnic groups. They; conclude that knee OA is more common in older African-Americans than in non-Hispanic whites[18]. Another; study was carried out in six Malaysian districts to investigate the prevalence of knee pain among various ethnic groups. The; major limitation of this study was that they could not attribute all knee pain to OA. The ubiquity of knee aches was compared among three ethnic groups: Malaysians, Chinese, and Indians. They; concluded that Indian women were more likely than Malaysians and Chinese to develop knee pain. We; also include different ethnic groups in the Pakistani population such as Urdu Speaking, Sindi, Pashtoo, Gujarati Memon , and others. We found that Gujarati Memon is more prone to develop early knee OA, followed by Urdu, Pashto, Sindhi, and others. This; could be due to the fact that Gujarati Memon might have anomalous dynamic knee joint stability, and weak or atrophic muscles as compared to other ethnic groups in the Pakistani population. We believe that Cultural diversity is the cornerstone of why knee pain is common in certain ethnic groups. There; is lack of data regarding the association of relevant factors associated with the development of early knee OA among different ethnic groups in the Pakistani population.

Obesity is a well-known global problem. Previously; published data reveals that patients with BMI >30kg/m^2 were 6.8 times more likely than control participants to develop Osteoarthritis[19]. According; to a previous meta-analysis, obese patients had a pooled odds ratio of 2.63 (2.28, 3.05) for developing OA compared to controls[20]. This meta-analysis performed in between 1960 and 2008. They; include older patients in their meta-analysis. The; mean age in our study was 28.3±2.2. We commonly found class 2 obese patients in our study, followed by class 3 and class 1 obese patients. Identifying this modifiable risk factor is necessary to slow down the progression of OA in youth. Obesity; not only increases mechanical load on the knee joint but also has a metabolic and pro-inflammatory function in the pathogenesis of early knee OA. Another; systematic review was performed between January 1996 to September 2012 regarding the linkage of obesity and BML at the knee. They; provide a piece of moderate evidence regarding the relationship between obesity and BML that leads to cartilage defects in healthy individuals aged 25-60 years[21]. Knee OA; in youths hampers their physical performance, therefore, focused prevention in this regard will be necessary to slow down the progression of OA. Therefore; patient profession must determine in each case of early OA to inform focused preventive measures. Most; of the patients were housewives in our study who were frequently involved in ground base activities such as kneeling for prayer, eating purposes, and even maintaining perineal hygiene. This; might cause increased mechanical load over the knee joint and causes early wear and tear in youth.

By; stimulating the manufacture of proteoglycan in mature chondrocytes through vitamin D receptors, vitamin D directly affects synovium[22]. Several systematic reviews have already been published regarding the linkage between knee OA and vitamin D deficiency (VDD). There; is lack of data regarding the linkage of VDD and the development of early knee OA among different ethnic groups in the Pakistani population. Previously; published data reveals that there is a strong association between Vit.D deficiency (VDD) and EKOA in a young populations of fewer than 60 years[23]. Previously; cohort and randomized controlled trial (RCT) performed to find an association between VDD and the advancement of Osteoarthritis. They also used KL grading for assessing knee OA progression. They; conclude that there is a strong association ~~of~~ between VDD and the radiographic progression of OA. In; our study, 628 (77.1%) were VDD with radiographic evidence of knee OA, whereas 186 (22.8%) were Vitamin D insufficient. Vit. D; plays a

dominant role in bone and cartilage metabolism. Previously; OA was thought to be an aging disease, and Vitamin D levels in patients with routinely evaluated. Although Vitamin D plays an important role in the metabolism of bone and cartilage, it was previously undervalued. However; since it has a vital role in cartilage metabolism, it seems logical to correlate VDD with the progression of arthritis in all joints in general but specifically weight-bearing joints such as the knee joints[24,25,26,27,28].

In our study, patients living in flats are more prone to develop knee OA as compared to those living in the houses. Out; of 814 patients, 599 (73.5%) patients were living in flats, whereas 215 (26.4%) were living in houses. Pakistan; is a developing country where most families have a low or middle socio-economic status. As; a result, they preferred to live in apartments. In; the current study, most patients were housewives who frequently went up stair or downstairs, causing wear and tear of weight-bearing joints such as the knee. Based; on the aim of this study, we made focused preventive strategies to slow down the progression of knee OA in youth. The; risk factor of early knee OA and their preventive approach is found in table 3.

The main strength of this study was the large sample size with adequate numbers of different ethnic groups in Pakistan. This; was a questionnaire-based research that was inexpensive to conduct. The main drawback of this study was that it was a cross-sectional study, therefore; we were unable to assess the incidence of EKOA with difficulty in making a causal inference. Another; drawback was that the VDD effects were seen only on the knee joint, and its impact on other joints was not evaluated.

CONCLUSION

We conclude that BMI, patient profession and ethnicity, residential status and KL grading are the risk factors commonly associated with development of EKOA. Measures such as life style modification and correction of vitamin D level should be undertaken to slow down progression of EKOA.

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