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FAMILY HISTORY AND CONSANGUINE MARRIAGES A GENETIC RISK PREDICTOR FOR KNEE OSTEOARTHRITIS: A CASE-CONTROL STUDY

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Abstract:
Objective: To evaluate the association and risk estimation between Knee Osteoarthritis (KOA) with family history and consanguineous marriages among parents of study population.
Methodology: This hospital-based case-control study was conducted at, Tertiary Care Hospital in Sindh, Pakistan from December 2019 to December 2022, to evaluate the risk of KOA, a very common musculoskeletal disease, and the association between study participants' family history and parental consanguinity outcome. Using non-probability convenience sampling, 949 study participants, 190 cases and 759 controls were selected. IBM-SPSS version 23.0 was used to analyze the data. Frequencies and percentages were calculated for categorical data. The Pearson Chi Square test was used to investigate the association. Binary Logistic Regression Analysis was performed using a Univariate and Multivariate Model for the variables associated with KOA, as parents' blood relation and family history.
Results: In the study 949 people were enlisted to participate. A positive family history of OA was found to be associated with knee OA (68.9%), with first-degree relatives accounting for 40% of cases. The results showed relatively high consanguinity rate of about 77.9% and 52.6% of these marriages are of the first cousin and closer marriage type. The Multivariate Logistic Regression Model of KOA

with the third degree parental consanguity pattern and history of OA among family members indicated a significant association (p=<0.05).
Conclusion: The study established a baseline and highlighted the significance of parental consanguity and family history as risk factors for KOA and illustrated the importance towards implementation of preventive measures.

Keyword: Knee Osteoarthritis, family history, consanguineous marriages

INTRODUCTION:

Knee Osteoarthritis (KOA) is a highly prevalent musculoskeletal condition causing cartilage and tissues to deteriorate and degenerate, resulting in significant pain, stiffness, restricted movement, disability and decline in the quality of life. Depending on the risk predictors, OA could be primary or secondary, but in any case there is no known cure. (1) (2)

According to WHO estimates, 18.0% and 9.6% of women and men over 60, are estimated to be affected by OA. It is expected that 100 million individuals globally suffer from OA, with knee OA (KOA) having the highest incidence. (3) Whereas among Asian population it ranges between 13.1% to 71.1. (4)

The chronic non-communicable diseases have several underlying causes that result from the interaction of environmental factors, behavioral patterns and genetic susceptibility. (5) Among them OA is accepted to be a heritable condition, however, the underlying genetic cause of the condition is not well understood. (1)

Although epidemiological and analytical methods to investigate the impact of genetic determinants of chronic diseases have made significant strides, but still DNA-based testing has significant limitations. (6)

And therefore based on epidemiological research, family history is considered a major and independent risk factor for KOA. Family history data has an advantage over genetic profiling in that it captures the intricate interactions between genetic, environmental, and behavioral factors, in addition to capturing the effects of multiple genetic factors, Consequently, genetic profiling may not be a very good indicator of disease risk compared to family history data. (5)

Family history is an important determinant for assessing health. When paired with a patient's personal medical history, family history has been shown to help guide risk assessment of underlying genetic predispositions. (7)

Consanguineous marriage or cousin marriage is a union between two blood relatives. It is estimated that globally 20% of people are in a relationship with biological relatives However, the frequency varies depending on the culture, religion, and ethnicity of the population. (8)(9)

First cousins' marriages make up 10.4% of consanguineous couples worldwide, making them the most common case. One of the main areas of study in medical genetics is how inbreeding and consanguinity affect human health. It has been discovered that consanguineous couples' children have certain mutation disorders. According to these analyses, compared to children in the general population, children of first consanguineous cousins are more likely to experience genetic disorders and congenital abnormalities. (9) The likelihood of congenital defects and autosomal recessive disorders is higher in children born to consanguineous parents. (10)

The literature has linked consanguineous marriage (CM) to a host of health issues, and children of CMs are associated with a higher risk of non-communicable diseases (NCDs). Studies indicate that CM may be associated with various illnesses, such as hemoglobinopathies, congenital glaucoma, lung, colorectal, breast, and prostate cancers, congenital heart diseases, cardiovascular disease (CVD), obesity, diabetes and blood disorders like anemia and thalassemia and many others. (8)(10)

Consanguinity rates are generally low in Western countries, with the exception of local immigrant populations (e.g., the Pakistani Muslim community in the Northwest of England). The highest percentages are found in Pakistan (up to 57%), Saudi Arabia (56%), Qatar (54%) and some urban areas in South India. (11)

Pakistan, a multicultural nation, has consistently demonstrated the highest consanguinity prevalence. Consanguineous marriages have been linked to a number of sociocultural and health-related consequences. Researchers and physicians in the medical field have continued to study health effects and disease burden due to consanguineous marriage and family history. (12) Burden of chronic non-communicable diseases have increased in developing countries, posing a public health concern in recent years.

The relationship between knee osteoarthritis and genetic heritability has been examined in a number of research studies. In Pakistan, cousin marriages account for the majority of marriages and are the primary means through which disorders are inherited by the progeny. Unfortunately, most of the data is from studies conducted abroad, which may not be appropriate, because of differences in genetic backgrounds. There is a lack of the baseline data required for our population. This study was aimed to look into the association of consanguineous marriage and family history as risk factors for knee osteoarthritis.

OBJECTIVES:

To assess the association between Knee Osteoarthritis with family history and consanguineous marriages among parents of study population.

MATERIAL AND METHOD:

This Case-Control study was conducted at a Tertiary Care Hospital in Sindh, Pakistan after getting approval of the study protocol from the Ethical Review Committee of the University (Letter No. LUMHS/REC/713 Dated 29/08/2018) from December 2019 to December 2022.

Epi Info version 3.0 was used for the calculation of sample size, where the prevalence for age below 50 years was considered 78.9% (13) with Odds Ratio of 2.0, Confidence Interval of 95% and 80% Power. For each case ratio of four control was selected. With these assumptions, total participated sample size was 949, with 190 cases and 759 controls.

The study was carried out in the Department of Orthopedics Surgery & Traumatology Out-Patient clinic at Liaquat University Hospital, Hyderabad. Based on clinical criteria of American College of Rheumatology (14) and radiological (15) criteria, an expert orthopedic surgeon diagnosed and verified the KOA cases.

The inclusion criteria for case was both genders of 30 years and above with confirm KOA, whereas the subjects having any congenital anomaly of lower limb, history of knee joint injury, rheumatoid arthritis, ankylosing spondylitis or any other type of osteoarthritis were excluded from the study. However, the controls' age and gender requirements remained the same, along with the criteria of "No" complaint of knee pain in past were selected.

Written informed consent from participants was obtained after briefing them nature and purpose of study. A pre-designed questionnaire was used to get information from the eligible participants. A detailed history about family members was obtained in relation to joint disease/ knee osteoarthritis of family members and blood relation of parents. To determine family history and consanguinity (parent marriages) first, second, third and fourth degree relatives were considered. First degree relatives were classified as immediate blood relatives as parents, siblings and children. Second degree were grand-parents, grand-children, aunts, uncles, nieces and nephews. Third degree were defined as first cousins, great uncles or aunts, great grand-parents, and great grand-children whereas fourth degree are mainly second cousins.

STATISTICAL ANALYSIS:

Results were compiled in IBM SPSS version 23.0 after editing, cleaning, and verifying the integrity of 949 participant's data in Microsoft Excel regarding family history and parental consanguinity. For qualitative variables, counts with percentages were given for the cases and controls. Pearson Chi Square test was applied to examine the relationship between KOA with family history and parental consanguinity. Binary Logistic Regression Analysis was performed for each studied variable of family history and parents' blood relation with knee osteoarthritis, using a Univariate and Multivariate

Model (Enter Method). Age and gender were fitted in the model to generate adjusted odds ratio and 95% confidence interval. Statistical significance was defined as P-values less than 0.05.

RESULTS:

In this hospital-based case-control study, a total of 949 subjects were assessed, with 190 cases of primary knee osteoarthritis who visited the Out-Patient Department (OPD) of Medicine and Orthopaedics and 759 controls without knee pain

Table 1: Association of KOA with Parental Consanguinity and Family History information

Variables		**Controls (n=759)**	**Cases (n=190)**	**P-value**
		n (%)	**n (%)**	
Are your parents blood relatives	No	278(36.6)	42(22.1)	0.00*
	Yes	481(63.4)	148(77.9)	
Are your parents blood relatives	No	278(36.6)	42(22.1)	0.00*
	Third Degree	263(34.7)	100(52.6)	
	Forth Degree	218(28.7)	48(25.3)	
Any family member with osteoarthritis	No	415(54.7)	59(31.1)	0.00*
	Yes	344(45.3)	131(68.9)	
Any family member with osteoarthritis	No	415(54.7)	59(31.1)	0.00*
	First Degree	117(15.4)	76(40)	
	Second Degree	138(18.2)	51(26.8)	
	Third Degree	89(11.7)	4(2.1)	
*p<0.05 was considered statistically significant using Pearson Chi Square test				

Table 1 compiles the descriptive statistics related to the association between KOA with the parental consanguinity and family history data in this study. The analysis of the blood relationships between the parents of study participants shows a predominance (77.9%) of relation in between them, with third degree (first cousin) relationships accounting for the majority among cases (52.6%). On the other hand, 68.9% of cases indicated that the condition affects family members, and 40% of first-degree relatives of cases have osteoarthritis (OA).

Table 2: Risk Estimation of KOA with Parental Consanguinity and Family History information

Variables		***Univariate***	***Multivariate***
		Odds Ratio (95% C.I)	Odds Ratio† (95% C.I)
Are your parents blood relatives	Third Degree	2.51*(1.69-3.74)	2.60* (1.66-4.08)
	Forth Degree	1.45(0.92-2.28)	1.24(0.74-2.07)
	No	Reference	Reference
Any family member with osteoarthritis	First Degree	4.56*(3.07-6.79)	3.39* (2.19-5.26)
	Second Degree	2.59*(1.70-3.96)	2.29* (1.41-3.70)
	Third Degree	0.31*(0.11-0.89)	0.25* (0.08-0.72)
	No	Reference	Reference
**Odds ratio considered significant with p<0.05* *† Adjusted with Age and Gender.*			

Table 2 depicts the Uni-variate and Multi-variate analysis of variables with KOA.
The results of univariate and multivariate analysis show significant increase in risk with presence of third degree (first cousin) relation among parents of study subjects with (OR=2.51, CI: 1.69-3.74) and (OR= 2.60, CI: 1.66-4.08), respectively.

When using univariate and multivariate models to analyze the risk estimation with presence of family history of osteoarthritis, significant associations are found between first and second degree relatives, while negative association is seen with third degree relatives. With p<0.05, all of these results were determined to be statistically significant.

DISCUSSION:

Knee osteoarthritis (KOA) is a type of degenerative arthritis related to the breakdown of the underlying bone and cartilage. The extracellular matrix and cells exhibit morphological, biochemical, molecular, and biomedical alterations in OA due to a combination of genetic and environmental factors. An increased risk of developing OA disease is linked to 50% of genetic factors. Variants of a gene linked to cartilage degradation have been found through heritable studies in OA. (16)

According to medical genetics specialists, families are "the most traditional diagnostic tool in clinical genetics". According to Robin Bennett, the family history is the "gateway to recognizing inherited disorders in a patient,". And hence family history is defined in genetics as an explanation of the genetic relationships. (17)

For population-based, pre-symptomatic disease detection of chronic disorders, DNA markers do not currently seem to be useful, and molecular testing is currently only advised when there is a family history of the illness. Therefore, family history analysis appears to be the most effective method for the initial identification and stratification of genetic risk for common, chronic illnesses. (18)

Numerous studies have provided evidence to support the theory that a person's risk of developing osteoarthritis is increased when one or more family members have the condition. Bushra et al. (2020) found a strong correlation between the disease and family history in Karachi, Pakistan (OR 3.61; 95% CI 2.69-4.85) (3)(2) This is further supported by an Indian study (2020) that found family history to be a crucial inherited factor for determining KOA. (19)

In support of the evidence, it was observed in a community-based cross-sectional study that reported positive family history of knee joint pain (17.6%.) among diagnosed patients of knee osteoarthritis. (20) It has long been known that family history is essential for identifying underlying genetic causes. With the help of this information, overlapping health risk indicators associated with genetic and family history can be defined. (7)

Numerous risk factors contribute to the debilitating and highly common KOA disease. It has been established that this disease has a genetic component, but the degree of genetic risk remains unknown. It has been discovered that heritability varies greatly between monozygotic and dizygotic twin studies, ranging from 6% to 84%. (21) OA is a polygenic disease, is brought on by the inheritance of several risk alleles. The odds ratios (ORs) for OA risk-conferring alleles are estimated as less than 1.5, which suggests its small effect sizes. (22)

In the literature, consanguineous marriage (CM) has been connected to a number of health-related problems. Additionally, children of CMs are linked to an increased risk of non-communicable diseases (NCDs). (8) DNA mutations are the root cause of genetic disorders. Genetic disorders can be classified as single-gene, X-linked dominant/recessive, or autosomal dominant/recessive. These disorders are inherited from the parents. One example of an autosomal dominant disorder that affects only one parent and is passed on to the offspring is Huntington's disease (HD). Autosomal recessive traits are the means by which a disease, like thalassemia, is passed down from both parents to child. The two most common inheritance patterns linked to consanguinity, according to earlier research, are multifactorial disorders (69.8%) and autosomal recessive disorders (78.8%). (23) Recently, 71 new genetic risk loci for the development of OA have been found by multiple genome-wide association studies. There are 16 genes known to be important in knee OA. (24)

Pakistan leads the world in the percentage of cousin marriages at 65%; it is followed by India at 55%, Saudi Arabia at 50%, Afghanistan at 40%, Iran at 30%, Egypt, and Turkey at 20%. (12)

A case-control study examining obesity in the offspring of first-cousin couples in the Saudi population found a strong genetic correlation between angiotensin-converting enzyme (ACE) and several metabolic disorders, including obesity, a risk factor for KOA. (9) According to Khan et al. children with a family history of KOA and relatives with total knee replacements are also more likely to have worsening of cartilage loss and an increase in radiographic OA progression. (25) Maryam et al. also concluded that positive maternal and paternal family histories and high body mass index (BMI) are significant risk factors for the development of both RA and OA. (26)

Examining the patient's family and parental consanguinity history is a crucial initial step in screening for a wide range of conditions, especially when diagnosing chronic illnesses influenced by shared

environments, common behaviors, and genetic susceptibility. This has potential applications in disease prevention, genetic testing predictiveness, diagnosis, and health promotion.

CONCLUSION:

In summary, the study revealed that parents' consanguineous or cousin marriages, as well as a positive maternal and paternal family history of joint disease or osteoarthritis, were significant predictors of KOA.

ETHICS STATEMENT:

The research protocol was approved by the university's Ethical Research Committee (ERC), and permission was granted by hospital authorities for the data collection procedure. All ethical requirements were adhered to throughout the study. Eligible participants were informed about the purpose of the study before they signed an informed consent form to participate.

CONFLICT OF INTEREST:

There are no disclosed conflicts of interest involving the authors.

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