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Evaluation for Kienböck's disease familial clustering: A population-based cohort study

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Abstract

Purpose: Kienböck's disease (KD) is rare, and its etiology remains unknown. As a result, the ideal treatment is also in question. Our primary purpose was to test the hypothesis that KD would demonstrate familial clustering in a large statewide population with comprehensive genealogical records, possibly suggesting a genetic etiologic contribution. Our secondary purpose was to evaluate for associations between KD and known risk factors for avascular necrosis.

Methods: Patients diagnosed with KD were identified by searching medical records from a comprehensive statewide database, the Utah Population Database (UPDB). This database contains pedigrees dating back to the early 1800's, which are linked to 31 million medical records for 11 million patients dating from 1996 to present. Affected individuals were then mapped to pedigrees to identify high-risk families with an increased incidence of KD relative to control pedigrees. The magnitude of familial risk of KD in related individuals was calculated using Cox regression models. Association of risk factors related to KD was analyzed using conditional logistic regression.

Results: We identified 394 affected individuals that are linked to 194 unrelated high-risk pedigrees with increased incidence of KD. The relative risk of developing KD was significantly

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elevated in first-degree relatives. There was a significant correlation between alcohol, glucocorticoid, and tobacco use and a history of diabetes with the diagnosis of KD.

Conclusions: Familial clustering of KD observed in the UPDB cohort indicates a potential genetic contribution to the etiology of the disease. Identification of causal gene variants in these high-risk families may provide insight into the genes and pathways that contribute to the onset and progression of KD.

Clinical Relevance Statement: This study suggests that there is a potential genetic contribution to the etiology of KD and the disease has a significant association with several risk factors.

Keywords

Aseptic necrosis; Familial standardized incidence ratio (FSIR); Genetics; Kienböck's disease; Lunate osteonecrosis; Lunatomalacia

Introduction:

Kienböck's disease, also referred to as lunatomalacia or osteonecrosis of the lunate, was first described in 1910 by Robert Kienböck.¹ This rare condition has a prevalence of less than 200,000 in the United States,^{2,3} and the etiology remains unclear.³⁻⁷ As succinctly summarized by Lichtman et al, "the precise etiological triggers and pathoanatomical events remain unclear".⁷ Simply stated, the cells and signaling pathways that need to be targeted for disease intervention are unknown, which limits our ability to treat Kienböck's disease. Furthermore, it is unclear whether the 20 or greater described operations for this condition are optimal treatments, or if any affect the natural history of the condition.^{4,8}

Prior literature has documented the skepticism among hand surgeons regarding the causal nature of proposed etiologies for Kienböck's disease that have been discussed in the literature.⁵ Proposed contributory pathophysiologic mechanisms include abnormal load through the lunate in association with negative ulnar variance,⁹⁻¹³ differences in lunate morphology,^{14,15} vascular inflow or outflow anomalies,¹⁶⁻¹⁹ and radiolunate coverage or ulnar translation of the carpus.²⁰ Coagulation disorders, sickle cell anemia, and glucocorticoid use have been associated with osteonecrosis of the femoral head, however their role in the development of Kienböck's disease is less clear.^{6,21,22} Furthermore, conflicting literature exists in regard to the possible effect of ulnar variance,^{23,24} radial inclination,^{25,26} and occupational vibratory exposure^{8,27} on the pathogenesis of Kienböck's disease. When interpreting these studies, association and causation must be differentiated from one another.

There currently is no strong evidence supporting a genetic etiology for Kienböck's disease.^{3,6} However, there have been two case reports of a mother and daughter with Kienböck's disease,^{28,29} and a clinical series with two affected sisters.³⁰ Although these reports suggest a potential genetic contribution to Kienböck's disease, a comprehensive analysis using a large population-wide cohort has not been used to assess the potential heritability of the disease. We utilized a unique resource, the Utah Population Database (UPDB), to identify families with an increased clustering of Kienböck's disease.³¹ Determining whether

Kienböck's disease has a strong genetic contribution in some families is necessary to understand any genetic basis for the disease, which may lead to development of therapeutic interventions.

The UPDB is the only database of its kind in the United States and is the world's largest resource for tracking diseases in families, with over 11 million people in large, multigenerational pedigrees. The UPDB is a dynamic database that is continuously updated, linking birth, death, and marriage records to >31 million statewide medical claims dating back to 1996 (for complete details, see: <https://uofuhealth.utah.edu/huntsman/utah-population-database/data/>). These data include ambulatory surgery records from hospital outpatient departments and ambulatory surgery centers as well as inpatient hospital discharge records. Given the ability to link these data with extensive genealogical records, the majority of families living in Utah are represented in the UPDB. Some pedigrees include tens of thousands of individuals. The UPDB previously has been used to demonstrate familial clustering for other human diseases, and was contributory to the discovery of heritable forms of breast and ovarian cancer (BRCA1 and BRCA2 genes),^{32–35} colon cancer (adenomatous polyposis coli; APC gene),^{36–38} melanoma (MLM locus),³⁹ and chronic lymphocytic leukemia (BAK1 gene).⁴⁰

Our primary purpose was to utilize the UPDB to perform a retrospective, population-based study to test our hypothesis that Kienböck's disease clusters in families, which would be suggestive of a genetic etiology. Our secondary purpose was to evaluate for associations between Kienböck's disease and known risk factors for avascular necrosis²² in the same large statewide population.

Methods:

Study Approval:

This study was approved by the Institutional Review Boards of the University of Utah and Intermountain Healthcare and by the Resource for Genetic and Epidemiologic Research.

Study Population:

We identified individuals diagnosed with Kienböck's disease by a medical provider in the UPDB using the International Classification of Diseases (ICD) Ninth and Tenth revisions codes; ICD-10: M93.1 (Kienböck's disease of adults), M92.21x (Osteochondrosis [juvenile] of carpal lunate [Kienböck]), and ICD-9: 732.3 (Osteochondrosis, carpal, lunate). Ambulatory surgery data and inpatient claims in the UPDB were queried from 1996 to present. More than 72% of the ambulatory surgery data and 91% of the inpatient hospital claims are linked to an individual in the UPDB. Affected individuals had to have relatives in the UPDB to be included in our study cohort so that we could link them to pedigrees. This resulted in identification 394 individuals diagnosed with Kienböck's disease that could be definitively linked to a pedigree.

High-Risk Pedigree Identification:

To determine if there was excess familial clustering (e.g., increased incidence or diagnosis) of Kienböck's disease in the UPDB, we utilized the Familial Standardized Incidence Ratio (FSIR)⁴¹. FSIR allows for the quantification of familial risk of a disease by comparing the incidence of a disease in a family to its expected incidence in the general population. FSIR is a statistical method that accounts for the number of biological relatives in a pedigree, the degree of relatedness, and the age at which an individual is diagnosed.⁴¹ Exact one-sided Poisson probabilities were calculated under the null hypothesis of no familial enrichment of Kienböck's disease. To determine the population-wide incidence ratio, both affected and unaffected individuals in the UPDB are grouped into 7 categories based on age (0-30, 31-40, 41-50, 51-60, 61-70, 71-80, and 81-120) and the ratio of the total affected to total unaffected individuals is determined. To determine the pedigree incidence ratio, the UPDB is analyzed to identify the founders of pedigrees containing an affected individual, the disease status of every individual in each pedigree is determined, and the ratio of the total affected to total unaffected individuals is calculated. The pedigree incidence ratio/whole population ratio is used to determine the FSIR. High-risk pedigrees were selected if they had 2 or more living affected individuals, and if the FSIR was ≥ 2 and significant ($p < 0.05$) using a chi-squared test, as described by Kerber.⁴¹

Risk Factor Analysis:

Specific ICD-9 and ICD-10 codes were used to identify risk factors among study patients that have been previously associated with avascular necrosis in the literature (Appendix A).²² Conditional logistic regression was used to examine the association between the potential risk factors and Kienböck's disease using a ratio of 5 controls per 1 affected individual. Odds ratios and 95% confidence intervals were calculated.

Familial Risk Determination:

The magnitude of familial risk was estimated from Cox regression models, adjusting for sex, birth year, the number of biological relatives, their degree of relatedness, and their person-years at risk as previously described.⁴² An approximate 5:1 ratio of controls to cases was used in the analysis. Relative risk and 95% confidence intervals (CI) were calculated.

Results:

Identification and demographic detail of the Kienböck's disease cohort:

To identify individuals diagnosed with Kienböck's disease, we searched the UPDB for individuals with the ICD-10 codes M93.1, M92.21x, or the ICD-9 code 732.3. This search criteria resulted in identification of 394 individuals diagnosed with Kienböck's disease that could be definitively linked to a pedigree. Of the 394 individuals used for the analyses, 49.3% were female and 50.7% were male, the average age at diagnosis was 41.3 years (± 17.1), and 85.8% of individuals were white (Table 1).

Familial Risk:

To determine if there is an increased risk of Kienböck's disease among closely related individuals, we examined the relative risk of developing Kienböck's disease in first, second, and third-degree relatives in our cohort. The risk of developing Kienböck's disease was elevated in first-degree relatives (Relative Risk, 11.08 [95% CI, 1.09 – 112.58]) (Table 2). We were unable to detect an elevated risk of Kienböck's disease in second or third-degree relatives.

Identification of High-Risk Pedigrees:

To test if there is increased familial clustering of Kienböck's disease, we analyzed individuals diagnosed with Kienböck's disease that linked to a pedigree using the familial standardized incidence ratio (FSIR) calculation.⁴¹ We identified 194 unrelated, multigenerational, high-risk pedigrees that had an increased clustering of Kienböck's disease defined by a FSIR ≥ 2 (p-value < 0.05) that had at least two living members. Of the 194 high-risk pedigrees, the FSIR ranged from 2.0 – 926.0 (mean 16.0). Founder birth year, number of descendants, number of affected individuals, and FSIR values are indicated for 10 representative high-risk pedigrees (Table 3). Figure 1 is an example of a multigenerational high-risk pedigree with at least 11 affected individuals and a FSIR of 4.5. Together with the familial risk analysis, these data indicate that Kienböck's disease has significant familial clustering, which suggests a potential genetic contribution to Kienböck's disease.

Risk Factors Associated with Kienböck's disease:

We analyzed the association of several risk factors with Kienböck's disease that have been previously associated with avascular necrosis (primarily of the hip)²² (see Appendix A for ICD-9 and ICD-10 codes). We examined the association of a history of tobacco use, history of diabetes, glucocorticoid use, sickle cell anemia, thalassemias, clotting disorders, alcohol use, and Gaucher's Disease with Kienböck's disease in our cohort of 394 individuals. An approximate 5:1 ratio of controls to cases was used in the analysis. We identified significant associations between history of tobacco use (Relative Risk, 2.53 [95% CI, 1.90 – 3.36]), history of diabetes (Relative Risk, 2.17 [95% CI, 1.48 – 3.17]), glucocorticoid use (Relative Risk, 6.0 [95% CI, 2.59 – 13.89]), and alcohol use (Relative Risk, 2.07 [95% CI, 1.12 – 3.82]) with diagnosis of Kienböck's disease (Table 4). These data indicate that avascular necrosis and Kienböck's disease have some overlapping risk factors.

Discussion:

Through use of a unique resource, the Utah Population Database (UPDB), we have collected a large cohort of individuals diagnosed with Kienböck's disease. From this cohort, we have identified 194 high-risk pedigrees demonstrating familial enrichment for Kienböck's disease, as defined as a familial standardized incidence ratio (FSIR) exceeding a value of 2.0 for each family and having at least two living affected individuals per family. We have also determined that first-degree relatives of an individual diagnosed with KD have an increased relative risk of developing Kienböck's disease. Although the FSIR and RR are dependent on several factors, including the prevalence of the disease in the population, our data are consistent with other studies examining the potential genetic contribution to other familial

diseases using the UPDB.^{43–46} Thus, the main finding of this study was that Kienböck's disease clusters in families within a large population-based cohort, which suggests that there may be a genetic basis to the etiology of this disease.

Although prior literature is inconclusive in terms of support for a genetic basis for Kienböck's disease, our results substantiate the findings of a limited number of published case reports describing multiple affected individuals in the same family.^{28–30} Templeman *et al* reported Kienböck's disease in a mother and daughter.²⁸ The mother demonstrated Stage IV disease with 1mm ulnar negative variance, and the daughter had Stage III disease with 2mm negative ulnar variance. No history of trauma was noted for either patient. In a series of 38 patients undergoing silicone replacement arthroplasty of the lunate, Lichtman *et al* reported Kienböck's disease involvement in two sisters, both of whom presented with Stage II disease and negative ulnar variance.³⁰ Lastly, Rubin *et al* reported mother-daughter unilateral Kienböck's disease involvement in a highly consanguineous family.²⁹ Both patients had ulnar-negative variance and a normal chromosomal analysis. The authors recommended further molecular investigation should additional familial cases arise, which now may be possible given the findings in the current study. Through use of the UPDB, the current study expands upon the findings of these three case reports by identifying an additional 194 large, multigenerational families with an increased incidence of Kienböck's disease.

Our findings regarding the potential genetic etiology of Kienböck's disease are relatively unique when compared those in the literature, which has been heavily focused upon identification of morphologic differences that may be associated with the development of this condition. Conflict within the literature exists regarding the role of ulnar variance and the development of Kienböck's disease, with some studies supporting that notion,^{9–13} and some suggesting no relationship.^{23,24} Differences in lunate morphology have been shown to affect the severity of Kienböck's disease at presentation, with a protective effect of type II lunates.¹⁴ However it has yet to be shown that differences in lunate morphology cause Kienböck's disease. The proposed roles of radial inclination^{25,26} and occupational vibratory exposure/repetitive trauma^{8,27,47} in the development of Kienböck's disease have also been described. Vascular inflow or outflow abnormalities have been proposed as potential causes of Kienböck's disease but the exact underlying pathophysiology is yet to be elucidated.^{16–19} Whether causal or associated with increased susceptibility to Kienböck's disease, the underlying pathogenesis of these proposed risk factors or associations remains unclear. Therefore, identification of gene variants that have an effect on susceptibility to Kienböck's disease may provide insight into the molecular and cellular mechanisms that lead to the clinical disease state. These biological pathways may include genes that regulate development of the wrist, or those affecting vascularization of the lunate.

Risk factors for avascular necrosis, most frequently studied in the hip, have been described.²² However, their role in the development of Kienböck's disease remains less clear. We found a significant association between Kienböck's disease and tobacco use, diabetes, chronic glucocorticoid use, and alcohol use. We did not find an association with blood dyscrasias including sickle cell anemia or thalassemias, clotting disorders, or Gaucher's disease. Despite a case report describing development of Kienböck's disease in an individual

on chronic glucocorticoids,⁴⁸ the metabolic factors we studied have not been definitively linked to the onset or progression of Kienböck's disease.⁷ A limitation of our risk factor analyses is that our data are restricted to the population of Utah, which is largely of European descent. As a result, risk factors that are present in other populations, such as sickle cell anemia and thalassemias, may not be fully represented in our study cohort. However, awareness of these comorbidities observed to be significantly associated with Kienböck's disease in the current study may help guide the clinical diagnosis of this condition in at-risk populations.

As for any condition with a genetic component, identification of genetic variants associated with the disease is important. Given that Kienböck's disease in these large high-risk pedigrees segregates as an apparent autosomal dominant trait with near complete penetrance, genomic analysis of very few affected and unaffected individuals is needed to identify a small number of candidate genes.⁴⁹ Functional analyses in model organisms may provide insight into the origin and biology of Kienböck's disease and provide pre-clinical animal models for development of treatments that may prevent the onset or limit the progression of Kienböck's disease.⁵⁰

This study has several limitations. As for all database studies, it is unclear how errors in diagnostic coding would have an impact on the study findings, and manual chart review was not performed for all affected and non-affected individuals included in the analysis. Although database coding accuracy may depend upon the phenotype under study and whether specific codes exist, prior studies have observed a 93-97% rate of accuracy upon manual chart review of patients identified through UPDB coding.^{51,52} It is possible that this could differ for Kienböck's disease however, it is unclear if this would change our results. Although we identified numerous pedigrees with Kienböck's disease involvement of distant relatives, we only identified one pedigree with affected first-degree relatives. Because of the small number of instances of first-degree relatives with a diagnosis of Kienböck's disease, our relative risk analysis has limited precision as evidenced by its wide 95% confidence interval. In other words, the relative risk is significantly elevated among first-degree relatives, but the precise magnitude of that risk is unclear. It is possible that the youngest generation is too young for the condition to have become clinically manifest. In addition, older individuals and those without access to healthcare (Utah has a high proportion of residents living in rural areas) may not have been diagnosed. Our high-risk pedigree analysis can only identify individuals that have been diagnosed in Utah, and as a result, our FSIR calculations are likely an underestimate of the heritability of the disease. Because of this, in high-risk pedigrees, we consider individuals without a Kienböck's disease diagnosis as 'status unknown' until we can definitively determine if they are unaffected or affected. Also, our study does not evaluate the extent to which Kienböck's disease is genetic. It is possible that the segregation of Kienböck's disease in families may be due to other factors besides genetics. There may be environmental (or gene-environment interactions) or mechanical influences that contribute to the phenotype in these families.

To conclude, we demonstrated that Kienböck's disease demonstrates familial enrichment and an increased relative risk among first-degree relatives. Taken together, these findings suggest that Kienböck's disease may have a genetic component to its etiology. Although our

data are consistent with a genetic contribution to Kienböck's disease, we cannot rule out a shared environmental or mechanical risk factor in these families. Genetic sequencing of affected and unaffected individuals within these high-risk pedigrees holds promise in identifying genetic variants associated with this condition. Furthermore, by identifying and studying gene variants that cause Kienböck's disease, we may learn about the biological mechanisms that lead to other forms of osteonecrosis, which may provide important insight into surgical treatment or therapeutic intervention.

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Appendix

- Alcohol related disorders:
 - ICD-9: 303.**.
 - ICD-10: F10.***.
- Clotting disorders:
 - ICD-9: 289.81 (primary hypercoagulation state).
 - ICD-10: D68.59 (Primary thrombophilia), D68.51 (activated protein C; Factor V Leiden), D68.52 (prothrombin gene), D68.61 (Antiphospholipid syndrome), and D68.62 (Lupus anticoagulant syndrome).
- Diabetes:
 - ICD-9: 250.**.
 - ICD-10: E08.*** (DM due to underlying condition), E90.*** (DM due to drug/chemical), E10.*** (Type 1 DM), E11.*** (Type 2 DM), E13.*** (Other DM).
- Gaucher's Disease:
 - ICD-9: 272.7.
 - ICD-10: E75.22.
- Glucocorticoid use:
 - ICD-9: V58.65 (Long-term current use of steroids) and V87.45 (Personal history of systemic steroid therapy).
 - ICD-10: Z79.5** (long term current use of steroids) and Z92.241 (personal history of systemic steroid therapy)
- Sickle cell anemia:
 - ICD-9: 282.6* (Sickle cell disease and sub-categories; not including thalassemia or spherocytosis).
 - ICD-10: D57.*** (Sickle cell disease and sub-categories).
- Thalassemias:
 - ICD-9: 282.4*.
 - ICD-10: D56.**.
- Tobacco use:
 - ICD-9: 305.1 (tobacco use disorder), and V15.82 (history of tobacco use).
 - ICD-10: F17.*** (Nicotine dependence), Z72.0 (tobacco use NOS), Z87.891 (history of tobacco dependence).

Appendix Figure 1 –.

Identification of risk factors for avascular necrosis using diagnostic coding.

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Figure 1 –.

Example of a high-risk pedigree identified in the UPDB. Circles = females, squares = males, asterisk = family founder, slashes = deceased. White circles/squares = affection status unknown. Black circles/squares = individuals affected with Kienböck's disease.

Table 1 –

Baseline Patient Characteristics of the Kienböck's Disease Cohort.

Number of Individuals *	394
Age (years)	43 ± 17.1 (Range 6-100)
Race	
White	338 (85.8%)
Non-white	56 (14.2%)
Sex	
Female	194 (49.3%)
Male	200 (50.7%)

* Individuals diagnosed with Kienböck's disease through ICD-9 and ICD-10 codes that linked to a pedigree

Table 2 –

Increased Familial Risk of Kienböck's disease.

Relationship	Relative Risk (Coefficient and 95% CI)	p-value
Proband	<i>Reference Group</i>	-
First-degree relative	11.08 (1.09 - 112.58)	p < 0.05

Abbreviations: CI - 95% confidence interval

Table 3 –

High-Risk Pedigrees with Excess Familial Clustering of Kienböck's disease. FSIR and p-values were calculated according to Kerber.⁴¹

Founder Number and Birth Year	Descendants	Number of Affected Living Individuals	FSIR	p-value
1 - 1749 *	31557	11	4.5	< 0.05
2 - 1778	17950	6	6.5	< 0.05
3 - 1771	15505	5	4.2	< 0.05
4 - 1777	5822	4	10.2	< 0.05
5 - 1739	5086	4	10.8	< 0.05
6 - 1792	2278	3	16.1	< 0.05
7 - 1788	4250	3	14.4	< 0.05
8 - 1794	2046	3	20.9	< 0.05
9 - 1728	3180	2	10.3	< 0.05
10 - 1844	463	2	89.0	< 0.05

Abbreviations: FSIR = familial standardized incidence ratio.

* indicates founder and pedigree represented in Figure 1.

Table 4 –

Potential Risk Factors Associated with Kienböck's Disease.

Risk Factor/Clinical Diagnosis	N (%)	N (%)	Relative Risk with 95% Confidence Interval	p-value
Total number of patients	394	1970	-	-
History of tobacco use	94 (23.86%)	232 (11.78%)	2.53 (1.90 - 3.36)	< 0.05
History of diabetes	47 (11.93%)	125 (6.35%)	2.17 (1.48 - 3.17)	< 0.05
Glucocorticoid use	12 (3.05%)	10 (0.51%)	6.00 (2.59 - 13.89)	< 0.05
Male	5 (1.02%)	3 (0.15%)		
Female	7 (1.77%)	7 (0.34%)		
Sickle cell anemia	0	0	N/A	-
Male	0	0		
Female	0	0		
Thalassemias	0	0	N/A	-
Male	0	0		
Female	0	0		
Clotting disorders	0	4 (0.20%)	N/A	-
Male	0	0		
Female	0	4 (0.20%)		
Alcohol Use	15 (3.81%)	38 (1.93%)	2.07 (1.12 - 3.82)	< 0.05
Male	10 (2.53%)	13 (0.66%)		
Female	5 (1.27%)	25 (1.27%)		
Gaucher's Disease	3 (0.76%)	0	N/A	-
Male	1 (0.25%)	0		
Female	2 (0.51%)	0		