LESION SIZE AS A PREDICTOR OF NON-OPERATIVE THERAPY FAILURE IN JUVENILE OSTEOCHONDRITIS DISSECANS OF THE KNEE

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Mark Roehr
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Mentor: Brian Kelly, MD

Lesion Size as a Predictor of Non-Operative Therapy Failure in Juvenile Osteochondritis Dissecans of the Knee

Mark Roehr[1] BS, Brian Kelly[1,2,3] MD, Jeffery Vaughn[2,3,4] DO, Kevin Wong[5] DO, Paul Kang[1] MS, MPH

1. University of Arizona College of Medicine - Phoenix
2. Phoenix Children's Hospital
3. Mayo Clinic Scottsdale
4. University of Arizona College of Medicine - Tucson
5. University of Arkansas College of Medicine

Mark Roehr: mroehr@email.arizona.edu.
- ORCID ID: https://orcid.org/0000-0002-4312-1414

Brain Kelly: bkelly@phoenixchildrens.com
Jeffery Vaughn: jvaughn1@phoenixchildrens.com
Kevin Wong: Kwong@uams.edu
Paul Kang: paulk@email.arizona.edu

Abstract:

Background:
The primary challenge in juvenile osteochondritis dissecans of the knee management lies in the lack of definitive non-operative treatment criteria. The purpose of this study was to evaluate the predictive nature of the lesion size and to determine a lesion size cutoff point beyond which a patient's likelihood of successful 3 month non-operative therapy significantly declines.

Methods:
36 knees were retrospectively identified that met the inclusion criteria of stable JOCD lesions that received a 3 month non-operative therapy treatment consisting of either unloader bracing and/or activity restriction. The primary outcome of interest was improved clinical status at three months with accompanying MRI evidence of reossification. Continuous and categorical variables including lesion size were analyzed using logistic regression to ascertain the likelihood of a surgical intervention following a non-operative treatment regimen.

Results:
Following three months of non-operative treatment, 23 of the 36 knees (64%) had progression toward healing. The mean starting age of the patients with lesions that progressed toward healing was 10.4 years +/- 2.10 years and the mean age that required surgical referral was 12.4 years +/- 1.18 years ($p = 0.002$). The mean surface area of the lesions that demonstrated progression toward healing was 185.0mm^2 +/- 103.7mm^2, and the mean surface area of the lesions that did not progress toward healing and were referred for surgical management was 266.6mm^2 +/- 95.5mm^2 ($p = 0.01$). The mean lesion surface area cut point >250mm^2 contained 13 knees. Of these 13 knees, 4 progressed toward healing (17.4% of the healing group), while 9 required surgical referral (69.2% of the surgery group) (OR = 6.84, 95% CI [1.17,39.8], $p = 0.032$).

Conclusion:
Increased lesion size and increased age were the strongest predictors of JOCD non-operative therapy failure. Stable lesions with a mean surface area that is > 250mm^2 are at an increased risk for non-opperative failure and should be considered for direct surgical referral on a case by case basis.

Background:

Juvenile Osteochondritis Dissecans (JOCD) is a disorder affecting the subchondral bone in skeletally immature patients. Lesions that fail to heal can become unstable leading to fragmentation of the overlying cartilage and eventual displacement of the fragment into the joint increasing the risk of premature arthritis. While the specific cause of JOCD is unknown, increased physical activity resulting in microtrauma to the subchondral bone, vasculature failures to the chondral tissue, and genetic and endocrine factors are believed to be involved in its pathogenesis [1,2,3,4,5,6]. The exact prevalence of JOCD is undetermined, but most reports cite between 2 - 31 cases per 100,000 [5,7,8]. There are well documented reports of success with non-operative treatment for stable JOCD lesions [7,9,10,11,12], signifying that many cases of JOCD of the knee are potentially reversible with joint immobilization, bracing, or activity restriction. This is generally recommended in skeletally-immature patients (patients with open physes) with stable lesions, as the probability of successful healing is thought to decrease with advancing age [7,13,14,]. JOCD lesions which fail to heal with conservative treatment are treated surgically to attempt to recruit pluripotent cells from the surrounding healthy bone and stabilize the lesion when necessary.

In patients with suspected JOCD of the knee, different imaging modalities can be utilized to identify and stage the lesion. Plain radiographs of both AP and lateral views are obtained first to rule out other bony injury and to evaluate skeletal maturity. Despite recent advances in musculoskeletal ultrasound [15] and reports of discrepancies between magnetic resonance imaging (MRI) versus arthroscopic lesion stability [16], there is a consensus that MRI is the best radiological modality for determining the stability and size of JOCD lesions with a diagnostic sensitivity approaching 100% [6,9,17,18,19]. Specifically, high T2 signals are often found surrounding stable JOCD lesions, and MRI provides the best visualization of cartilaginous loose bodies, articular cartilage defects, and subchondral cysts [9,17,20,21].

Currently, the primary issue surrounding JOCD of the knee is determining the appropriate treatment strategy for stable lesions. The size of the lesion, integrity of the articular surface, and the patient's skeletal maturity have been accepted as critical factors for establishing treatment decisions [9,22,23,24]. However, more effective distinctions are necessary. The American Association of Orthopedic Surgeons has a consensus recommendation for surgery as an option for symptomatic patients with unstable JOCD lesions, but has inconclusive recommendations for symptomatic patients with stable lesions [25]. Reports of success with non-operative treatment for JOCD vary considerably, ranging from 33% to 67% [5,7,9,10,11,26]. Some authors have simply recommended non-operative treatment for all patients with open femoral growth plates and small lesion size [24]. Increasing size of the lesion has demonstrated promise in several studies as one of the best prognostic markers for non-operative failure [9,10,21,22,27], and additional research on this parameter has been recommended for more appropriate clinical management [9].

The approach to non-operative therapy itself is quite varied in terms of the clinical implementation and length of treatment. Cast immobilization, specialty bracing with hinged unloader braces, or simply reduced physical activity have been all been assessed without clear advantage in outcomes [6,7,9,18,12]. Currently, several authors suggest a three phase approach consisting of knee immobilization for four to six weeks, followed by weight bearing as tolerated for approximately six weeks, and finally the slow return to activity with clinical improvement [5,7]. Due to concerns surrounding muscle atrophy, cartilage degradation, and joint stiffness, however, the duration of immobilization must be carefully monitored [18,28], and immobilization presents a greater inconvenience to the patient. Regardless of which therapy is applied, it's duration is highly variable in the literature consisting of anywhere from three to twelve months [5,6,9,10,11,21,29]. Recent systematic reviews have recommended additional research in both of these areas to determine the most effective approach [5,6,7].

Overall, the primary challenge in JOCD of the knee management lies in the lack of definitive non-operative treatment criteria. Given the reported increased risk of non-operative therapy failure with increasing lesion size, the purpose of this present study was to determine lesion size cutoff points, beyond which a patient's likelihood of successful three month non-operative therapy significantly declines. In addition, our study will attempt to provide more evidence on unloader bracing and activity restriction versus joint immobilization for non-operative management.

Methods:

Study Population

This study was reviewed and approved by the institution's institutional review board (IRB) in November 2017. Using ICD-9 and ICD-10 codes, 369 patient charts were identified with an osteochondritis dissecans diagnosis between the years 2008-2018 at a single institution. Of these patients there were 64 knees that fit within the inclusion criteria of the study which included patients ages 6 to 14 years old, stable lesions, lesions that were not immediately referred for surgical repair, open growth plates, completion of the three month non-operative therapy period, separate pre and post non-operative therapy MRIs, no previous avascular necrosis in the affected knees, and complete medical records. Of the 305 patients excluded, the vast majority were due to age, immediate surgical referral, incomplete medical records, incomplete imaging records, or extended non-operative period duration. An additional 28 patients were excluded due to inability to locate the second MRI at the end of the three month non-operative treatment period. The final 35 patients (36 knees) identified ranged in age from 7 to 14 years old.

Each patient had conventional knee radiographs taken at the time of diagnosis consisting of anteroposterior and lateral views. MRIs were performed at various radiology centers in proximity to the institution with T1 and T2 weighted sequences obtained in the axial, sagittal, and coronal planes. Criteria for a stable OCD lesions on MRI were defined as no breach in the articular cartilage or subchondral bone with low signal changes.

Treatment

The nonoperative treatment consisted of primarily activity restriction that included no running, jumping, sports participation, or physical education at school. Depending upon the severity of the clinical presentation (including reported pain, reduced mobility, and duration of symptoms, in addition to patient/family preferences), patients were managed with either an unloader specialty brace (20 knees) or simple activity restriction with no bracing (16 knees). This treatment was to last for 3 months, after which they would receive a second MRI to evaluate the lesion along with reported clinical symptoms.

Data Collection

The age, sex, affected knee, and athletic participation of each patient was completed by review of their medical documents. The lesion location, size, surface area, and volume were determined from the MRI files. The location was determined as either the medial femoral condyle or lateral femoral condyle on the coronal view. The length, width, and depth of the lesion was determined on T1 weighted magnetic resonance images of sagittal and coronal views with electronic calipers. Surface area of the lesions was calculated as the product of the sagittal length and coronal width of the lesion. Normalized length, normalized width, and scaled surface area were determined by measuring the maximal length and width of the femoral condyles and calculating the lesion as a percentage of that corresponding measurement with electronic calipers on the sagittal and coronal views. This calculation is reported as the "normalized lesion size". All electronic caliper measurements were consistently completed by measuring to the inner border of the lesion differentiation point.

Coronal view demonstrating measurements of JOCD lesion and femoral condyle widths

Sagittal view demonstrating measurements of JOCD lesion and femoral condyle lengths

Outcome Measurement

After the three months of nonoperative therapy patients' outcomes were categorized into either the no surgery group (progression toward healing) or the surgery group (no progression requiring referral for surgical management). Patients in the healing group demonstrated MRI evidence of reossification or lack of inflammatory or lesion size progression, while patients in the failure group had no reossification, increased lesion size, unstable lesions, or markedly worsened clinical symptoms. Determination of the lesion outcome was recorded primarily on the basis of the clinician's documentation at the 3 month visit according to the clinical outcome (progression toward healing or referral to surgery) and there were no patients with significant discordance on their accompanying second MRI.

Statistical Analysis
The demographic and clinical characteristics were analyzed according to the type of variable. The non-categorical continuous variables (surface area, lesion length, lesion width, lesion depth, femoral condyle length, femoral condyle width, length percentage, and width percentage) were presented as means and standard deviations. The categorical variables (knee side and sagittal versus coronal location) were presented as percentages and frequencies. The independent T-Test and Chi-squared analysis were used to compare continuous and categorical across 2-samples, respectively. The Wilcoxon Rank-Sum and Fishers' Exact test were used for variables that observed a non-normal distribution. Logistic regression was implemented to report Odds Ratios and 95% confidence intervals to ascertain the likelihood of a surgical intervention following a non-operative treatment regimen. All p-values were two sided and $p < 0.05$ was considered statistically significant.

Results:

After 3 months of nonoperative therapy, 23 of the 36 knees (63.9%) progressed toward healing. Table I presents the description of the study sample. The mean starting age of the patients with lesions that progressed toward healing was 10.4 years +/- 2.10 years and the mean age that required surgical referral was 12.4 years +/- 1.18 years ($p = 0.002$). Of the 20 patients who were prescribed the unloader brace in conjunction with activity restriction, 12 progressed toward healing while 8 required surgery ($p = .59$). The mean surface area (and standard deviation) of the lesions that demonstrated progression toward healing was 185.0mm^2 +/- 103.7mm^2, and the mean surface area of the lesions that did not progress toward healing and were referred for surgical management was 266.6mm^2 +/- 95.5mm^2 ($p = 0.01$). The mean scaled surface area (in relation to the femur surface area) for the lesions that progressed toward healing was 15.3% +/- 8.11%, in contrast to the scaled surface area of the lesions requiring surgical referral of 21.2% +/- 8.65% ($p = 0.03$).

Table I				
Variables	Overall N=36	No Surgery N=23	Surgery N=13	P-value
Age at start of Tx (mean, SD)	11.1 (2.06)	10.4 (2.10)	12.4 (1.18)	0.002
Sex (male, %)	23 (63.9)	13 (56.5)	10 (76.9)	0.29
Affected Knee (right, %)	18 (50.0)	12 (52.2)	6 (46.2)	1
Location (lateral, %)	6 (16.7)	4 (17.4)	2 (15.4)	1
Type of Immobilization (Brace, %)	20 (55.6)	12 (52.2)	8 (61.5)	0.59

Lesion Length, mm (mean, SD)	16.6 (55.5)	15.4 (4.43)	18.5 (4.19)	0.06
Lesion Width, mm (mean, SD)	12.3 (3.23)	11.3 (3.14)	14.0 (2.74)	0.006
Lesion Depth, mm (mean, SD)	4.33 (1.14)	4.13 (1.18)	4.69 (1.03)	0.11
Lesion Surface Area, mm^2 (mean, SD)	214.5 (107.1)	185.0 (103.7)	266.6 (95.5)	0.01
Normalized Length (% (mean, SD)	35.2 (10.4)	33.1 (10.2)	38.9 (10.0)	0.08
Normalized Width (% (mean, SD)	46.9 (11.7)	43.8 (11.7)	52.6 (9.59)	0.03
Scaled Surface Area % (mean, SD)	17.4 (8.68)	15.3 (8.11)	21.2 (8.65)	0.03

Table II provides an analysis of the lesion size characteristic cut points that were chosen to maximize the specificity of those who would fail conservative nonoperative management. This was achieved using ROC curves followed by Lowess Smoothers to ascertain clinical thresholds to categorize continuous predictors. Logistic regression in this model adjusted for age and sex. The mean lesion surface area cut point was >250mm^2 that contained a total of 13 knees. Of these 13 knees, 4 progressed toward healing (17.4% of the healing group), while 9 required surgical referral (69.2% of the surgery group) (OR = 6.84, 95% CI [1.17,39.8], p = 0.032). The scaled surface area (in relation to the femur surface area) cut point was >20% that comprised 12 total knees. Of these knees, 5 would progress toward healing (21.7% of the knees in the healing group) while 7 would require surgical referral (53.8% of the knees in the surgical referral group) (p=.12).

Table II				
Variables	No Surgery N=23	Surgery N=13	OR (95% CI)	P-value
	N, %	N=%		
Lesion Length, mm (>18)	7 (30.4)	10 (76.9)	5.87 (1.02, 33.6)	0.047
Lesion Width, mm (>14)	5 (21.7)	9 (69.2)	5.70 (1.04, 31.3)	0.045
Lesion Depth, mm (>4)	18 (78.3)	12 (92.3)	10.7 (0.62, 183.2)	0.1
Lesion Surface Area, mm^2 (>250)	4 (17.4)	9 (69.2)	6.84 (1.17, 39.8)	0.032
Normalized Length, mm (>40)	4 (17.4)	6 (46.2)	2.66 (0.46, 15.4)	0.27
Normalized Width, mm (>50)	7 (30.4)	9 (69.2)	6.39 (1.01, 40.5)	0.049
Scaled Surface Area, mm (>20)	5 (21.7)	7 (53.8)	3.96 (0.72, 21.9)	0.12

Discussion:

The primary finding of this study was that an increased size of the JOCD lesion as measured on MRI was a strong prognostic variable for subsequent failure of nonoperative therapy. The mean lesion surface area size in the healing group was 185 mm^2, versus 267 mm^2 in the surgical referral group. In a very similar study, Wall et al.[9] reported comparable lesion sizes with their healing group mean lesion size being 209mm^2 and their failure group mean lesion size being 288mm^2. Similarly, Pill et al.[21] noted nonoperative failure occurred most often with a larger lesion size (194mm^2) versus success with smaller lesions (152mm^2) in younger patients. In their limited sample size of 8 knees, Bellelli et al[30] reported a 100% healing rate in lesions <20mm in length after an extended period of therapy lasting 24 months. Our finding that scaled surface area was another predictor of nonoperative therapy outcome was also in accordance with previous studies [9]. These results add to the growing body of evidence of the relationship between increased lesion size and eventual requirement for surgical management.

Versus previous studies that utilized predictive models or nomograms that included lesion size, age, clinical symptoms, or cyst like lesions on MRI [9,10], we focused on the lesion size alone. To provide improved data points for clinical decision making based off MRI measurements, we chose cut points that would maximize the specificity for those who would fail nonoperative management. For JOCD patients with a stable lesion surface area of >250mm^2, our data suggests a 6.84 times greater risk for failure of non-operative therapy versus lesions smaller than that cut point ($p = 0.032$). To our knowledge, we are the first to use this type of statistical analysis in the approach to JOCD lesions. While this data is from a limited sample, we recommend further research as this would provide improved evidence for patients/families choosing between non-operative vs operative management.

Overall, our approach of activity restriction alone, or in conjunction with an unloader brace, did not result in a significantly higher failure rate (36%) versus previous studies that utilized the three phase therapy which includes four to six weeks of immobilization [7,9,10,]. When comparing the 20 patients who received the unloader brace versus those with only activity restriction, we observed no significant difference in outcome as 12 progressed toward healing while 8 required surgery. The three month duration of our conservative therapy was shorter than the majority of other similar studies [9,10,21,30], but also resulted in comparable outcomes. Although patient compliance in non-operative therapy has been a significant limitation to all JOCD studies of this nature, our results suggest the utility of a shorter and less constraining treatment approach.

Other secondary variables that were examined besides the lesion size demonstrated general consistency in terms of their prediction of outcome success with previous literature. Increased patient age was a significant predictor of therapy failure in our population with the mean starting age of the patients with lesions that progressed toward healing being 10.4 years compared to those requiring surgical referral at 12.4 years. There has been slight inconsistency in regards to advancing age as a risk factor for non-operative therapy failure in previous studies, with some reporting no significant effect [9,22,] while the majority reporting greater success in younger patients [10,13,14,24,31,]. The majority of the JOCD lesions in our study were located on the medial femoral condyle (83%) in agreement with all previous reviews [5,6,7,9,13,32]. Previous studies have described that medial femoral condyle lesions have higher failure rates compared to the lateral condyle [9,33]. We did not observe significant differences between the rates of failure according to lesion site, with a failure rate of 33% for lateral lesions and a failure rate of 37% for medial lesions. However, this could be explained by our small sample size. There were no significant differences on the outcome according to the sex of the patient in our results.

Similar to other studies that have excluded unstable lesions [9], all the knees in our study are considered to have Grade I lesions according to either the Di Paola classification system for MRI findings [34] or other classifications systems utilizing radiographs or arthroscopy [35,36]. This limited our ability to perform more detailed analysis on MRI grade, but following the approach of Wall et al [9], we did not exclude any lesions on account of high-intensity signal lines between the lesion and the epiphyseal bone. This high-intensity signal was considered as a marker of instability by De Smet et al [24], but there continues to be debate regarding if this is instead indicative of healing granulation tissue [30,37].

There are several limitations in the present study that warrant discussion. First, as with other comparable study designs, patient compliance is difficult to achieve on a standardized basis. Given that our therapy duration was shorter and did not employ immobilization, this could have had less of an effect versus other studies on the progression toward healing outcome, but is still a concern. JOCD patients are often active and participate in various sports with repetitive impacting movements. Despite clear instructions to the patient and their family that the patient was to abstain from running, jumping, athletic participation, or physical education, many of them could have been non-compliant. Furthermore, when examining the use of the hinged unloader braces, varying levels of usage undoubtedly occurred despite specific directions regarding their use with any significant mobility. This could have led to a lower success rate in our patients undergoing non-operative therapy, but is also likely in concordance with expectations for “real life” clinical practice. Secondly, this study was retrospective in nature and had difficulties with obtaining complete medical records for many patients that would have otherwise fit our inclusion criteria. This included 28 patients that underwent three month non-operative therapy, but that either did not receive a second MRI or that we were unable to locate a second MRI. This could have influenced our final data in regards to the lesion size cutoffs and secondary variables associated with healing outcomes. Thirdly, in determining whether a patient was progressing toward healing or required surgical management, we ultimately followed the clinical course determined by the treating physician rather than relying solely on evidence of reossification on MRI. While this is reasonable from a clinical perspective, it does limit comparisons with our data against other studies where patients’ outcomes were evaluated primarily by MRI findings. We did not encounter a patient in our population where the second MRI findings had significant inconsistency compared to the clinical outcome. Fourthly, even with consistent focus on electronic caliper measurements that were completed by measuring to the inner border of the lesion differentiation point on MRI, there is certainly a small level of error in lesion measurement. This was slightly more difficult to control versus other single institution studies, as a number of different MRI machines were used with patients commonly receiving MRIs on an outpatient basis at our practice. We concur that future prospective investigational study designs are required to validate our results and confirm the utility of the lesion cut points for clinical practice.

On the basis of our results, we conclude that the lesion size is one of the primary determinates of outcome in non-operative JOCD therapy. Furthermore, we suggest that stable lesions with a mean surface area that is >250mm^2 are at an increased risk for non-opperative failure and should be considered for surgical management on a case by case basis. Additional research is necessary to validate this specific cutoff point, and we anticipate future prospective studies on this parameter. Overall, this project adds to the current body of work regarding JOCD of the knee to provide better prognostic information that will allow physicians to tailor protocols for individual patients and their families. Because pediatric JOCD often occurs in physically active adolescents, determining the correct treatment regimen from the initial patient visit is imperative to ensuring children return to their athletic participation and active lifestyles as quickly as possible.

Declarations

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There were no external or internal sources of funding for this research project. The project was completed using the facilities and technology of Phoenix Children's Hospital and the University

of Arizona College of Medicine – Phoenix, which were provided voluntarily for no financial compensation.

Conflicts of interest/Competing interests:
All authors declare that they have no conflicts of interest nor competing interests relating to the contents of this project or any of the related entities described within.

Availability of data and material:
The data generated and analyzed during this study are included in this published article and its supplementary information files. Additional tables reporting the individualized knee's demographic data and MRI measurements are available from the corresponding author upon reasonable request.

Code availability:
Not applicable

Ethics approval:
This study was reviewed and approved by the Phoenix Children's Hospital Institutional Review Board in November 2017 (IRB #17-163). The study qualified for exempt status under the guideline 45CFR 46.101(b), with a waiver of HIPAA authorization. The IRB approval period was: 11/20/2017 – 11/19/2020

Consent to participate:
The study qualified for exempt status under the guideline 45CFR 46.101(b), with a waiver of Informed Consent/Assent being granted from the Phoenix Children's Hospital IRB chair.

Consent to publication:
All details and images contained in this manuscript were covered in a waiver of informed consent as noted above for this project and its publication.

Author's contributions:
BK, JV, and MR developed the original research study design. MR completed the acquisition of data. KW completed MRI scoring and radiologic analysis. PK and MR completed data analysis. JV, BK, and MR drafted the initial manuscript, and all authors were involved in its final revision.

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