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MODEL

Destabilization of the medial meniscus in geriatric mice captures functional decline in age-associated osteoarthritis

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Abstract

Osteoarthritis (OA) disproportionately affects older adults, yet most preclinical models rely on young animals and fail to incorporate biological aging. Here, we establish a geriatric murine model of OA using destabilization of the medial meniscus (DMM) in 18–19-month-old C57BL/6J mice. Surgical induction produced joint pathology consistent with OA, including loss of cartilage integrity and osteophytic remodeling. Functionally, OA mice exhibited increased composite ethogram scores and reduced rearing behavior, indicating impaired mobility and weight-bearing capacity. These findings demonstrate that DMM surgery in aged mice induces both structural and functional features of OA. This model provides a practical and physiologically relevant platform for studying age-associated joint degeneration and evaluating therapeutics in an aging context.
Keywords: Osteoarthritis, aging, destabilization of the medial meniscus, C57BL/6J mouse model, knee joint degeneration, functional impairment

Introduction

Osteoarthritis (OA) is the most prevalent joint disorder in older adults and a leading cause of disability, characterized by progressive cartilage degeneration, chronic pain, and loss of mobility [1]. Although traditionally viewed as a degenerative condition of aging, a substantial proportion of OA arises following joint injury, including meniscal damage, ligament rupture, and intra-articular fractures [2, 3]. These injuries often initiate structural deterioration but occur within an aging biological environment marked by reduced tissue repair capacity, chronic low-grade inflammation, and altered joint homeostasis [4]. As a result, aging not only increases susceptibility to OA but also fundamentally shapes disease progression and severity.

Animal models are essential for studying OA pathogenesis and evaluating therapeutic strategies [5, 6]. Among these, the destabilization of the medial meniscus (DMM) model is widely used due to its reproducibility and ability to recapitulate key structural features of post-traumatic OA [7]. However, most studies employing DMM are performed in young adult mice, limiting their relevance to aging-associated disease [8]. Aging fundamentally alters joint biology through processes including cellular senescence, extracellular matrix degradation, and impaired anabolic signaling, all of which contribute to OA progression [4, 9].

To address this limitation, we demonstrated the validity of the DMM model in aged C57BL/6J mice. We hypothesized that induction of OA in aged animals would produce not only structural joint degeneration but also measurable functional impairment, thereby providing a more translationally relevant platform for studying age-associated OA.

Materials and Methods

Animals

Eighteen-month-old male and female C57BL/6J mice were obtained from the National Institute on Aging Aged Rodent Colony (Charles River, Inc.) and housed under specific pathogen-free conditions (≤ 5 per cage) with standard chow (Labdiet 5LG6, TestDiet Inc, Richmond, IN) and water provided *ad libitum*. All procedures were

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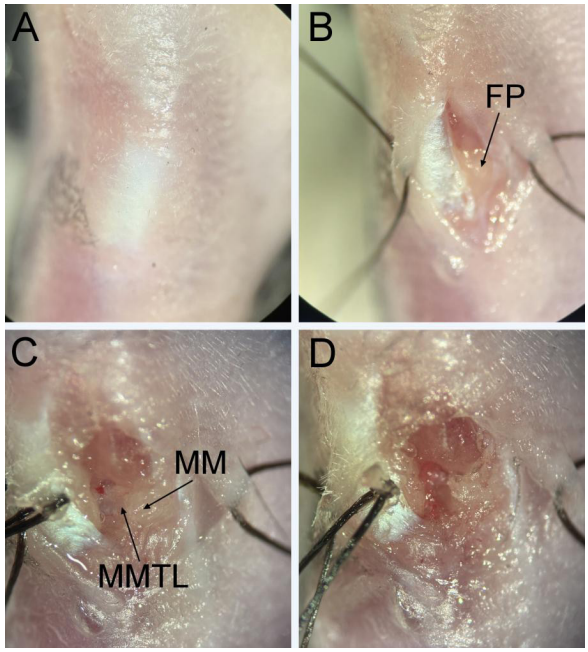

Figure 1. Surgical induction of osteoarthritis via destabilization of the medial meniscus. A progressive set of images is shown. **(A)** The cleaned and prepared area of surgery; **(B)** The skin is retracted to show the fat pad within the knee joint; **(C)** The medial meniscus and the meniscotibial ligament are exposed; **(D)** The knee joint after the meniscotibial ligament has been transected. MM, medial meniscus; MMTL, medial meniscotibial ligament; FP, fat pad.

approved by the University of Washington Institutional Animal Care and Use Committee.

Surgical induction of OA

OA was induced at 19 months of age via DMM in the right knee, as described [7] (Figure 1). Mice were anesthetized with isoflurane and administered carprofen and sustained-release buprenorphine, as well as a local block using lidocaine. A medial parapatellar incision was performed, the joint capsule opened, and the medial meniscotibial ligament transected. Sham-operated mice underwent capsulotomy without ligament transection. The joint capsule and skin were closed with standard sutures.

Functional assessments

Ethogram

Animals were monitored beginning the week post-surgery using a composite ethogram assessing activity, gait, posture, grooming, and body condition [10, 11] (Table 1). Each parameter was scored on a 0–2 scale and summed to generate a composite score. Scoring was performed by a blinded observer.

Open field rearing

Rearing behavior was quantified as a measure of hindlimb weight-bearing [12]. Mice were observed in the home cage for 5 minutes, and the number of vertical rearing events (both forepaws elevated) was recorded. Measurements were obtained prior to surgery and at 9 weeks post-surgery and expressed as count difference from baseline.

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Histological analysis

At study endpoint, mice were euthanized by CO_2 inhalation, and hind limbs were fixed, decalcified, paraffin-embedded, sectioned (4 μm), and stained with hematoxylin and eosin and Safranin O. Slides were scanned using a Nanozoomer Digital Pathology slide scanner (Hamamatsu, Bridgewater, NJ) with a 20× objective. Images were captured from scanned slides. Original magnification is indicated, and a scale bar is provided.

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 9.5.1 (GraphPad Software, San Diego, CA, USA). Comparisons between experimental groups were performed using two-way analysis of variance (ANOVA), followed by Dunn's post hoc test for multiple comparisons where appropriate. Statistical significance was defined as $P < 0.05$. Data distributions were evaluated for normality prior to analysis using GraphPad Prism's built-in normality tests to confirm the suitability of parametric analyses.

Results

Structural features of OA in aged mice

Histological analysis of operated joints demonstrated features consistent with OA, including loss of cartilage integrity, reduced Safranin O staining, and osteophyte formation (Figure 2). These findings confirm that DMM surgery in aged mice produces characteristic structural features of OA.

Functional decline following OA induction

Functional assessment revealed clear behavioral impairments following OA induction. Composite ethogram scores were elevated in OA mice relative to baseline, reflecting reduced activity, altered gait, and impaired overall condition (Figure 3A). Consistent with impaired weight-bearing, rearing behavior was reduced following DMM surgery, with mice exhibiting fewer vertical movements compared to baseline levels (Figure 3B).

Discussion

In this study, we establish a geriatric murine model of OA using DMM and demonstrate that induction of joint instability in aged mice produces both structural and functional features consistent with disease. Histological evaluation confirmed lesions of the cartilage and joint remodeling that have been previously described in mice following

Table 1. Ethogram parameter scoring system.

Parameter		Score
Nest Quality	Built-up nest; fully or partially domed	0
	Nestlet used but nest is flat	1
	Nestlet is less than 50% used in a span of 2 days	2
General Activity	Bright and alert	0
	Quiet but alert to handler, rouses and explores when cage lid is off	1
	Quiet and not alert to handler or manipulation of cage; does not rouse unless touched	2
Rearing	Rearing activity comparable to cage-mates, rears to reach food and explore	0
	Rearing activity has reduced frequency or shorter duration, or rearing favors non-surgery leg	1
	Rearing activity is not seen at all during period of observation	2
Gait	Normal	0
	Toe-touching or mild lameness on affected leg when moving	1
	Not bearing any weight on affected leg	2
Grooming Quality	Normal	0
	Mouse is slightly piloerect or ungroomed	1
	Mouse is completely piloerect and ungroomed or mouse is slightly piloerect and affected leg is overgroomed	2
Mouse Grimace Score	Average score = 0, total score = 0–2	0
	Average score = 1, total score = 3–7	1
	Average score = 2, total score = 8–10	2
Kyphosis	None	0
	Mild	1
	Severe	2
BCS	3+	0
	2	1
	1	2
Hydration	Adequate	0
	1–5% dehydrated	1
	6–10% dehydrated	2
Weight Loss	0–5% from baseline	0
	5–14% from baseline	1
	15–19% from baseline	2

surgical destabilization [13], while behavioral assessments revealed increased ethogram scores and reduced rearing activity, indicating impaired mobility and weight-bearing capacity. Together, these findings support the utility of this model for capturing clinically relevant manifestations of OA in an aging context.

A key strength of this model is the incorporation of biological aging, which more closely reflects the clinical population affected by OA. While DMM is widely used to model post-traumatic OA, it is most often performed in young animals that lack the senescent, inflammatory, and repair-impaired joint environment characteristic of aging. Aging fundamentally alters cartilage homeostasis, matrix turnover, and inflammatory signaling, thereby shaping both disease susceptibility and progression [4]. By applying DMM in geriatric mice, this model provides a more physiologically relevant platform for studying OA pathobiology and therapeutic response.

Importantly in this study, an ethogram was used as a functional assessment. Functional impairment was observed following OA induction, extending beyond structural characterization. Preclinical OA studies frequently rely on histological endpoints, which do not fully capture the functional consequences of disease. Importantly, optimal positioning of joints for histology is crucial to allow for critical scoring using methods such as the OARSI scoring system [14] across joint compartments, and can be performed only at the study endpoint. In contrast, measures such as rearing behavior and composite welfare scoring provide added insight into mobility, weight-bearing, and overall condition and can be performed at multiple time points during the study [15]. The observed decline in rearing activity is consistent with reduced hindlimb loading and pain-associated behavioral changes described in murine OA models [11]. These findings highlight the value of incorporating functional readouts into preclinical studies, particularly in the context of aging where functional decline is a central feature of disease.

The translational relevance of this model is further underscored by its potential utility in evaluating emerging non-

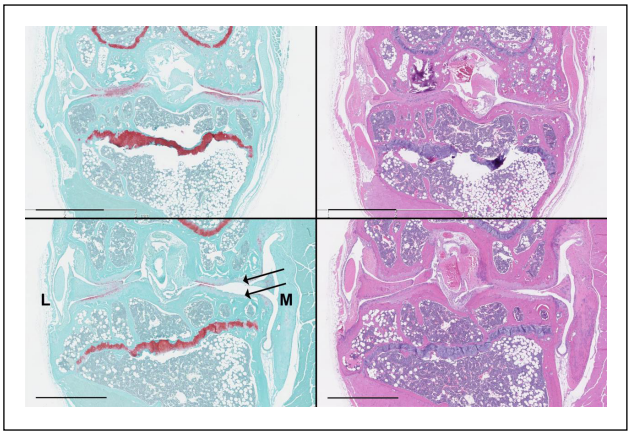

Figure 2. Representative Safranin O/Fast Green (left) and hematoxylin and eosin (H&E, right) stained coronal (frontal) sections of knee joints from sham-operated (top) and DMM-operated (bottom) aged mice. DMM-operated joints demonstrate loss of Safranin-O staining, cartilage fibrillation, and cartilage erosion involving the medial tibial plateau (bottom arrow) and medial femoral condyle (top arrow) as well as osteophyte formation at the medial aspect of the stifle. Scale bar = 1 mm. Images were acquired at 2.5× magnification. "M" indicates medial; "L" indicates lateral.

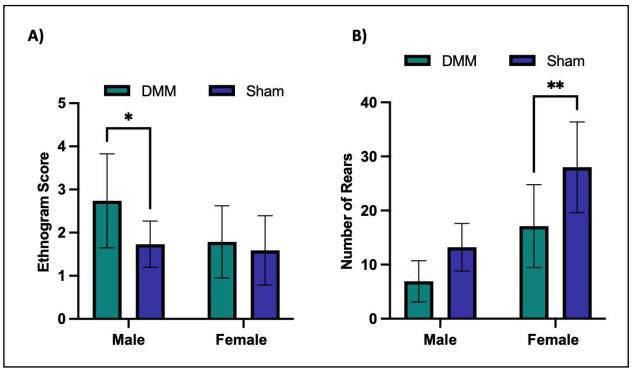

Figure 3. Functional assessments. **(A)** Composite ethogram **(B)** Rearing behavior. Two-way analysis of variance with post hoc Dunn's test for multiple comparisons at 0.05 significance level. Analyses and data visualization were performed in GraphPad Prism 9.5.1. $^{*}P < 0.05$, $^{**}P < 0.01$.

surgical therapies. There is increasing interest in intra-articular interventions, including biologics, biomaterials, and peptide-based therapies, aimed at modifying the joint microenvironment and promoting repair [16-18]. Because treatment responses may differ substantially in aged versus young tissue, a geriatric model provides a more appropriate platform for preclinical evaluation of candidate OA therapies.

This study has several limitations. Although sham-operated animals were included as surgical controls for the behavioral assessment, quantitative OARSI histopathology scoring of all animals was not performed, precluding statistical comparison of cartilage degeneration between sham and DMM-operated groups. Histological evaluation in this study was used to confirm the presence of characteristic OA changes following DMM surgery, but future studies could incorporate standardized OARSI scoring to enable quantitative assessment of disease severity, comparison of histologic changes with functional assessment scores, and direct comparison between experimental groups. Prior studies have demonstrated minimal cartilage degeneration following sham procedures in young and old DMM models, supporting the interpretation that the observed changes reflect OA pathology [7, 13]. Additionally, behavioral assessments were limited to a subset of functional measures, and future studies incorporating longitudinal and multimodal phenotyping will further strengthen the model. Another limitation is that baseline joint status was not assessed prior to DMM surgery, preventing direct evaluation of pre-existing age-related osteoarthritic changes in individual animals. Although histological assessment before surgery is not feasible in the same mice, future studies could incorporate noninvasive imaging or age-matched baseline cohorts to better distinguish spontaneous age-related degeneration from surgically induced pathology. C57BL/6J mice may develop spontaneous OA with advancing age; however, this process is variable and generally less severe than the characteristic lesions produced by DMM surgery [19]. A previous study has shown very mild, non-structural spontaneous OA cartilage changes in 19-month-old C57BL/6 mice [13].

Conclusions

In summary, we present a geriatric DMM mouse model that reproduces structural and functional features consistent with OA in the context of aging. By integrating biological aging and functional assessment into a well-established surgical model, this platform provides a practical framework for studying age-associated joint. While additional studies to further refine and characterize the functional assessment in the context of quantitative histopathological assessment and baseline joint characterization will further strengthen the model, our findings support the use of aged animal models for improving the translational relevance of preclinical OA research.

Declarations

Availability of data and materials: Not applicable.

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Conflicts of interest: Warren Ladiges is a member of the editorial board of *Aging Pathobiology and Therapeutics*. The authors declare that they have no conflicts and were not involved in the journal's review or decision regarding this manuscript.

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