



Review of the Development of Meniscus Centralization

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Abstract

Purpose of Review With an aging population, extending healthy life expectancy is a global challenge. Maintaining healthy knee joint function is one of the essential factors to preserve the ability to walk and extend healthy life expectancy. Meniscus centralization was introduced in 2012 as a procedure for meniscus extrusion, one of the causes of knee osteoarthritis (OA). Initially, it was performed only for lateral meniscus (LM) extrusion, and favorable 2-year results were reported in 2016. Gradually, basic studies supporting the effectiveness of meniscus centralization have been reported, and it has also been performed for medial meniscus (MM) extrusion, with some positive results reported. Although the surgical procedures vary among the institutions, the basic concept is to reattach the loosened meniscotibial ligament to the edge of the tibial plateau to re-tension it. This review will discuss the history of development and the current status of meniscus centralization.

Recent Findings Current research shows that meniscus centralization is not performed in isolation but is often used as an augmentation along with the conventional repair of meniscus injuries, particularly posterior root tears. Biomechanical studies demonstrated that MM centralization with a posteromedial anchor can better restore meniscus function.

Conclusion Despite its relatively short publication history of just over ten years, meniscus centralization has shown potential as a treatment to curb the progression of knee OA and extend a healthy life. While more evidence is needed, this conclusion underscores the promising role for meniscus centralization, making it a topic of significant interest for knee surgeons and researchers.

Keywords Meniscus centralization · Meniscus extrusion · Capsular advancement · Knee functional preservation · Clinical outcome · Basic research

Introduction

Meniscus extrusion is caused by disruption of the hoop structure of the meniscus. It is often associated with a posterior root or radial tear that disrupts the hoop, or secondary to a degenerated meniscus, postoperative meniscectomy, and after meniscopectomy for the discoid lateral meniscus (DLM). LM extrusion is particularly common after resection of the LM due to the fragility of the structure, which has a popliteal hiatus [1, 2]. Meniscus extrusion correlates with the pathology of knee OA [3, 4] and, in some cases, progresses rapidly [5].

Meniscus centralization is a surgical procedure in which an anchor is used to centralize the extruded meniscus [6–8]. When a partial meniscectomy is performed, the hoop function is easily disrupted, resulting in meniscus extrusion [1]. DLM is often associated with abnormal collagen fiber alignment and degeneration of the remaining meniscus, resulting in postoperative meniscus extrusion and rapid OA progression [5]. Biomechanical studies of meniscus centralization have confirmed that this technique can restore the load-distribution function of the meniscus [9, 10], and it has also been shown to improve the knee joint rotational laxity caused by LM dysfunction accompanied with anterior cruciate ligament reconstruction (ACLR) [11, 12]. Recently, it has often been performed as an augmentation after repairing the injury that caused the extrusion by conventional suturing procedures.

Meniscus centralization is indicated not only for LM extrusion but also for MM extrusion. In recent years, attention has been focused on knee joint functional preservation treatment in the early OA stage, many of which are

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associated with meniscus tear or meniscus extrusion resulting in meniscus dysfunction. Although advances in surgical techniques and devices have made it possible to repair posterior root and radial tears [13, 14], meniscus extrusion is not fully addressed by isolated repair of radial or root tears [15]. In addition, postoperative meniscus extrusion significantly increases when more sutures are utilized for the inside-out meniscus suture technique [16]. In such cases, the combined use of MM centralization supports the effect of the conventional method, and good clinical results have been reported. Recently, an anchoring technique of the posteromedial aspect of the MM, which is most frequently extruded, has been reported [17], and basic studies have verified this technique's effectiveness in restoring meniscus function.

The primary purpose of this review is to summarize the articles published to date on meniscus centralization and to clarify the characteristics of this treatment and what is known about it.

Meniscus Centralization in the Early Days

The first report on meniscus centralization was published in 2012 by Koga et al. in a technical note [6] (Fig. 1). This report introduced it as a method for repairing LM extrusion and preventing extrusion after discoid lateral meniscus (DLM) saucerization. The procedure involved using the Jugger Knot Soft Anchor (Biomet, Warsaw, IN) with the anchor placed just anterior to the popliteal hiatus, a Micro Suture Lasso Small Curve with Nitinol Wire Loop (Arthrex, Naples, FL) is passed from superior to inferior between the meniscus and the capsule to relay the anchor thread. This procedure is performed twice to create a mattress suture. Another anchor was placed 1 cm anterior to the first anchor, and the same procedure was performed to push back the extruded mid-body of LM into the appropriate position (Fig. 2).

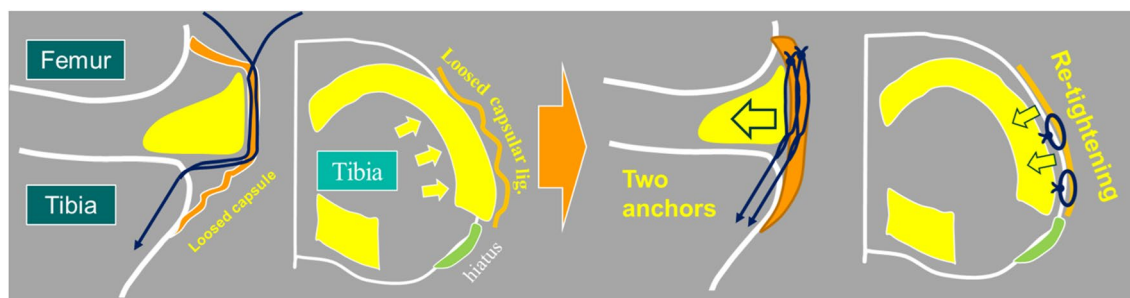


Fig. 1 Schematic drawing of the meniscus centralization

Various Applications of Meniscus Centralization

Although Ozeki et al. reported a capsulodesis method to augment the repair of Wrisberg variant DLM [18] in 2022, there have been mainly reports of meniscus centralization for MM extrusion, one of the causes of knee OA since 2017. This is mostly in conjunction with the repair of medial meniscus posterior root tears (MMPRT), a common cause of MM extrusion. In 2017, Koga et al. reported on MMPRT pull-out repair with MM centralization as an augmentation [19]. Later, in 2018, Nakamura et al. reported MM centralization combined with medial-opening wedge high tibial osteotomy (MOWHTO) for MMPRT cases along with repair [20].

On the other hand, the anchor placement tends to be anterior because it must be avoided to hurt the MCL when MM centralization is performed the same way as LM centralization. In 2021, Koga et al. reported a new method of meniscus centralization [21••], in which an accessory portal is created at the posteromedial aspect of the MM, where the meniscus is most vulnerable to extrusion. Placing an anchor in the posteromedial of the MM, which is the most prone to meniscus extrusion, has been used to achieve more effective centralization and augmentation. The unique feature of this method is the use of a 1.8-mm Knotless FiberTak Soft Anchor (Arthrex) to bridge the repair suture between the anchors (Fig. 3). This method allows for horizontal plane centralization, a more robust centralization force than the point centralization used in the first reported meniscus centralization.

At the same time, Leafblad et al. and Wu et al. reported similar methods [22, 23]. They similarly placed 2–3 anchors, including the MM posteromedial anchor, but with a mattress suture technique at the repair suture of each anchor.

Mameri et al. reported meniscus centralization without anchors [24], in which a tibial tunnel is created at the posteromedial tibial edge using an aiming guide. They passed a suture tape through the margin of the meniscus and pulled out.

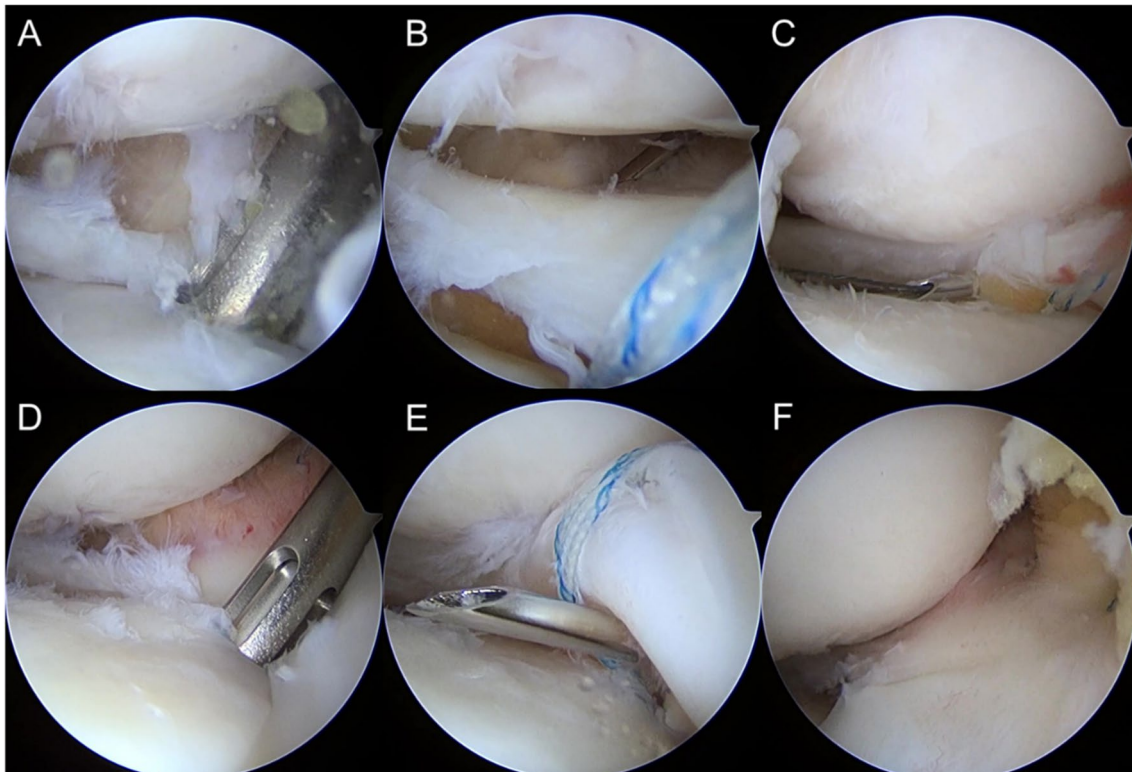
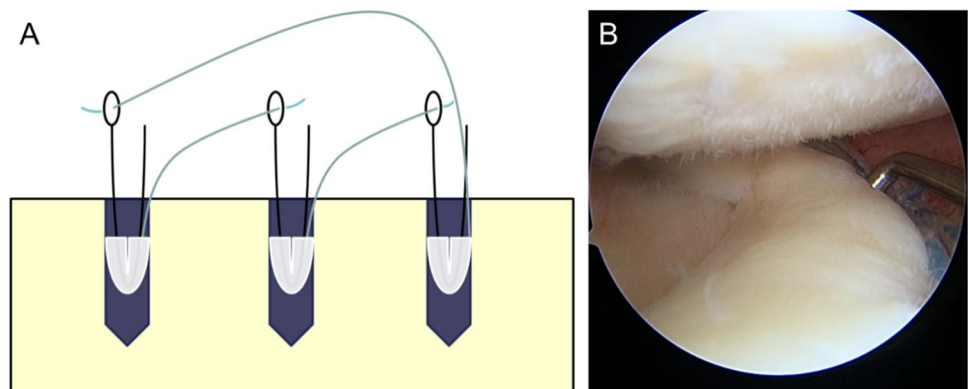


Fig. 2 LM centralization procedures (Left knee). **A** Insert the first anchor just anterior to the popliteal hiatus. **B, C** A suture passer is inserted through the synovium between the LM and the capsule and passes through from the superior to the inferior of the LM. **D** The

second anchor is inserted 1 cm anterior to the first. **E**: A suture passer is inserted similarly, relaying the thread. **F** Complete the two mattress sutures

Fig. 3 Novel MM centralization. **A** Schematic diagram. Relaying the repair suture (blue) using the adjacent anchor shuttling suture (black) allows extensive centralization of the meniscus. **B** After centralization. The MM has been repositioned in the anatomic native location



Various meniscus centralization techniques for MM extrusion have been reported (Table 1), all with the same basic concept. Anchors are placed at the margin of the tibial articular surface, anterior and/or posterior to the MCL in the area corresponding to the mid-body of the meniscus, and anchor threads are passed between the meniscus and the capsule and tightened to achieve centralization.

Clinical Outcome

Meniscus Centralization was a revolutionary method to address meniscus extrusion that could not be previously treated, but has been performed only at a few institutions. In 2016, Koga et al. reported clinical results two years after LM centralization [7]. They reported favorable

Table 1 Various centralization procedures

Procedures	MM/LM	Anchor	Relay	Anchor location	Features
Koga et al. (2012)	LM	JuggerKnot ×2	Micro Suture Lasso	1. just anterior to popliteal hiatus 2. 1 cm anterior to the 1st	- First report
Koga et al. (2017)	MM	JuggerKnot ×2	Micro Suture Lasso	1. as posterior as possible in MTP 2. 1 cm anterior to the 1st	- Combined with MMPRT repair as an augmentation
Nakamura et al. (2018)	MM	JuggerKnot ×1	Accu-Pass	The medial edge of the MTP (no further description)	- Combined with MMPRT repair as an augmentation and MOWHTO
Koga et al. (2021)	MM	Knotless FiberTak ×3	Scorpion FiberLink Micro Suture Lasso	1. Posteromedial in MTP 2. 1 cm anterior to the 1st 3. 1 cm anterior to the 2nd	- 1st anchor inserted via the low posteromedial portal - Realizes the horizontal centralization
Leafblad et al. (2021)	MM	Knotless FiberTak ×2–3	Scorpion with FiberLink Micro Suture Lasso	1. Posteromedial in MTP 2. 1 cm anterior to the 1st 3. 1 cm anterior to the 2nd	- Mattress suture on each anchor thread
Wu et al. (2022)	MM	Knotless BioComposite SutureTak ×2	Scorpion with FiberWire QuickPass Lasso	1. Posterior to the MCL 2. Anteromedial (not described)	- Anchors placed 3 mm in from the anteromedial tibial rim
Ozeki et al. (2022)	DLM	Knotless FiberTak ×3	No relay	1. Posteromedial in MTP 2. 1 cm anterior to the 1st 3. 1 cm anterior to the 2nd	- Capsulodesis from outside - Secure the meniscotibial ligament horizontally - Possible under direct view
Nakamura et al. (2023)	MM	JuggerKnot ×2	Accu-Pass	1. Posteromedial in MTP 2. 1 cm anterior to the 1st	- Bridging suture between anchors for horizontal centralization
Mameri et al. (2023)	MM	No anchor	2.7-mm cannulated sheath Self-retrieving suture device	Transtibial tunnel in MTP	- Horizontal mattress suture by pull-out technique

MM medial meniscus, *LM* lateral meniscus, *DLM* discoid lateral meniscus, *MTP* medial tibial plateau, *MMPRT* medial meniscus posterior root tear, *MOWHTO* medial open-wedge high tibial osteotomy

clinical outcomes of centralization for LM extrusion and DLM, with no apparent adverse events. Magnetic resonance imaging (MRI) showed reduced LM extrusion and radiographic findings showed a widening of the lateral joint space (LJS). In DLM, they noted that the LJS was maintained after the saucerization. On the other hand, Ohnishi et al. reported no significant difference in clinical outcomes with or without meniscus centralization in the saucerization for DLM cases younger than 13 years [25].

Koga et al. reported capsular advancement, which applies the meniscus centralization technique to OA of the lateral compartment with the meniscus defect after LM meniscectomy [26]. The osteophyte is resected, and the meniscotibial capsule is released to allow mobility of the surrounding synovial membrane and the capsule, and the anchor thread of meniscus centralization is passed widely to the surrounding synovial membrane to pull the synovial tissue into the

weight bearing area as a substitute for the meniscus. They also reported a favorable two-year clinical outcome without significant adverse events, the amount of meniscus extrusion was suppressed on MRI, and radiographic findings showed maintaining LJS widening.

The clinical results of MM centralization have been reported mainly as a treatment option for medial OA with MM extrusion or MMPRT. MM centralization is not evaluated as a stand-alone procedure but as an augmentation to the surgical treatment of each pathology, and the clinical results are analyzed.

Katagiri et al. retrospectively evaluated MOWHTO alone for medial OA without MM extrusion and combined MOWHTO and MM centralization for OA with MM extrusion. MOWHTO was performed aiming at neutral alignment (%MA = 57) and reported similar clinical outcomes up to 3 years postoperatively with no significant differences. Wang et al. reported a

Table 2 Postoperative outcome of meniscus centralization

Study	Study design F/U period	MM/LM	Centralization procedure	Post-operative management	Outcome
Koga et al. (2016)	Case series 21 knees F/U minimum 2y Avg. age: 29yo M/F= 11/10 LM extrusion: 9 + ACLR 6 + Mosaicplasty 1 + Cyst resection 1 Primary DLM: 12	LM	- JiggerKnot×2 - Micro Suture Lasso - Posterior anchor: placed just anterior to the popliteal hiatus - Anterior anchor: placed 1 cm anteriorly	No limit ROM -4w FWB with immobilizer 2.5 M- Running 3 M- Deep squatting 4 M- Full activity	- No ROM-limited cases - Revision 1 - McMurray test positive (click, no pain) 1 - Significant improvement of Lysholm score, Patient satisfaction, Sports performance level, and KOOS - Lateral joint space increased in the extrusion group and maintained in both groups until postoperative 2y on radiographic assessment - LM extrusion width decreased and main- tained until postoperative 1y on MRI - No significant differences in IKDC scores and Lysholm scores at the final follow-up between repair and centralization - Clinical outcomes of saucerization for DLM are better in < 13y group, with or without centralization
Ohnishi et al. (2018)	Retrospective 56 knees F/U minimum 2y Age < 13y 18 M/F=9/7 Saucerization 8 + repair 2 + centralization 1 Age ≥ 13y 38 M/F= 19/17 Saucerization 18 + repair 5 + centralization 8	DLM	- Suturefix ultra × 1 - Accu-Pass - Anchor placed just anterior to the popliteal hiatus	No limit ROM -3w NWB 5w- FWB 3 M- Deep squatting	- No revision cases during 2y F/U - DFO performed 3y after surgery 1 - Significant improvement of Lysholm score, Subjective recovery, Sports performance level, IKDC subjective score, and KOOS - Swelling 4, McMurray test (pain) 2, McMurray test (click) 4 were remaining - Lateral joint space increased in the extrusion group and maintained in both groups until postoperative 2y on radiographic assessment - LM extrusion width decreased and maintained until postoperative 1y on MRI - 10 cases showed meniscus tissue-like regeneration
Koga et al. (2020)	Case series of lateral OA with LM defect 27 knees F/U minimum 2y M/F= 12/15 Avg. age: 43yo + Microfracture 7 + ACLR 1 Previous subtotal meniscectomy 20 - DLM 7	LM	- Capsular advancement - JiggerKnot×2 - Micro Suture Lasso - Posterior anchor: placed just anterior to the popliteal hiatus - Anterior anchor: placed 1 cm anteriorly - Additional suture between remain- ing LM and advanced synovium	No limit ROM -4w FWB with immobilizer 4-6w PWB 3 M- Deep squatting 6 M- Full activity	- No revision cases during 2y F/U - DFO performed 3y after surgery 1 - Significant improvement of Lysholm score, Subjective recovery, Sports performance level, IKDC subjective score, and KOOS - Swelling 4, McMurray test (pain) 2, McMurray test (click) 4 were remaining - Lateral joint space increased in the extrusion group and maintained in both groups until postoperative 2y on radiographic assessment - LM extrusion width decreased and maintained until postoperative 1y on MRI - 10 cases showed meniscus tissue-like regeneration

Table 2 (continued)

Study	Study design F/U period	MM/LM	Centralization procedure	Post-operative management	Outcome
Katagiri et al. (2021)	Comparing OWHTO ± MM centralization retrospectively 39 knees F/U minimum 2y MOWHTO 18 +centralization 21 MOWHTO aimed %MA = 57	MM	- Juggerknot × 2 - Micro Suture Lasso - Posterior anchor: placed as posterior as possible - Anterior anchor: placed 1 cm anteriorly	No limit ROM -2w 1/3–2/3PWB 2w- FWB 3 M- Running 6 M- Full activity (depends on bone union)	- No significant difference between the MOWHTO group and centralization group in NRS and patient satisfaction score until postoperative 3y - Medial joint space width was significantly larger in the centralization group than in the MOWHTO group in postoperative 2y
Mochizuki et al. (2021)	Case series of MMPRT repair + centralization 26 knees F/U minimum 2y M/F = 8/18 Avg. age: 62.1yo	MM	- Suturefix ultra × 2 - Micro Suture Lasso - Posterior anchor: placed slightly posterior to the center of MTP - Anterior anchor: placed 10–15 mm anteriorly - MMPRT repaired by pull-out technique	- 1w Fixed ROM at 20-degree flexion 1w- No limit ROM -2w NWB 2-4w PWB 4w- FWB 4 M- Running 6 M- Full activity	- Significant improvement of Lysholm score and KOOS - MM extrusion distance significantly decreased - OA progression 1 - TKA 2
Wang et al. (2023)	Case series of MOWHTO + MM centralization 24 knees 2y F/U all cases M/F = 11/13 Avg. age: 56yo MOWHTO aimed %MA = 60	MM	- Anchor × 2 - No precise description of the devices and anchor placement site	N/A	- Significant improvement of Knee score and Functional score
Krych et al. (2023)	Case series of MOWHTO + MM centralization 25 knees F/U average 2y M/F = 6/19 Avg. age: 50.1yo	MM	- Knotless FiberTak × 2 - Micro Suture Lasso - Posterior anchor: placed posteromedial aspect of MTP - Repeated anteriorly 1 or 2 more times - MMPRT repaired by pull-out technique	-4w NWB and limited ROM by 90 degrees of flexion 4-6w FWB allowed as tolerated 8-16w Full activity	- Significant improvement of VAS pain, IKDC score, and KOOS - No significant OA progression - No revision nor TKA cases

MM medial meniscus, LM lateral meniscus, DLM discoid lateral meniscus, MTP medial tibial plateau, MMPRT medial meniscus posterior root tear, ROM range of motion, NWB non-weight bearing, PWB partial-weight bearing, FWB full-weight bearing, IKDC International Knee Documentation Committee, KOOS Knee injury and Osteoarthritis Outcome Score, DFO distal femoral osteotomy, MRI magnetic resonance imaging, TKA total knee arthroplasty, NRS numerical rating scale, VAS visual analog scale, OA osteoarthritis

Table 3 Basic research for meniscus centralization

Study	MM/LM	Subject	Findings
Ozeki et al. (2017)	MM	Rat	<ul style="list-style-type: none"> - Histological and macroscopic study of articular cartilage - MM extrusion model: induced by the release of the anterior synovial capsule and the transection of the meniscotibial ligament model - Centralized by a pull-out suture technique - Centralization delayed cartilage degeneration
Nakamura et al. (2019)	LM	Pig	<ul style="list-style-type: none"> - Biomechanical study by robotic testing - LM extrusion model: massive meniscus defect in the middle segment of LM accompanied with ACL reconstruction - Centralized by 2 anchors [6] - Centralization improved the residual rotational laxity of the ACL reconstructed knee
Daney et al. (2019)	MM	Human	<ul style="list-style-type: none"> - Biomechanical study by dynamic tensile testing machine (Instron) with tibiofemoral contact pressure sensors - MM extrusion model: creating MMPRT and repairing anatomically and non-anatomically - Centralized by a pull-out suture technique - Extrusion was maximum in the posterior border of the MCL, and centralized there works best
Kubota et al. (2020)	LM	Pig	<ul style="list-style-type: none"> - Biomechanical study by a universal tester with pressure sensors and markers in various knee angles - LM extrusion model: remove 1 cm of the posterior root and cut the posterior capsule - Centralized by 2 anchors [6] - Centralization reduced the amount of extrusion and restored the load distribution function in the anterior and middle LM but not in the posterior LM
Ozeki et al. (2020)	LM	Pig	<ul style="list-style-type: none"> - Biomechanical study by a universal tester with pressure sensors and markers - LM extrusion model: remove 1 cm of the posterior root and cut the posterior capsule - Centralized by 2 anchors [6] - Centralization reduced the amount of extrusion and restored the load distribution function close to the intact knees
Kohno et al. (2021)	LM	Pig	<ul style="list-style-type: none"> - Biomechanical study by a universal tester with pressure sensors - LM extrusion model: remove 1 cm of the posterior root and cut the posterior capsule - Centralized by 1 or 2 anchors [6] with or without capsular advancement - Centralization using 2 anchors and additional capsular advancement best restored the load distribution function
Nakamura et al. (2021)	LM	Human	<ul style="list-style-type: none"> - Biomechanical study by robotic testing - LM extrusion model: meniscus defect (20% of LM anteroposterior length) at the popliteal hiatus - Centralized by 2 anchors [6] - Centralization improved the residual rotational laxity of the ACL reconstructed knee
Debieux et al. (2021)	MM	Human	<ul style="list-style-type: none"> - Biomechanical study by material testing system machine with pressure sensors - MM extrusion model: pulled by the sutures passed in the peripheral legion of the meniscus, and meniscotibial ligament released gradually if needed - Capsulodesis by 2 anchors in the medial edge of the tibial plateau, 1 cm distal to the joint, horizontal mattress - Centralization restored the medial compartment contact area to an intact state
Ueki et al. (2022)	MM	Human	<ul style="list-style-type: none"> - Biomechanical study by robotic testing - MM extrusion model: defect in the MM posterior root accompanied with ACL reconstruction - Centralized by 2 anchors - Centralization decreased the extrusion of the MM and restored the anterior tibial translation
Amano et al. (2023)	MM	Pig	<ul style="list-style-type: none"> - Biomechanical study by a universal tester with pressure mapping sensors - MM extrusion model: creating MMPRT and repairing non-anatomically - Centralized by 2 or 3 anchors horizontally [21••] - Centralization with 3 anchors best-restored load distribution function
Morales-Avalos et al. (2023)	LM	Pig	<ul style="list-style-type: none"> - Biomechanical study by a universal tester with markers for measuring extrusion distance - LM extrusion model: release of meniscotibial ligament and menisconfibular ligament - Centralization by 3 anchors for meniscotibial and menisconfibular ligament repair, and capsulodesis by pull-out technique - Both centralization and capsulodesis reduced LM extrusion

MM medial meniscus, *LM* lateral meniscus, *DLM* discoid lateral meniscus, *MTP* medial tibial plateau, *MMPRT* medial meniscus posterior root tear, *ACL* anterior cruciate ligament

case series of MOWHTO and MM centralization for varus knee with MM extrusion with good 2-year results [27].

For MMPRT, Mochizuki et al. reported a case series of 26 cases in 2021 [28], in which MMPRT was performed with pull-out repair and MM centralization as augmentation, with good clinical results two years postoperatively. Krych et al. reported a similar series of 25 cases with good clinical outcomes averaging two years postoperatively. In that study, they used 2–3 anchors for meniscus centralization and approaching the posterior medial aspect, which is unique [29]. While early results are promising, prospective studies or RCTs have yet to be conducted, and no reports of long-term results have been provided. Therefore, further investigation is warranted (Table 2).

Basic Research for Meniscus Centralization

After good clinical results were reported in 2016, basic studies gradually reported supporting meniscus centralization's effectiveness (Table 3). In 2017, Ozeki et al. established an MM extrusion model by releasing the anterior synovial capsule and transecting the meniscotibial ligament of the MM in rats. They reported that MM centralization suppresses MM extrusion and delays articular cartilage degeneration [30].

Daney et al. reported in human cadavers that the amount of MM extrusion is largest at the posterior margin of the MCL, so putting the anchors for centralization there is more effective [17].

Amano et al. established a porcine MMPRT model. They reported less extrusion and better load distribution with MMPRT repair augmented by MM centralization than with MMPRT repair alone. They revealed that it was more effective with three anchors with the posteromedial anchor than two anchors without it [31•].

Using the porcine LM extrusion model, Kubota et al. and Ozeki et al. found that meniscus centralization reduces the amount of extrusion, improving the load distribution function and the contact pressure near normal. Kohno et al. reported that meniscus centralization with capsular advancement achieves better centralization in the same porcine model [9, 10, 32].

Debieux et al. cut the meniscotibial ligament in a human cadaver to create a model to adjust the amount of MM extrusion. The results showed that more than 4 mm of extrusion reduced the tibiofemoral contact area but improved it by repairing the meniscotibial ligament with capsulodesis [33•].

Morales-Avalos et al. similarly reported in a porcine model that damage to the lateral meniscotibial and meniscofibular ligaments causes LM extrusion and revealed that meniscus centralization or pull-out capsulodesis can improve LM extrusion [34].

Although most of these studies have focused on the load distribution function of the meniscus, several kinematic studies on the knee joint stabilization function of the meniscus have been reported. Nakamura et al. reported that centralization of the LM improved rotational stability in a model

of residual rotational laxity due to LM deficiency accompanied by ACL reconstruction in pig and human cadavers [11, 12•]. Similarly, Ueki et al. reported that MM centralization, accompanied by ACL reconstruction, can improve anterior laxity to normal levels in a human cadaver model of combined ACL injury and MMPRT [35].

Conclusion

The practice of meniscus centralization, while relatively new, has not yet been comprehensively evaluated in terms of its long-term effectiveness. Current clinical outcomes and translational research suggest that meniscus centralization may not function as an independent procedure but could enhance the efficacy of traditional meniscus repair. However, the surgical technique involved in meniscus centralization is notably complex, necessitating further refinement of both methods and devices to facilitate its broader application. There remains a need for future high-quality prospective research and randomized controlled trials (RCTs), to provide stronger evidence. Overall, meniscus centralization represents a promising approach to addressing knee joint dysfunction resulting from meniscus extrusion, playing a critical role in preserving meniscus function and mitigating the progression of osteoarthritis.

Author contributions T.N. wrote the main manuscript and H.K. reviewed the manuscript.

Data Availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Competing Interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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