

Preliminary Results From a US Clinical Trial of a Novel Synthetic Polymer Meniscal Implant

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Background: At least 760,000 outpatient meniscectomies are performed in the United States each year, making this the most common musculoskeletal procedure. However, meniscal resection can alter the joint biomechanics and overload the articular cartilage, which may contribute to degenerative changes and the need for knee replacement. Avoiding or delaying knee replacement is particularly important in younger or more active patients. Synthetic meniscal implants have been developed in an attempt to restore the natural joint biomechanics, alleviate pain and disability, and potentially minimize degenerative changes in patients who require meniscectomy.

Purpose: To evaluate the preliminary results from 2 ongoing trials that are evaluating the safety and effectiveness of a synthetic polymer meniscal implant (NUsurface; Active Implants, LLC).

Study Design: Cohort study; Level of evidence, 2.

Methods: This was a preliminary analysis of the first 100 patients enrolled across 2 studies for 12 months: a single-arm, intervention-only study and a randomized controlled trial comparing the investigational meniscal implant with nonsurgical therapy. There were 65 patients in the implant group (30 randomized) and 35 in the control group. Outcomes included Knee Injury and Osteoarthritis Outcome Score (KOOS) and adverse events (AEs) collected at baseline and follow-up visits of 6 weeks, 6 months, and 12 months.

Results: No statistically significant differences were found in baseline characteristics between the implant and control groups. At 12 months, follow-up KOOS data were available for 87% of the 100 included patients. Significantly greater improvements from baseline were observed in the implant group compared with controls in all KOOS subcomponents, except for symptoms (119%-177% greater improvement at 12 months). AEs were reported at similar rates between the 2 groups, with 12 AEs among 11 patients in the implant group (16.9%) versus 5 AEs among 5 patients (14.3%) in the control group ($P = .99$).

Conclusion: These preliminary results suggest significant improvements in pain and function scores with the implant over nonsurgical therapy and a similar adverse event rate.

Keywords: meniscus; knee; meniscectomy; meniscal injury; meniscal replacement; NUsurface; synthetic meniscal implant

Meniscectomy is the most common outpatient musculoskeletal operation in the United States, with 760,000 procedures performed annually as of 2010.¹⁹ At an average cost of \$3843 per procedure,⁴ this amounts to \$2.9 billion per year in direct health care costs. In general, meniscectomy is effective at relieving pain and symptoms²⁵; however, patients who experience degenerative changes and worse clinical outcomes may have mechanical factors associated with altered joint biomechanics and overloading of the articular cartilage.^{7,12,26,28} Studies have observed that 13% to 76% of patients with previous meniscectomy have

persistent or recurrent pain and symptoms, and 5% to 36% are not satisfied with the outcome.^{8,20,38} These high rates may reflect a need for more careful patient selection when considering meniscectomy.²

After partial or total meniscectomy, the remaining treatment options are very limited for patients with persistent or recurrent pain. Current standards of care include nonsurgical interventions, such as intra-articular injections, unloading braces, and physical therapy. Although some patients respond to nonsurgical care, many seek surgery to alleviate their pain and restore function, as evidenced by 20% to 30% crossover from physical therapy to meniscectomy within 6 to 14 months.^{18,22,24}

The general goal of surgery is to alleviate pain and symptoms and to restore function, but the current surgical options

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for patients who have had meniscectomy are significantly limited. Repeat meniscectomy further decreases the remaining meniscal tissue. More extensive meniscal resection is associated with increased contact pressure on the articular cartilage,¹⁶ worse patient-reported outcomes for pain or function (eg, Lysholm score), and greater degeneration seen on radiographs.^{1,6,13,29,33} Meniscal allograft transplantation is used to restore function by providing mechanical support similar to that of the native meniscus, but the specific patient indications and surgeon experience must be carefully considered.¹⁷ Allografts also undergo remodeling after implantation, causing shrinkage and reduced mechanical strength.^{30,31,40} By 10 and 20 years after transplant, allograft failure rates exceed 25% and 60%, respectively, with the risk of failure 2.3 times greater in patients at least 35 years of age.⁴¹ Finally, unicompartmental knee arthroplasty (UKA) or total knee arthroplasty (TKA) is generally not indicated in this population, considering that >80% of patients who receive partial meniscectomy are younger than 65 years.¹⁹ The lifetime risk of TKA revision exceeds 35% for younger (<60 years) male patients and 15% to 20% for younger female patients.⁵ Considering the limitations of each of these surgical approaches, an apparent treatment gap exists for patients who are in pain after meniscectomy and do not respond to nonsurgical care.

To address this treatment gap, a polymeric medial meniscal implant was developed that closely mimics the physical characteristics of the natural meniscus and has been shown to dissipate peak contact stresses in the meniscus-deficient knee through cadaveric studies.^{11,15,27,37,42} We hypothesized that this implant would improve patient-reported outcomes of pain and function when compared with those of a nonsurgical control group. This cohort analysis examined the preliminary results of 2 ongoing clinical trials that are evaluating the safety and effectiveness of this polymeric medial meniscal implant in symptomatic patients who have had meniscectomy.

METHODS

Study Design

This cohort analysis evaluated patients in the MERCURY study group, which comprises a cohort of patients treated with the meniscal implant (NUsurface Meniscus Implant; Active Implants LLC) and a cohort treated with nonsurgical care. These patients are enrolled in 2 ongoing clinical trials studying the meniscal implant. The “Verifying the Effectiveness of the NUsurface System” study (VENUS; ClinicalTrials.gov: NCT02108496) is a randomized controlled clinical trial comparing the medial meniscal implant (n = 61) with nonsurgical care as the control (n = 66). The “Safety Using NUsurface” study (SUN; ClinicalTrials.gov: NCT02483988) is a single-arm study examining the safety and effectiveness of the medial meniscal implant (n = 115). For each study, institutional review board approval was obtained from all study sites before recruitment of patients, and patients gave written informed consent for participation before enrollment.

Patient Population

As noted, the VENUS trial is a prospective, randomized controlled trial comparing the meniscal implant (intervention) with nonsurgical therapy (control). The control group treatment regimen included weight loss programs, activity restrictions, bracing, physical therapy, drugs, cortisone injections, and/or hyaluronic acid injections. In the VENUS trial, eligible patients were randomized in a 1:1 ratio at 1 of 10 study sites, with no one site enrolling >35% of the total number of patients. The SUN clinical trial is a single-arm study using the identical device, methods of evaluation, and follow-up times, but it does not have a control group. The 2 studies combined (MERCURY study group) have 8 common inclusion criteria and 35 common exclusion criteria. The 8 common inclusion criteria and 6 of the most important exclusion criteria are listed in Table 1. The VENUS trial had 1 additional inclusion criterion that required a patient

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Ethical approval for this study was obtained from Western Institutional Review Board (protocol No. 00249).

TABLE 1
Major Inclusion and Exclusion Criteria for the 2 Clinical Studies^a

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Previous medial meniscectomy as confirmed by diagnostic magnetic resonance imaging and patient history at least 6 months before the start of study treatment • Pain score ≤ 75 on the Knee injury and Osteoarthritis Outcome Score, with 100 being normal • ≥ 2 mm intact meniscal rim and capable of receiving NUsurface device, if used • Age between 30 and 75 years at the start of study treatment • Neutral alignment $\pm 5^\circ$ of the mechanical axis • Willing and able to follow the study protocol • Able to understand and willing and able to sign the informed consent form • Able to read and understand English 	<ul style="list-style-type: none"> • Evidence of Outerbridge grade IV articular cartilage loss on the medial tibial plateau or femoral condyle that could contact the NUsurface implant (eg, a focal lesion >0.5 cm²) • Varus/valgus knee deformity $>5^\circ$ • Knee laxity level $>II$ on the International Cartilage Repair Society evaluation, secondary to previous injury of the anterior cruciate ligament, posterior cruciate ligament, lateral collateral ligament, and/or medial collateral ligament • Patellar compartment pain and/or patellar articular cartilage damage $>grade II$ • Anterior cruciate ligament reconstruction performed <9 months before implantation of NUsurface implant • Excessive obesity (body mass index >32.5)

^aNUsurface Meniscus Implant; Active Implants, LLC.



Figure 1. Synthetic polymer meniscal implant (NUsurface Meniscus Implant; Active Implants, LLC).

to be willing to be entered into either arm of the study because of the randomized study design. The interested reader is referred to ClinicalTrials.gov for the full list of eligibility criteria. A total of 127 patients were enrolled in VENUS between January 21, 2015, and June 12, 2018, and 115 were enrolled in SUN between May 19, 2016, and June 14, 2018. For this preliminary cohort analysis, the first 100 patients who were enrolled in either study for a period of 12 months were included. Analyses were carried out on an as-treated basis.

Synthetic Polymer Meniscal Implant

The synthetic polymer meniscal implant (Figure 1) was developed to treat patients with painful medial knee compartment meniscal deficiencies. The implant is composed of 2 biocompatible polymers: a polycarbonate-urethane matrix, circumferentially reinforced with ultra high molecular weight polyethylene fibers. The device is a flexible, self-centering, nonanchored, discoid-shaped, composite polymeric meniscal replacement implant that is placed directly between the articular cartilage surfaces of the medial femoral condyle and medial tibial plateau of the knee. The implant is nonanchored and partially seated

within the intercondylar notch to improve stability during translation over the tibial plateau, which preserves the natural range of motion and kinematics between the femur and tibia. The synthetic polymer implant closely mimics the biomechanical characteristics of the natural meniscus regarding construction, stiffness, pressure distribution, and hydrophilicity.^{15,27} The design's incorporation of circumferential winding of ultra high molecular weight polyethylene fibers within the polycarbonate-urethane matrix mimics the radial mechanical construction and properties of a healthy meniscus. These design features are intended to help restore the natural biomechanical characteristics of the knee joint by alleviating the excessive loads and non-physiological pressure distributions on the articular cartilage that are associated with a meniscus-deficient knee joint.^{11,15,27,37}

During surgery, trial implants are available to help the surgeon intraoperatively select the best fit and final implant size for each patient. The trial and the final implant are available in 7 sizes, for both the left and the right knees. The use of the meniscal implant has been described in detail previously.^{14,15,27} In brief, the surgical technique is as follows: After first performing an arthroscopic approach to the medial meniscus, the surgeon performs a subtotal meniscectomy, leaving a 2- to 4-mm rim. A careful notchplasty of any osteophytes on the lateral wall of the medial femoral condyle is performed to avoid impingement on the implant. A minimal arthrotomy allows for insertion of the sizing trials and the final implant, which is positioned between the medial tibial and femoral articular cartilage surfaces (Figure 2).

A suggested rehabilitation program was prospectively described in the study protocols. In the implant group, a locking straight-leg knee immobilizer was used during the first 1 week after surgery, and patients were allowed to bear weight as tolerated with a cane or crutches. The patient was instructed to remove the immobilizer for active range of motion exercise 3 or 4 times daily during the first week. Range of motion exercises were progressed during the second week, and the patient was allowed full

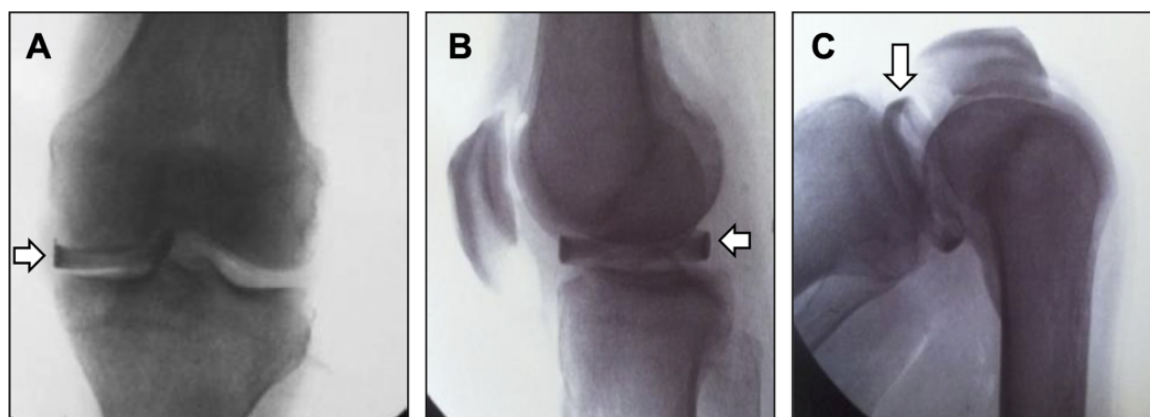


Figure 2. Fluoroscopic images demonstrating the position of the implant from the (A) coronal view in extension and the sagittal view in (B) extension and (C) deep flexion. Arrows indicate the meniscal implant.

weightbearing without assistance, as tolerated. Strengthening exercises, particularly for the quadriceps, were prescribed throughout the rehabilitation protocol. Closed kinetic chain exercises were permitted beyond 2 weeks, and open kinetic chain exercises were permitted beyond 6 weeks. Return to contact sports or other excessive loading activities (eg, running or soccer) was not recommended for participants in either the implant or control group.

Outcomes

Primary outcomes for this preliminary analysis were the baseline, 1.5-month, 6-month, and 12-month scores on each of the 5 separately scored subscales of the Knee injury Osteoarthritis Outcomes Score (KOOS): Pain, Symptoms, Activities of Daily Living (ADL), Sports and Recreation, and Quality of Life (QOL). The KOOS is recognized as a reliable and responsive instrument for measuring patient-reported changes in pain and function and has been validated for multiple surgical operations of the knee, including meniscectomy, anterior cruciate ligament reconstruction, and TKA.^{35,36} Secondary outcomes included adverse events (AEs) through 12 months of follow-up. AE data are currently unaudited and pending adjudication by the principal investigator upon study completion. Additional data collected at baseline included descriptive data, such as age, sex, body mass index, laterality, and time since previous meniscectomy.

Statistical Analysis

At baseline, continuous variables were compared between the treatment groups by use of unpaired *t* test or Mann-Whitney test, and categorical data were analyzed using the Fisher exact test. The frequencies of patients experiencing an adverse event were also compared by use of the Fisher exact test.

Two analyses were performed to evaluate follow-up scores for each of the KOOS subscales: (1) whether the change from baseline was significant at each follow-up

TABLE 2
Summary of Baseline Descriptive Data^a

	Implant Group	Control Group	<i>P</i> Value
No. of patients treated	65	35	
Age, y	48.7 (30-69)	48.1 (31-67)	.77
Sex, % male	63.1	74.3	.28
Index knee, % left	53.8	57.1	.83
Body mass index, kg/m ²	27.0 (20.4-32.5)	26.4 (19.1-32.3)	.42
Baseline KOOS	51.4 (19.4-75)	56.4 (25-75)	.08
Pain score			
Median time since last meniscectomy, mo	40 (7-350)	28 (5-430)	.09

^aData are displayed as mean (range) unless otherwise noted. KOOS, Knee injury and Osteoarthritis Outcome Score.

within each treatment group and (2) whether there was a significantly different change from baseline between the 2 groups at each follow-up. Repeated-measures 2-way analysis of variance (ANOVA) was used to make comparisons in the KOOS over time. The Sidak multiple comparison test was used to analyze differences between baseline and each follow-up time point within each group. When values were missing, a mixed effects model was fit through use of the restricted maximum likelihood method. The change in KOOS from baseline to each follow-up was calculated for each patient, and a second repeated-measures 2-way ANOVA or a mixed effects model was used to evaluate the difference in score change at each timepoint between the 2 treatment groups. The Sidak multiple comparison test was used to analyze differences between treatment groups at each time point. Data were confirmed to follow a normal distribution through use of the D'Agostino and Pearson normality test. For all comparisons, statistical significance was accepted at an alpha level of .05. Statistical analyses were performed using GraphPad Prism Version 7.0 (Graph-Pad Software).

TABLE 3
Summary of Nonsurgical Therapies Used in
the Control Group^a

Nonsurgical Control Treatment	Primary Intervention	Subsequent Intervention(s)
Intra-articular corticosteroid injection	6 (17)	7 (19)
Intra-articular hyaluronic acid injection	15 (43)	17 (46)
Nonprescription drugs, creams, vitamins, or supplements	7 (20)	8 (22)
Prescription or nonprescription NSAIDs	11 (31)	11 (30)
Nonweightbearing exercises	16 (46)	2 (5)
Ice or heat therapy	11 (31)	6 (16)
Compression sleeves, braces, crutches, or canes	17 (49)	15 (41)
Body weight reduction	3 (9)	1 (3)
Limitation in activities	12 (34)	5 (14)
Shoe inserts or other orthotic devices	2 (6)	4 (11)

^aValues are expressed as n (%) (number of patients [frequency per population]). NSAID, nonsteroidal anti-inflammatory drug.

RESULTS

Study Population and Descriptive Data

A total of 18 sites are participating in the VENUS and SUN studies. For this early cohort analysis, 65 patients (30 implant, 35 control) were included from the VENUS trial and 35 patients were included from the SUN trial, which represents the first 100 patients enrolled across both trials. The descriptive data for each of these cohorts are summarized in Table 2. No statistically significant differences were observed between the 2 treatment groups for any descriptive or baseline outcomes, including the time between the initial meniscectomy and study enrollment. Baseline subgroup analysis of the randomized and nonrandomized implant subgroups revealed a significantly higher proportion of male patients in the randomized subgroup (76.7% vs 51.4%; $P = .04$), but all other baseline characteristics were not significantly different between the 2 implant subgroups.

In the nonsurgical control group, the most common primary treatment consisted of assistive devices such as braces, compression sleeves, crutches, or canes (49%) (Table 3). Nonweightbearing exercises (46%) or hyaluronic acid injections (43%) were also common primary interventions. The majority of patients (83%) were treated with >1 therapeutic approach and had subsequent interventions for ongoing symptoms during the first 1 year. The most common follow-up interventions were hyaluronic acid injection (46%), followed by the use of braces, compression sleeves, crutches, or canes (41%).

Patient Follow-up

Among the 100 included patients, 12-month follow-up KOOS data were available for 60 patients in the implant group and

27 patients in the control group (87 total; 87%). A total of 5 patients from the implant group did not have 12-month KOOS data. Further, 3 (4.6%) of those patients exited the study because of device removal, and 2 (3%) patients missed the 12-month reporting window. In the control group, 5 (14.3%) patients exited the study because a surgical intervention was required, 2 (5.7%) were lost to follow-up, and 1 (2.9%) withdrew from the study (Figure 3).

KOOS Values

Pain. Significant improvements over baseline were observed in KOOS Pain values at the 6- and 12-month follow-ups in both the implant group (6 months mean difference [MD]: 24.9, $P < .0001$; 12 months MD: 30.4, $P < .001$) and the control group (6 months MD: 8.7, $P = .007$; 12 months MD: 13.9, $P < .001$). The magnitudes of these improvements were significantly greater in the implant group, by 186% and 119% at 6 and 12 months, respectively ($P < .01$) (Figure 4).

Symptoms. The implant group had significantly improved KOOS Symptoms over baseline at both 6-month (MD: 8.7; $P = .001$) and 12-month follow-ups (MD: 16.1; $P < .0001$) after an initial significant decline at 1.5 months during the postsurgical recovery period (MD: -13.2; $P < .0001$). In the control group, changes in KOOS Symptoms from baseline were statistically significant by 12 months (MD: 8.0; $P = .04$). Aside from the temporary decline in KOOS Symptoms during the postsurgical recovery period in the implant group, the magnitude of KOOS Symptoms improvement was not significantly different from that of controls (Figure 5).

Activities of Daily Living. At both 6- and 12-month follow-ups, statistically significant improvements over baseline for KOOS ADL were observed in both the implant group (6 months MD: 23.2, $P < .0001$; 12 months MD: 26.5, $P < .0001$) and control group (6 months MD: 8.1, $P = .08$; 12 months MD: 11.2, $P = .02$). The magnitudes of these improvements were significantly greater in the implant group compared with the control group, by 186% ($P = .006$) and 137% ($P = .005$) at 6 months and 12 months, respectively (Figure 6).

Sports and Recreation. At the 6- and 12-month follow-ups, significant improvements over baseline for KOOS Sports and Recreation were observed in the implant group (6 months MD: 28.9, $P < .0001$; 12 months MD: 34.6, $P < .0001$), but changes from baseline in the control group were not statistically significant (6 months MD: 8.5, $P = .19$; 12 months MD: 12.5, $P = .07$). The magnitude of these improvements from baseline was significantly greater in the implant group compared with the control group, by 240% ($P = .004$) and 177% ($P = .007$) at 6 and 12 months, respectively (Figure 7).

Quality of Life. Significant improvements in KOOS QOL over baseline were observed at all follow-up timepoints in the implant group ($P < .001$), and these improvements were significantly greater than those experienced by participants in the control group, by 254% and 159% at 6 and 12 months, respectively ($P < .001$) (Figure 8).

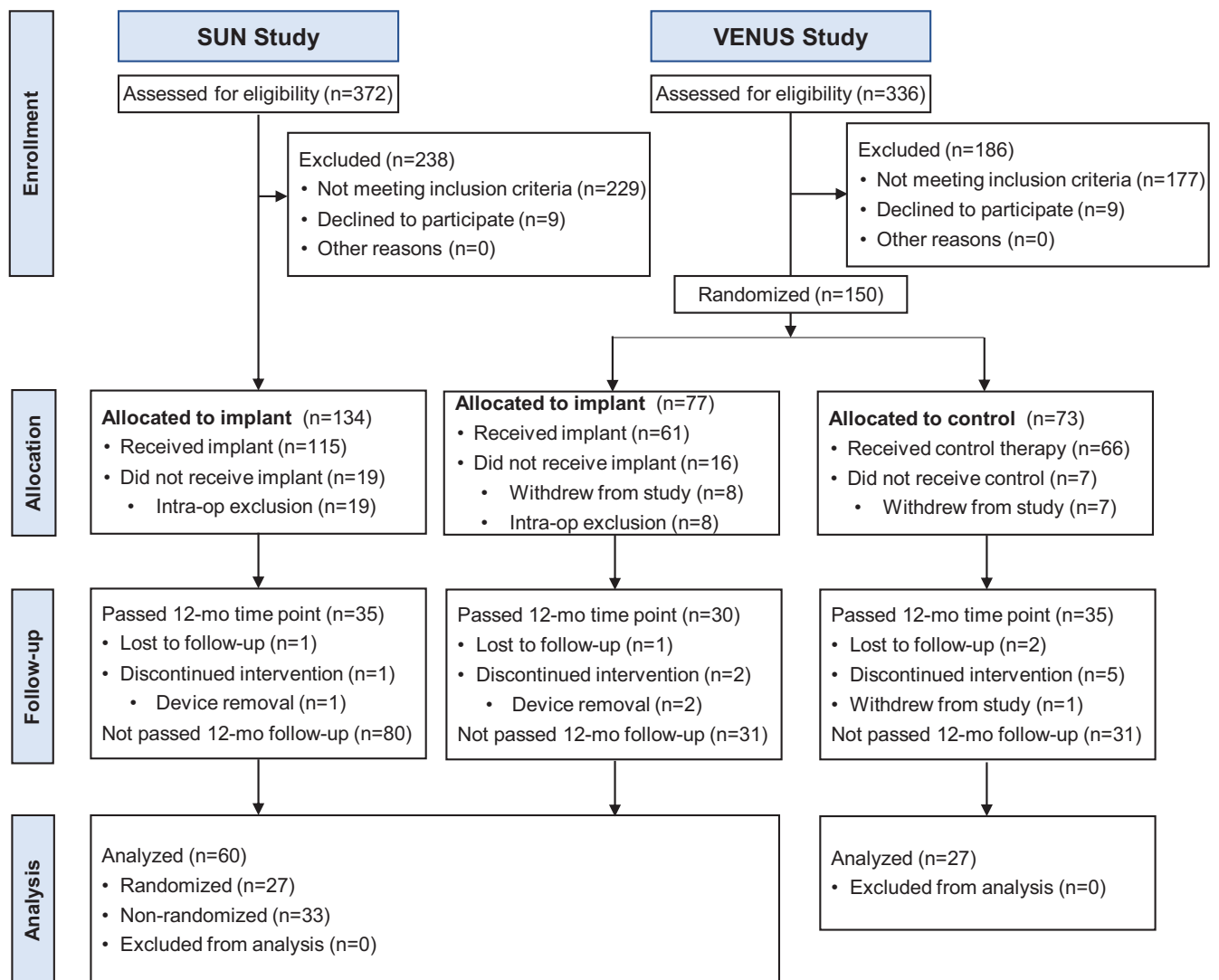


Figure 3. Patient flow diagram for inclusion in this preliminary analysis. Intra-op, intraoperative.

Adverse Events and Subsequent Surgical Procedures

By 12 months of follow-up, patients experienced an AE or subsequent surgical procedure at a rate of 16.9% in the implant group (12 AEs in 11 patients) and 14.3% in the control group (5 AEs in 5 patients; $P = .99$). There were 11 subsequent surgical procedures in 10 participants in the implant group (15.4%) and 5 in the control group (14.3%; $P = .99$) (Table 4). In the implant group, 3 patients (4.6%) required device replacement and 3 (4.6%) underwent permanent removal of the implant, with only 1 of those 3 patients progressing to a UKA. There was no incidence of death in either treatment group.

We noted that 2 patients in the implant group required device repositioning after posterior dislocation of the device. After repositioning, both patients experienced immediate symptom relief and recovered without additional sequelae. A similar scenario occurred in a third patient; however, that

patient later required a device replacement because of abrasion of the device. Among the 2 other patients who required device replacement, 1 device was replaced because of a suspected infection, which was unconfirmed upon culture, and the other was replaced because of abrasion of the device. In each case where the implant was repositioned or replaced, the state of the articular cartilage was deemed to have met the study eligibility criteria.

In 3 other patients, the device was permanently removed. In 1 patient, the removal was because of excessive abrasion (ie, abrasion greater than superficial marking) of the device and device failure associated with a trauma. In the second patient, a vertical osteophyte and grade IV Outerbridge lesion were observed in the articular cartilage, which likely contributed to severe abrasion of the device. The third patient experienced a partial (grade II) medial collateral ligament tear, which may have compromised the stability of the joint, and ultimately underwent UKA.

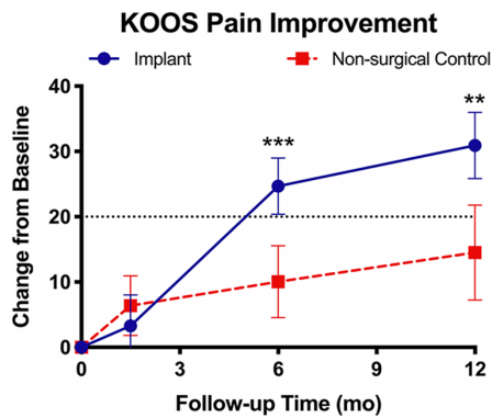


Figure 4. Summary of Knee injury and Osteoarthritis Outcome Score (KOOS) for Pain improvement. More positive scores indicate better improvements. Data points represent the mean, and error bars represent 95% CIs. A 20-point change denotes clinically significant improvement.⁹ *** $P < .001$ and ** $P < .01$ for implant group vs control group. P values were adjusted to correct for comparisons at multiple time points.

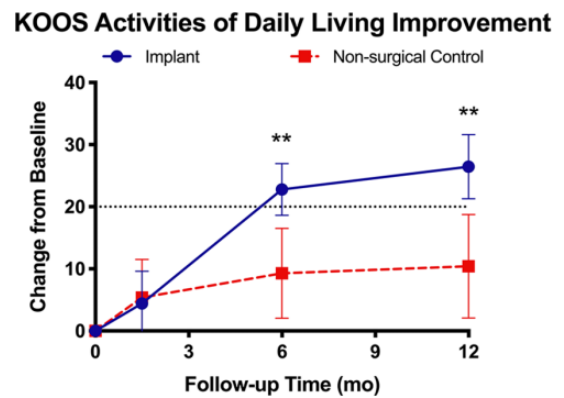


Figure 6. Summary of Knee injury and Osteoarthritis Outcome Score (KOOS) for Activities of Daily Living improvement. More positive scores indicate better improvements. Data points represent the mean, and error bars represent 95% CIs. A 20-point change denotes clinically significant improvement.⁹ *** $P < .01$ for implant group vs control group. P values were adjusted to correct for comparisons at multiple time points.

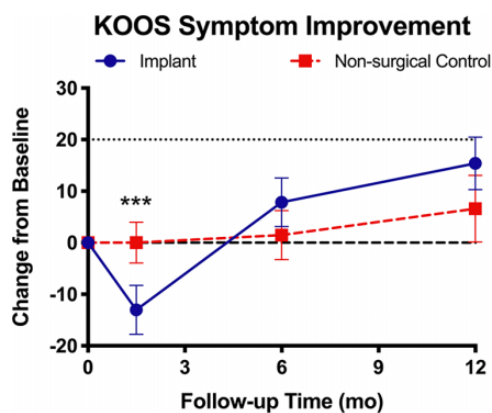


Figure 5. Summary of Knee injury and Osteoarthritis Outcome Score (KOOS) for Symptoms improvement. More positive scores indicate better improvements. Data points represent the mean, and error bars represent 95% CIs. A 20-point change denotes clinically significant improvement.⁹ *** $P < .001$ for implant group vs control group. P values were adjusted to correct for comparisons at multiple time points.

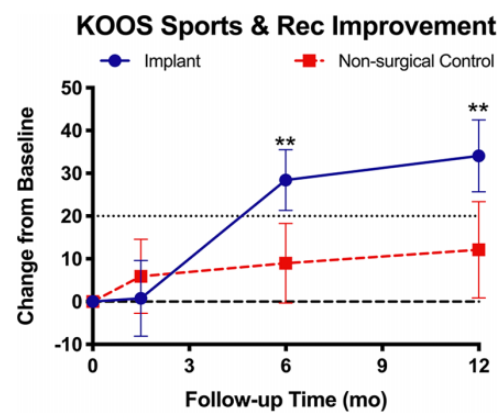


Figure 7. Summary of Knee injury and Osteoarthritis Outcome Score (KOOS) for Sports and Recreation (Rec) improvement. More positive scores indicate better improvements. Data points represent the mean, and error bars represent 95% CIs. A 20-point change denotes clinically significant improvement.⁹ *** $P < .01$ for implant group vs control group. P values were adjusted to correct for comparisons at multiple time points.

In the control group, the 5 surgical interventions included 1 UKA; 1 high tibial osteotomy; 1 osteochondral allograft; 1 posterolateral corner reconstruction; and 1 arthroscopy that included chondroplasty of the medial femoral condyle, medial partial meniscectomy for a complex flap tear, and minor synovectomy in the patellofemoral joint.

DISCUSSION

Patients who experience persistent or recurrent pain after meniscectomy have limited options for further treatment.

The standard of care in these patients is nonsurgical therapy, which may alleviate patients' symptoms but does not address the underlying disease state, leaving patients at risk for degenerative changes and subsequent arthroplasty in the meniscus-deficient knee.³⁴ This study focused on the utility of a polymeric medial meniscal replacement for alleviating pain and restoring function compared with nonsurgical management.

In all KOOS subscales except for the Symptoms subscale, significantly greater improvement was seen in the implant group compared with the control group. Transient

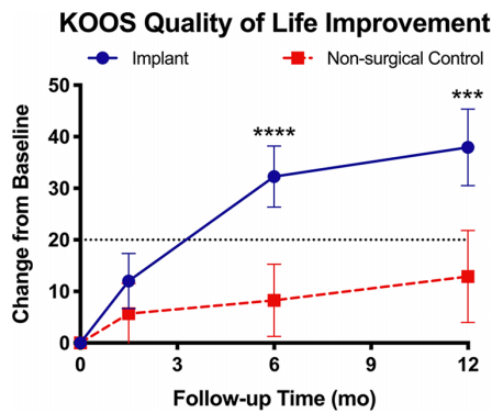


Figure 8. Summary of Knee injury and Osteoarthritis Outcome Score (KOOS) for Quality of Life improvement. More positive scores indicate better improvements. Data points represent the mean, and error bars represent 95% CIs. A 20-point change denotes clinically significant improvement.⁹ **** $P < .0001$ and *** $P < .001$ for implant group vs control group. P values were adjusted to correct for comparisons at multiple time points.

TABLE 4
Adverse Events or Subsequent Surgical Interventions
During the 12-Month Follow-up^a

	Implant Group (n = 65)	Control Group (n = 35)	P
Unplanned arthroscopy	2 (3.1)	1 (2.9)	.99
Deep vein thrombosis	1 (1.5)	0	.99
Device repositioning	3 (4.6)	NA	NA
Device replacement	2 (3.1)	NA	NA
Suspected infection and device replacement	1 (1.5)	NA	NA
Permanent device removal	2 (3.1)	NA	NA
Unilateral knee arthroplasty ^b	1 (1.5)	1 (2.9)	.99
Other surgery ^c	0	3 (8.6)	.04
Total AEs	12 (18.5)	5 (14.3)	— ^d
Total patients with at least 1 AE	11 (16.9)	5 (14.3)	.99

^aValues are expressed as n (%) (number of patients [frequency per population]). No patient experienced any AE more than once. One patient in the implant group experienced both a repositioning and a replacement. AE, adverse event; NA, not applicable.

^bIn the implant group, arthroplasty also required device removal.

^cOther surgeries included 1 high tibial osteotomy, 1 osteochondral allograft, and 1 posterolateral corner reconstruction in the control group.

^d P value for total events was not calculated because only 1 patient experienced >1 event.

worsening of Symptoms subscale scores was observed during the early postoperative period (1.5 months after surgery) in the implant group, which is likely related to the recovery time from the surgery itself and physiological adjustment to the implant. After the surgical recovery period, scores in the implant group significantly improved

by the 6-month follow-up. We found that 4 of the 5 KOOS subscales had average improvements exceeding 20 points in the implant group at the 12-month follow-up, which is clinically significant.⁹

None of the AEs found at the 12-month follow-up were unanticipated because they were consistent with the AEs previously documented in the literature.^{21,24} Device removal or replacement was required in 6 patients, attributable to abrasion of the implant in 5 patients and suspected infection in 1 patient. In 4 of the patients, the abrasion occurred where the lateral wall of the implant met the intercondylar notch. The abrasion on the implant was likely due to insufficient preparation of the notch (eg, failure to remove osteophytes that may interfere with the device), suboptimal implant size selection, trauma, or excessive patient activity. In the fifth patient, the abrasion was located anteromedially on the implant and was associated with a vertical osteophyte located at a grade IV chondral lesion. Evolving the surgical technique as experience increases is an important component of all new procedures and devices. For this meniscal replacement, sufficient notchplasty is important to reduce the risk of impingement and excessive abrasion of the device.

Device-related complications were addressable through repositioning or replacement of the device. A low rate of patients progressing to UKA was observed in the implant group (1/65; 1.5%) and the control group (1/35; 2.9%). Katz et al²⁴ reported a 12-month rate of progression to TKA of 2.9% in patients who underwent partial meniscectomy. Rongen et al³⁴ reported that 18.8% of patients who underwent arthroscopic meniscectomy progressed to TKA during a 108-month follow-up.

The patients in the current study represent a “middle-aged” population (mean age, 48.5 years; range, 30-69 years) with chronic pain after a past meniscectomy (median, 40 months postoperative). Aside from nonsurgical care, current treatment options for these patients may include meniscal allograft transplant, a collagen or polyurethane meniscal scaffold, UKA, or TKA. Meniscal allograft transplant has tight indications and high failure rates, particularly in patients older than 35 years.⁴¹ Collagen or polyurethane meniscal scaffolds likely have similar restrictions on indications, cannot be used as a full meniscal replacement, lack high-quality data, and have failure rates of 32% over 5 years.²³ These options are far from ideal for the majority of patients in this cohort. Due to the chronicity of pain and symptoms, these patients may turn to arthroplasty in the absence of other viable surgical treatments. However, the lifetime risk of TKA revision is 15% to 35% for younger (<60 years) patients.⁵ In contrast to arthroplasty, which is an end-stage intervention, the meniscal implant procedure does not preclude removal of the device or limit subsequent surgical interventions, if necessary. Therefore, this implant may serve as a therapy for bridging the gap between partial meniscectomy and arthroplasty in indicated patients.

The UniSpacer system (Zimmer, Inc) is a cobalt-chrome self-centering tibial implant for treatment of similar patients. However, failure rates with conversion to TKA were 33% to 35% within 2.5 years.^{3,10,32,39} Although the

UniSpacer and NUsurface are both single-component, uni-condylar, self-centering devices for the medial compartment, key differences exist. First, the soft material nature of the polymeric composition of NUsurface mimics the properties of the native meniscus, enabling high conformity and distributed contact pressures²⁷ compared with those of the rigid, metal construction of the UniSpacer. Second, the surgical technique for the UniSpacer requires total meniscectomy along with complete removal of the posterior horn and trimming of the articular cartilage to allow free translation of the rigid device.³ In contrast, the NUsurface device can be used after partial meniscectomy, and the articular cartilage can be left intact, with the exception of osteophyte debridement. Third, the current evidence suggests a low rate of conversion to arthroplasty for the NUsurface, but complete 2-year data from the VENUS and SUN trials will be important to corroborate these preliminary findings. In comparison with the natural meniscus, NUsurface provides similar load distributions and contact pressures^{15,27} but achieves this functionality through free translation without attachment to the tibial plateau.

This is a preliminary analysis based on the first 100 patients of a 242-patient study at a preliminary timepoint. Such preliminary analyses are important to ensure that patients are not being exposed to unanticipated AEs or undergoing surgical interventions that are unlikely to be of benefit. We noted differences in the proportion of male patients between the randomized and nonrandomized implant subgroups within these first 100 patients, but no significant differences were found between the pooled implant group and the control group. Additional analyses with the full set of patients will be important to confirm poolability of the study populations and comparison with the randomized control group.

CONCLUSION

The preliminary clinical findings of this analysis suggest statistically and clinically significant improvements in 4 of 5 KOOS subscales in patients who received the synthetic meniscal implant compared with nonsurgical controls and a similar rate of AEs or subsequent surgical procedures. Although these preliminary results are encouraging, the studies are ongoing, and further data analyses of the full patient population at the primary 2-year endpoint will be important for more definitive conclusions. Whether meniscal function is lost through acute trauma or chronic degeneration, restoring the meniscal function is key for alleviating pain, improving function, and enhancing long-term health of the knee.

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REFERENCES

- Andersson-Molina H, Karlsson H, Rockborn P. Arthroscopic partial and total meniscectomy: a long-term follow-up study with matched controls. *Arthroscopy*. 2002;18(2):183-189.
- Azam M, Shenoy R. The role of arthroscopic partial meniscectomy in the management of degenerative meniscus tears: a review of the recent literature. *Open Orthop J*. 2016;10:797-804.
- Baillie AG, Lewis PL, Brumby SA, Roy S, Paterson RS, Campbell DG. The Unispace knee implant: early clinical results. *J Bone Joint Surg Br*. 2008;90(4):446-450.
- Barnds B, Morris B, Mullen S, Schroepel JP, Tarakemeh A, Vopat BG. Increased rates of knee arthroplasty and cost of patients with meniscal tears treated with arthroscopic partial meniscectomy versus non-operative management. *Knee Surg Sports Traumatol Arthrosc*. 2019;27(7):2316-2321.
- Bayliss LE, Culliford D, Monk AP, et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. *Lancet*. 2017;389(10077):1424-1430.
- Bonneux I, Vandekerckhove B. Arthroscopic partial lateral meniscectomy long-term results in athletes. *Acta Orthop Belg*. 2002;68(4):356-361.
- Carey RE, Zheng L, Aiyangar AK, Harner CD, Zhang X. Subject-specific finite element modeling of the tibiofemoral joint based on CT, magnetic resonance imaging and dynamic stereoradiography data in vivo. *J Biomech Eng*. 2014;136(4):0410041-0410048.
- Chatain F, Adeleine P, Chambat P, Neyret P; Societe Francaise d'Arthroscopie. A comparative study of medial versus lateral arthroscopic partial meniscectomy on stable knees: 10-year minimum follow-up. *Arthroscopy*. 2003;19(8):842-849.
- Collins NJ, Prinsen CA, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. *Osteoarthritis Cartilage*. 2016;24(8):1317-1329.
- Danna NR, Beutel BG, Ramme AJ, Kirsch T, Kennedy OD, Strauss E. The effect of growth hormone on chondral defect repair. *Cartilage*. 2018;9(1):63-70.
- De Coninck T, Elsner JJ, Linder-Ganz E, et al. In-vivo evaluation of the kinematic behavior of an artificial medial meniscus implant: a pilot study using open-MRI. *Clin Biomech (Bristol, Avon)*. 2014;29(8):898-905.
- Dong Y, Hu G, Dong Y, Hu Y, Xu Q. The effect of meniscal tears and resultant partial meniscectomies on the knee contact stresses: a finite element analysis. *Comput Methods Biomech Biomed Engin*. 2014;17(13):1452-1463.
- Eijgenraam SM, Reijman M, Bierma-Zeinstra SMA, van Yperen DT, Meuffels DE. Can we predict the clinical outcome of arthroscopic partial meniscectomy? A systematic review. *Br J Sports Med*. 2018;52(8):514-521.
- Elsner JJ, Portnoy S, Guilak F, Shterling A, Linder-Ganz E. MRI-based characterization of bone anatomy in the human knee for size matching of a medial meniscal implant. *J Biomech Eng*. 2010;132(10):101008.
- Elsner JJ, Portnoy S, Zur G, Guilak F, Shterling A, Linder-Ganz E. Design of a free-floating polycarbonate-urethane meniscal implant using finite element modeling and experimental validation. *J Biomech Eng*. 2010;132(9):095001.
- Feeley BT, Lau BC. Biomechanics and clinical outcomes of partial meniscectomy. *J Am Acad Orthop Surg*. 2018;26(24):853-863.

17. Frank RM, Cole BJ. Meniscus transplantation. *Curr Rev Musculoskelet Med*. 2015;8(4):443-450.
18. Gauffin H, Tagesson S, Meunier A, Magnusson H, Kvist J. Knee arthroscopic surgery is beneficial to middle-aged patients with meniscal symptoms: a prospective, randomised, single-blinded study. *Osteoarthritis Cartilage*. 2014;22(11):1808-1816.
19. Hall MJ, Schwartzman A, Zhang J, Liu X. Ambulatory surgery data from hospitals and ambulatory surgery centers: United States, 2010. *Natl Health Stat Report*. 2017;102:1-15.
20. Harrison MM, Morrell J, Hopman WM. Influence of obesity on outcome after knee arthroscopy. *Arthroscopy*. 2004;20(7):691-695.
21. Hawker G, Guan J, Judge A, Dieppe P. Knee arthroscopy in England and Ontario: patterns of use, changes over time, and relationship to total knee replacement. *J Bone Joint Surg Am*. 2008;90(11):2337-2345.
22. Herrlin SV, Wange PO, Lapidus G, Hallander M, Werner S, Weidenhielm L. Is arthroscopic surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? A five year follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(2):358-364.
23. Houck DA, Kraeutler MJ, Belk JW, McCarty EC, Bravman JT. Similar clinical outcomes following collagen or polyurethane meniscal scaffold implantation: a systematic review. *Knee Surg Sports Traumatol Arthrosc*. 2018;26(8):2259-2269.
24. Katz JN, Brophy RH, Chaisson CE, et al. Surgery versus physical therapy for a meniscal tear and osteoarthritis. *N Engl J Med*. 2013;368(18):1675-1684.
25. Katz JN, Losina E. Arthroscopic partial meniscectomy for degenerative tears: where do we stand? *Osteoarthritis Cartilage*. 2014;22(11):1749-1751.
26. Kazemi M, Li LP, Buschmann MD, Savard P. Partial meniscectomy changes fluid pressurization in articular cartilage in human knees. *J Biomech Eng*. 2012;134(2):021001.
27. Linder-Ganz E, Elsner JJ, Danino A, Guilak F, Shterling A. A novel quantitative approach for evaluating contact mechanics of meniscal replacements. *J Biomech Eng*. 2010;132(2):024501.
28. McDermott ID, Amis AA. The consequences of meniscectomy. *J Bone Joint Surg Br*. 2006;88(12):1549-1556.
29. Meredith DS, Losina E, Mahomed NN, Wright J, Katz JN. Factors predicting functional and radiographic outcomes after arthroscopic partial meniscectomy: a review of the literature. *Arthroscopy*. 2005;21(2):211-223.
30. Milachowski KA, Weismeier K, Wirth CJ. Homologous meniscus transplantation: experimental and clinical results. *Int Orthop*. 1989;13(1):1-11.
31. Noyes FR, Barber-Westin SD, Rankin M. Meniscal transplantation in symptomatic patients less than fifty years old. *J Bone Joint Surg Am*. 2004;86(7):1392-1404.
32. Quanezar H, Blakeney WG, Fernandes LR, et al. Clinical outcomes of single anteromedial bundle biologic augmentation technique for anterior cruciate ligament reconstruction with consideration of tibial remnant size. *Arthroscopy*. 2018;34(3):714-722.
33. Rockborn P, Gillquist J. Outcome of arthroscopic meniscectomy: a 13-year physical and radiographic follow-up of 43 patients under 23 years of age. *Acta Orthop Scand*. 1995;66(2):113-117.
34. Rongen JJ, Rovers MM, van Tienen TG, Buma P, Hannink G. Increased risk for knee replacement surgery after arthroscopic surgery for degenerative meniscal tears: a multi-center longitudinal observational study using data from the osteoarthritis initiative. *Osteoarthritis Cartilage*. 2017;25(1):23-29.
35. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64.
36. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS)—validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes*. 2003;1:17.
37. Shemesh M, Asher R, Zylberberg E, Guilak F, Linder-Ganz E, Elsner JJ. Viscoelastic properties of a synthetic meniscus implant. *J Mech Behav Biomed Mater*. 2014;29:42-55.
38. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy versus placebo surgery for a degenerative meniscus tear: a 2-year follow-up of the randomised controlled trial. *Ann Rheum Dis*. 2018;77(2):188-195.
39. Sisto DJ, Mitchell IL. UniSpacer arthroplasty of the knee. *J Bone Joint Surg Am*. 2005;87(8):1706-1711.
40. van Arkel ER, de Boer HH. Survival analysis of human meniscal transplantations. *J Bone Joint Surg Br*. 2002;84(2):227-231.
41. Van Der Straeten C, Bytтеbier P, Eeckhoudt A, Victor J. Meniscal allograft transplantation does not prevent or delay progression of knee osteoarthritis. *PLoS One*. 2016;11(5):e0156183.
42. Zur G, Linder-Ganz E, Elsner JJ, et al. Chondroprotective effects of a polycarbonate-urethane meniscal implant: histopathological results in a sheep model. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(2):255-263.