Outcomes after Anatomic Double-Bundle Posterior Cruciate Ligament Reconstructions Using Transtibial and Tibial Inlay Techniques

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Abstract

Surgical reconstruction is recommended for symptomatic posterior cruciate ligament (PCL) deficiency. While anatomic double-bundle PCL reconstruction (PCLR) has been reported to be associated with biomechanical and clinical advantages over other methods, there is still debate regarding the optimal technique for tibial positioning and fixation. Based on reported advantages and disadvantages, we employed two tibial fixation techniques, transtibial (TT) and tibial inlay (TI) for anatomic double-bundle PCLR with technique selection based on body mass index, comorbidities, and primary versus revision surgery. This study aimed to compare clinical outcomes following PCLR utilizing either TT or TI techniques to validate relative advantages, disadvantages, and indications for each based on the review of prospectively collected registry data. For 37 patients meeting inclusion criteria, 26 underwent arthroscopic TT PCLR using all-soft-tissue allograft with suspensory fixation in the tibia and 11 patients underwent open TI PCLR using an allograft with calcaneal bone block and screw fixation in the tibia. There were no significant preoperative differences between cohorts. Success rates were 96% for TT and 91% for TI with all successful cases documented to be associated with good-to-excellent posterior stability and range of motion in the knee at the final follow-up. In addition, patient-reported outcome scores were within clinically meaningful ranges for pain, function, and mental health after PCLR in both cohorts, suggesting similarly favorable functional, social, and psychological outcomes. Patient-reported pain scores at 6 months postoperatively were significantly (p = 0.042) lower in the TT cohort, which was the only statistically significant difference in outcomes noted. The results of this study support the use of TT and TI techniques for double-bundle anatomic PCLR in restoring knee stability and patient function when used for the treatment of isolated and multiligamentous PCL injuries. The choice between tibial fixation methods for PCLR can be appropriately based on patient and injury characteristics that optimize respective advantages for each technique.

Keywords

- posterior cruciate ligament
- reconstruction
- transtibial inlay
- ► tibial inlay

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November 11, 2022 accepted December 7, 2022 accepted manuscript online December 10, 2022 article published online February 7, 2023 © 2023. Thieme. All rights reserved. Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA DOI https://doi.org/ 10.1055/a-1996-1153. ISSN 1538-8506. The posterior cruciate ligament (PCL) has two main bundles that act synergistically as important stabilizers for the knee joint.^{1,2} PCL injuries can result from high- or low-energy trauma and occur in isolation (approximately 3% of cases)³ or, more commonly, in conjunction with multiligament injuries to the knee.^{3,4} PCL deficiency, alone or with knee comorbidities, has the potential to progress to chronic knee instability, pain, dysfunction, and osteoarthritis with associated financial, mental, and quality of life costs.^{5–9} As such, symptomatic PCL deficiency is indicated for surgical reconstruction.^{3,5,10–14}

While anatomic double-bundle PCL reconstruction (PCLR) has been reported to be associated with biomechanical and clinical advantages over other methods, there is still debate regarding the optimal technique for tibial positioning and fixation.^{6,15–19} Techniques for PCL graft positioning and fixation have focused on the unique anatomy of the tibial insertion of the native PCL and the associated "killer turn" that PCL grafts are subjected to for anatomic PCLR.^{20,21} Each technique encompasses respective complication types and risks, including neurovascular injury, compartment syndrome, infection, loss of motion, and treatment failure.^{2,22–25} Persistent posterior laxity has been the most commonly reported complication of PCLR with single-bundle and isometric techniques associated with the highest incidences.^{26–29}

Based on reported advantages and disadvantages, we have employed two tibial fixation techniques, transtibial (TT)^{4,30} with all-soft tissue graft³⁰⁻³² and tibial inlay (TI) with a bone block,^{33,34} for anatomic double-bundle PCLRs. The selection of TT versus TI has been primarily governed by the presence of additional injuries to the knee, previous attempts at PCLR, and the patient's body mass index (BMI). However, these subjective selection criteria have not been critically evaluated. Therefore, the goal of this study was to compare clinical outcomes following anatomic double-bundle PCLR utilizing either TT or TI techniques to delineate relative advantages, disadvantages, and indications for each.

Methods

Study Population

After institutional review board approval (#2048943), prospectively collected data for patients included in a dedicated registry for following outcomes after knee ligament injuries were reviewed. Patients who underwent PCLR for isolated PCL deficiency or in combination with other ligament reconstructions in the same knee between January 2016 and February 2021 and had at least 1 year of follow-up data available were included for analysis. Exclusion criteria included incomplete follow-up data and/or patients that were lost to follow-up.

Surgical Procedures

All patients underwent PCLR performed by a single surgeon (J.P.S.) utilizing Achilles tendon allograft reinforced with a synthetic suture tape internal brace (FiberTape, Arthrex Inc., Naples FL).^{34–36} Indication for PCLR was determined by the

diagnosis of symptomatic PCL deficiency based on physical examination and/or diagnostic imaging findings. All PCL reconstructions were performed using an anatomic double-bundle technique. Femoral graft positioning and stabilization were performed arthroscopically using separate sockets for anterolateral (AL) and posteromedial (PM) all-soft-tissue bundles with cortical suspensory fixation for each, as previously described.^{34,37} Based on the presence of additional injuries to the knee, previous attempts at PCLR, and the patient's BMI, tibial graft positioning and stabilization were performed using one of the two previously described techniques (**~Fig. 1**).^{4,30,32-34}

- TT: Arthroscopic-assisted creation of a socket in the tibial PCL insertion footprint for cortical suspensory fixation of an all-soft tissue Achilles tendon allograft. In general, TT was selected for primary PCLR in patients with a BMI <35 kg/m² and an intact posterior medial corner (PMC).
- TI: Open posterior-medial approach to the tibial to create a recipient bone bed in the tibial PCL insertion footprint for compression screw-and-washer fixation of a calcaneal bone block on Achilles tendon allograft. In general, TI was selected for primary PCLR in patients with BMI \geq 35 kg/m² and/or requiring concomitant PMC reconstruction and/or for revision PLCR.

For both techniques, tibial fixation was completed first followed by sequential fixation with tensioning and retensioning of the femoral graft bundles. This is accomplished by placing the knee in 90 degrees of flexion and tightening the AL bundle, then placing the knee in 0 degrees of flexion and tightening the PM bundle. The knee is then placed through a range of motion (ROM) at least 10 times, the grafts are stressed, and the tightening sequence is repeated. This process is repeated, effectively eliminating the creep from the graft, until desired tension and stability are achieved.

Postoperative Management and Follow-Up

Postoperative rehabilitation was individualized to the patient based on the severity of the injury and surgical procedures performed. In general, patients with one or two ligaments reconstructed were placed in a hinged leg brace postoperatively. When three or more ligaments were reconstructed, a compass-hinged external fixator was typically utilized.³⁸ Goals for the first 4 postoperative weeks included control of swelling, progression to full knee extension, and reestablishing quadriceps muscle control.³⁸ Patients were instructed to remain nonweight bearing with the use of assistive devices for at least the first 2 weeks, followed by weight-bearing as tolerated with crutches and the knee locked in full extension based on healing progression. Patients began ROM from 0 to 30 degrees during the first 2 weeks, and between 3 and 4 weeks postoperatively, the hinged knee brace was unlocked during weight-bearing activities. Outpatient physical therapy started after the first 2 weeks, and by 8 weeks, the patient was expected to have 0 to 110 degrees of active and passive knee motion, good patellar mobility, and normal walking gait without crutches. Use of brace was discontinued between weeks 11 and 12



Fig. 1 Illustrations of anatomic double-bundle PCLR using (A) transtibial technique and (B) tibial inlay techniques for tibial fixation. PCLR, posterior cruciate ligament reconstruction.

once quadriceps muscle control was reestablished, with transition to a functional knee brace for up to 18 months after surgery during activities. Strengthening began between 9 and 12 weeks postoperatively. Return to heavy work and sports was gradually allowed between 9 and 12 months after surgery, pending required activity level, patient progress, and knee stability metrics.³⁰

Outcome Measures

Patient demographics and operative data, including age, sex, BMI, tobacco use, injury cause and pattern, concomitant injuries to the affected knee, and surgical procedures performed, as well as postoperative complications, reoperations, and treatment failure data, were obtained from the electronic medical record. Each patient was evaluated at 6 months, 1 year, and 2 years postoperatively by physical examination, which included posterior drawer and ROM assessments of the affected knee performed by the attending surgeon. Posterior knee stability was evaluated using Lachman and posterior drawer tests in comparison with the uninjured knee with laxity graded as negative (0), 1+, 2+, or 3+, and soft or firm endpoint.^{39–45} Knee ROM measurements were obtained by a trained observer (physical therapist, nurse practitioner, or physician) who was blinded to the treatment group. End extension, end flexion, and total ROM were determined using a goniometer to measure active knee motion from extension to flexion at each postoperative appointment.

In addition, patient-reported outcomes (PROs),^{46–48} including Visual Analog Scale (VAS) Pain, Patient Reported Outcomes Measurement Information System (PROMIS) Global Health, PROMIS Mental Health, PROMIS Physical Function, and PROMIS Pain Interference scores, were obtained at the same postoperative time points via electronic data capture into a secure HIPAA- and HITECH-compliant database (PatientIQ).

Statistical Analysis

Patients were included for analysis when at least 1 year of follow-up data regarding treatment success/failure and reoperations were available. The primary outcome measure for analysis was the success rate. Success was defined as patients having a self-reported pain score ≤ 2 , documented PCL stability (0 or 1 +) based on surgeon assessment, and return to work (RTW) at any level with no need for revision at \geq 1 year after PCLR. Treatment failure was defined as the lack of meeting success criteria and/or need for knee arthroplasty, arthrodesis, or amputation for any reason. Secondary

outcome measures included complication rates, reoperation rates, PCLR revision rates, posterior stability grades, knee ROM, and PRO scores. Cohorts were compared for statistically significant (p < 0.05) differences using *t*-tests for normally distributed continuous variables, rank sum tests for nonparametric and/or categorical variables, and Fisher's exact tests for proportions.

Results

A total of 49 patients in the registry were considered eligible; however, 12 patients lacked adequate follow-up data for inclusion and did not respond to subsequent contact attempts. As such, a total of 37 patients (75.5%) were analyzed, including 26 patients (male = 20) in the TT cohort and 11 patients (male = 6) in the TI cohort (**- Fig. 2**). Mean final follow-up duration was 20.6 ± 15.5 months for the TT group and 22.5 ± 12.3 months for the TI group (p = 0.25).

Patient demographics and injury data are presented in **-Table 1**. There were no significant differences noted for sex (p = 0.24), age (p = 0.35), smoking status (p = 0.07), or BMI (p = 0.09) between the TT and TI cohorts. The mechanism of injury included motor vehicle accidents, sports or recreational activities, falls (high- and low-velocity), and others. There were no significant differences in mechanisms of injury (p > 0.75), concurrent ligamentous injuries (p > 0.78), or concurrent neurovascular injury (p > 0.40) between cohorts. One patient in the TI cohort experienced an intraoperative complication in the form of a popliteal vein injury that was successfully repaired prior to the completion of PCLR.

Outcomes data are presented in **-Table 2**. The PCLR success rate was 94.6% (35 out of 37 patients) for all cases combined based on 96.2% (25 out of 26 patients) success for the TT cohort and 90.9% (10 out of 11 patients) success for the TI cohort (**-Fig. 2**). There were no significant differences for the incidence of complications (p = 0.32), reoperation rate (p = 0.73), revision rate (p = 1), posterior stability (p = 0.67), or ROM (p = 0.34) between cohorts. PCL reconstruction technique (p = 0.54), patient sex (p = 0.08), nicotine use (p = 1), primary versus revision status (p = 0.46), BMI (p = 0.46), age (p = 0.25), and compass hinge use (p = 0.46)



Fig. 2 Consort flow diagram for study population inclusion and analysis.

	Transtibial group ($n = 26$)	Tibial inlay ($n = 11$)	<i>p</i> -Value	
Male:Female	3.3:1	1.2:1	NSD, <i>p</i> = 0.24	
Age	35.1±13.4	28.1±12.2	NSD, <i>p</i> = 0.35	
BMI mean, SD	32.4±6.0	36.8±14.3	p=0.086	
Smoking status			NSD, $p = 0.07$	
No	19	11		
Yes	7	0		
Follow-up, month	20.6 ± 15.5	22.5±12.3	NSD, <i>p</i> = 0.25	
PCL only	1	2	NSD for any proportions in these categories ($p > 0.78$)	
PCL and ACL	1	-		
PCL and PLC	6	1		
PCL and PMC	3	_		
Multiligament Knee dislocation (KD)	15	7		
KD III L	5	2		
KD III M	2	2		
KD IV	6	3	1	
KD V	2	1	1	
Motor vehicle accident	11	3	NSD for any proportions in these categories ($p > 0.75$)	
Recreation/Sport	8	5		
Fall	5	3		
Other	2	-]	
Peroneal nerve injury	6	4	NSD, <i>p</i> > 0.40	
Vascular injury	2	2		

Table 1 Patient demographics and injury characteristics

Abbreviations: ACL, anterior cruciate ligament; NSD, no statistically significant difference; PCL, posterior cruciate ligament; PLC, posterior lateral corner; PMC, posterior medial corner; SD, standard deviation.

were not associated with a significantly higher likelihood for treatment failure.

The failure in the TI cohort occurred in one 14-year-old patient with a severe knee dislocation and vascular injury who developed recurrent subluxation including 2+ posterior drawer at 7 months postoperatively, leading the patient to pursue a knee arthrodesis. A 29-year-old female TT patient experienced posterior laxity (2 +) 5 months after PCLR. This patient underwent cancellous allograft bone grafting in the PCL tunnels and subsequent revision TI PCL reconstruction, resulting in a successful outcome at the time of analysis based on *a priori* criteria.

Reoperation was the most common postoperative complication related to PCLR, which was documented in three patients (11.5%) in the TT cohort and two patients (18.2%) in the TI cohort. Two patients (1 TT, 1 TI) underwent lysis of adhesions to address arthrofibrosis, two patients (1 TT, 1 TI) underwent irrigation and debridement for wound complications, and one TT patient underwent irrigation and debridement with PCL implant (button) removal for wound complications.

All successful cases with recorded posterior drawer at final follow-up (n = 33) were documented to have good (1 + ,

19%) to excellent (0, 81%) posterior stability, knee ROM (mean > 105 degrees), and radiographic findings (**¬Fig. 3**) at final follow-up. PRO scores are presented in **¬Table 3**. Patient reported VAS pain scores were significantly (p = 0.042) better in the TT cohort at 6 months postoperatively compared with the TI cohort (1.7 ± 1.8 vs. 3.4 ± 2.7 , respectively). There were no other significant differences noted between cohorts for any PRO at any other time point assessed.

Discussion

In the study population, TT and TI techniques for anatomic double-bundle PCLR resulted in consistently favorable outcomes for up to 2 years after surgery in a diverse cohort of patients. Overall success rates were 96.2% for TT and 90.9% for TI with all successful cases documented to be associated with pain relief, good to excellent posterior stability (0 or + laxity), and acceptable knee ROM at final follow-up. In addition, PROMIS scores reported following PCLR were within one standard deviation of the normal healthy adult population for pain, function, and mental health in both cohorts, suggesting similarly favorable functional, social, and

	Transtibial (n = 26)	Tibial inlay (n = 11)	p-Value	
Success	25 (96.2%)	10 (90.9%)	0.54	
Posterior drawer (FFU)	0: 19 (73.1%)	0: 6 (54.5%)	0.67	
	1+:3 (11.5%)	1+:3 (27.3%)		
	2+:1 (3.8%)	2+:1 (9.1%)		
	Not documented ^a : 3 (11.5%)	Not documented ^a : 1 (9.1%)		
ROM (FFU)	Mean extension (SD): 1.4 (2.9)	Mean extension (SD): 0.6 (1.7)	0.80	
	Mean flexion (SD): 114.5 (18.5)	Mean flexion (SD): 100.1 (20.8)	0.37	
Arthrodesis	0	1	1	
ТКА	0	0		
Above knee amputation	0	0		
Revision	1	0		
Compass hinge	7	5	0.46	
Reoperation	3	2	NSD for any proportions	
Irrigation & debridement	2	1	in these categories $(n > 0.62)$	
Lysis of adhesions	1	1	(p > 0.02)	
PCL implant removal	1	0		

 Table 2
 Outcomes data, surgical data for transtibial and tibial inlay PCL cohorts

Abbreviations: += 1 + laxity; ++= 2 + laxity; 0, negative posterior drawer; FFU, final follow-up; NSD, no statistically significant different; PCL, posterior cruciate ligament; ROM, range of motion; SD, standard deviation; TKA, total knee arthroplasty.

^aFinal follow-up posterior drawer testing not performed due to unrelated postoperative complications interfering with knee manipulation.

psychological outcomes. One patient in the TI cohort failed and opted for knee arthrodesis. One patient in the TT cohort required revision using anatomic double-bundle PCLR with TI tibial fixation, which resulted in a successful outcome. Of the variables analyzed, no significant risk factors for treatment failure were identified in this population of patients.

While reoperation and complication rates for patients in the present study are similar to those reported in previous studies, 17, 49-53 our data regarding functional success and posterior stability are more favorable. Previous studies report 1+ laxity in 35 to 91% of patients and 2+ laxity in 9 to 77% of cases at final follow-up.^{26,28,29,49,54} In the present study, excellent stability (0 laxity) was documented in 73.5% and 1+ laxity was documented in 17.6% of patients, with 2+ laxity only noted in the two treatment failures. The improved stability noted in our patients is most likely related to the use of the anatomic double-bundle PCLR with an internal brace for both tibial fixation techniques. Previous studies comparing TT and TI techniques have done so using single-bundle PCLR and have consistently reported a significant number of patients with remaining 2+ posterior laxity.²⁶⁻²⁹ While long-term clinical outcomes data comparing single- versus double-bundle PCLR are limited, double-bundle PCL reconstruction has consistently been reported to be associated with biomechanical superiority. This superiority has been demonstrated to be primarily related to the more anatomic recapitulation of two bundles that can undergo differential tensioning and function in a codominant manner, with graft bulk also playing a role.^{12,55,56} Additionally, all-soft-tissue suspensory fixation in sockets was utilized for femoral PCLR in both the TI and TT cohorts in this study, which has been associated with improved tendon-to-bone healing when compared with interference fixation in tunnels.⁵³ Lastly, all PCL allograft constructs were augmented with a load-sharing suture tape internal brace, which has been documented to enhance graft strength and reduce graft elongation.^{37,57,58} In summation, the biomechanical advantages associated with anatomic double-bundle reconstruction with suture tape augmentation for femoral suspensory fixation appear to have provided sustained stability for both TT and TI tibial fixation techniques that is superior to what has been previously reported after PCLR and is associated with successful outcomes in >90% of patients.

While BMI was not statistically different between cohorts, patients with BMI kg/m² > 35 were more likely to undergo TI PCLR. Preoperative BMI was higher in the TI cohort as obesity (BMI >35 kg/m²) is used as a decision-making criterion in our treatment algorithm for TT versus TI techniques. Importantly, the application of this criterion to the choice of tibial fixation technique resulted in negation of BMI as a statistically significant risk factor for PCLR-related complications in this patient population. Previous studies have suggested that BMI > 30 is associated with up to nine times higher complication rates in multiligament knee injuries patients.^{59–61} As such, the TI tibial fixation technique appears to be advantageous and indicated for anatomic double-bundle PCLR in obese patients. In contrast, the significantly lower 6-month pain scores noted for TT patients, most likely related to



Fig. 3 Representative radiographs at final follow-up for successful TI and TT patients. (A) Radiographic views of patient in the present study 17 months after tibial inlay (TI) with bone block tibial fixation for anatomic double-bundle PCL reconstruction and concurrent PLC reconstruction with subsequent ACL reconstruction. (B) Radiographic views of patient in the present study 22 months after transtibial (TT) tibial fixation for anatomic double-bundle PCL reconstruction, and PLC reconstruction with subsequent ACL reconstruction and concurrent medial meniscus repair, PMC reconstruction, and PLC reconstruction with subsequent ACL reconstruction. ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; PLC, posterior lateral corner; PMC, posterior medial corner.

arthroscopic versus open approaches, suggest short-term advantages for pain management and related patient satisfaction with the TT technique, when indicated.

This study was limited by the relatively small patient population analyzed, due in part to the proportion excluded because of incomplete follow-up data. Together with the design as a single-center, single-surgeon study to control for related variables, the generalizability of the results is limited. In addition, while the follow-up duration allows for conclusions regarding surgery-related complications, reoperations, treatment failures, and functional recovery after PCLR, conclusions regarding long-term outcomes with respect to the longevity of restoration of knee function and development of posttraumatic osteoarthritis cannot be made based on these data. Further, the study was not designed as a randomized controlled trial based on ethical, patient acceptance, and feasibility factors, but rather as a clinical cohort study critically evaluating outcomes associated with two different PCLR tibial fixation techniques implemented based on subjective selection criteria. This experimental design inherently resulted in considerable variability between cohorts with respect to obesity and concomitant injuries to the knee, which limits the conclusions to the stated objective to compare clinical outcomes associated with these techniques to delineate relative advantages, disadvantages, and indications for each.

Conclusion

TT and TI techniques used for anatomic double-bundle PCLR were successful in restoring knee stability and patient

	Transtibial group	Tibial inlay group	p-Value
6 mo			
VAS	1.7 ± 1.8	3.4±2.7	p = 0.042
PROMIS Global Health	43.7 ± 3.8	44.6 ± 5.1	NSD, $p = 0.75$
PROMIS Mental Health	51.3 ± 4.3	50.7 ± 13.6	NSD, $p = 0.92$
PROMIS Physical Function	34.8±11.1	33.4 ± 9.6	NSD, <i>p</i> = 0.61
PROMIS Pain Interference	57.2 ± 6.9	62.1±5.3	NSD, $p = 0.21$
1 y			
VAS	1.7 ± 1.9	2.5 ± 3.0	NSD, $p = 0.38$
PROMIS Global Health	45.7 ± 9.0	45.1±4.5	NSD, $p = 0.9$
PROMIS Mental Health	50.7 ± 8.2	45.9 ± 3.4	NSD, $p = 0.29$
PROMIS Physical Function	38.4±7.9	37.0 ± 6.6	NSD, $p = 0.73$
PROMIS Pain Interference	56.0 ± 11.8	53.6 ± 8.7	NSD, $p = 0.68$
2 у			
VAS	1.8 ± 2.0	1.3 ± 1.5	NSD, $p = 0.58$
PROMIS Global Health	41.2 ± 6.4	43.8 ± 5.6	NSD, $p = 0.66$
PROMIS Mental Health	51.1 ± 9.9	53 ± 13.4	NSD, $p = 0.71$
PROMIS Physical Function	41.6 ± 5.4	41.6±6.2	NSD, $p = 0.93$
PROMIS Pain Interference	57.8±4.9	54.7 ± 6.0	NSD, $p = 0.33$

Table 3 Patient reported outcomes

Abbreviations: NSD, no statistically significant different; PROMIS, Patient Reported Outcomes Measurement Information System; VAS, visual analog scale for pain.

^{*}Bold denotes statistically significant figure (*p*<0.05).

function when used for the treatment of isolated and multiligamentous PCL injuries. The choice between these tibial fixation methods for PCLR can be appropriately based on patient and injury characteristics that optimize respective advantages for each technique.

Conflicts of Interest

• J.L.C. received research support from AO Trauma, received IP royalties and is a paid consultant for Arthrex, Inc; received research support from Collagen Matrix Inc; received research support from DePuy, A Johnson & Johnson Company; is on the editorial or governing board of the Journal of Knee Surgery; is a board or committee member for Midwest Transplant Network; is a board or committee member; received IP royalties and research support from Musculoskeletal Transplant Foundation; received research support from National Institutes of Health (NIAMS & NICHD); received research support from Orthopaedic Trauma Association; received research support from Purina; received research support from Regenosine; received research support from SITES Medical; received publishing royalties, financial, or material support from Thieme; is a paid consultant for Trupanion; and received research support from the U.S. Department of Defense.

• J.P.S. is a board or committee member for the American Orthopaedic Association; is a board or committee member for AO Foundation; is a board or committee member for AO North America; is a paid consultant and receives research support from Arthrex, Inc; is a paid consultant for DePuy, A Johnson & Johnson Company; is on the editorial or governing board for the Journal of Knee Surgery; is a board or committee member for Mid-America Orthopaedic Association; receives research support from the National Institutes of Health (NIAMS & NICHD); is a paid consultant for Orthopedic Designs North America; is a paid consultant for Smith & Nephew; received publishing royalties, financial or material support from Thieme and received research support from the U.S. Department of Defense.

• J.T., K.R., A.M., and J.B.deA. II declare no conflict of interest.

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