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Original article

High tibial osteotomy is equally effective for varus malaligned knees with either virgin or wrecked medial meniscus: An age and gender-matched secondary analysis of a Francophone Arthroscopy Society Symposium

Ahmed Mabrouk[a,b], Matthieu Ollivier[b,*], Jean-Marie Fayard[c], Cécile Batailler[d], Nicolas Bouguennec[e], Nicolas Tardy[f], Goulven Rochcongar[g]

[a] Leeds Teaching Hospitals, Department of trauma and Orthopaedics, Leeds, United Kingdom
[b] Aix-Marseille University, AP–HM, CNRS, ISM, Sainte-Marguerite Hospital, Institute for Locomotion, Marseille, France
[c] Hôpital Privé Jean Mermoz, Ramsay-Générale de Santé, Lyon, France
[d] Department of Orthopaedic Surgery, Croix-Rousse Hospital, Lyon University Hospital, Lyon, France
[e] Sport Clinique of, Bordeaux-Mérignac, France
[f] Centre Ostéo-Articulaire Des Cèdres, Clinique Des Cèdres, 5, rue des Tropiques, 38130 Échirolles, France
[g] Orthopaedics and Traumatology Department, Normandie University, UNICAEN, CHU de Caen Normandie, 14000 Caen, France

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ABSTRACT

Introduction: Despite the growing concept of meniscal preservation, partial meniscectomy could be the definitive procedure in specific scenarios. And total meniscectomy was once before a frequent procedure, with current sequelae of degenerate knees. High tibial osteotomy (HTO) is an effective treatment for patients suffering from unicompartmental degenerative changes, and substantial deformities. However, it is yet to be answered, whether HTO is similarly effective in both post-meniscectomy knees and knees with not previously operated meniscus.
Hypothesis: Outcomes of HTO is similar with or without previous history of total or subtotal meniscectomy.
Methods: This study compared the clinical and radiological outcomes of 41 patients who received HTO and had no previous history of surgery in the ipsilateral knee (group I), and 41 age, and gender-matched patients who had meniscectomy surgery in the ipsilateral knee (group II). Preoperatively and postoperatively, all patients were clinically evaluated; the visual analogue scale scores, Tegner activity score, and the Western Ontario and Macmaster University scores were reported. Radiographically, osteoarthritis grade and pre- and postoperative parameters were reported, including hip-knee-ankle angle, femoral mechanical angle, medial proximal tibial angle, joint line convergence angle, proximal posterior tibial angle, and limb length discrepancy. Perioperative details and complications were reported.
Results: A total of 82 patients were included; group I ($n=41$) and group II ($n=41$). The mean age was 51.18 ± 8.64 (27–68) and 90.24% were male. The duration since the onset of symptoms was longer in group II vs. group I, 43.34 ± 41.03 versus 38.07 ± 36.11 months respectively. No significant differences in the clinical evaluation between the two groups with a greater proportion of patients demonstrating moderate degenerative changes. Similar preoperative and postoperative radiographic parameters were reported, in group I, Δ HKA was 7.19 ± 4.14 versus 7.65 ± 3.16 in group II. Preoperative pain VAS scores were slightly higher in group II vs. group I, 79.23 ± 26.35 vs. 76.31 ± 24.45, respectively. However, postoperatively, the pain scores significantly improved in group I vs. group II, 22.84 ± 3.65 vs. 41.69 ± 17.33, respectively. Tegner activity scores and WOMAC scores were comparable between both groups preoperatively and postoperatively. Only the WOMAC function scores were better in group I when compared to group II, 26.13 ± 25.84 versus 20.01 ± 17.98. All patients returned to work at an average of 0.82 ± 0.38 months.

* Corresponding author.
E-mail addresses: ollivier.matthieu@yahoo.fr, ollivier.mt@gmail.com (M. Ollivier).

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Conclusion: Knee preservation with high tibial osteotomy is equally effective in managing unicompartmental degenerative changes in varus malaligned knees with either no previous history of meniscal surgeries or where a meniscal sacrifice was inevitable, either with subtotal or total meniscectomy.
Level of evidence: III, retrospective case-control study.

1. Introduction

Meniscal tears are the most common knee injury, and partial meniscectomies are the most common orthopaedic surgical procedures [1,2]. Following meniscectomy, contact stresses across the knee joint remarkably increase [3,4]. A linear relationship was reported between the volume of the removed meniscus and the increase in contact stresses [3]. Hence, the meniscus-deficient knee compartment can progress to early degenerative changes, and joint space narrowing with evolving osteoarthritis [5–9].

The clinical manifestations of knee osteoarthritis (OA) are more severe when associated with varus malalignment [10]. The effectiveness of high tibial osteotomy (HTO) in unloading the medial compartment and enhancing cartilage regeneration, clinically and radiologically, is extensively reported in the literature [11–23]. However, there is a paucity of literature regarding the outcomes of high tibial osteotomy following meniscectomy surgeries [24].

The purpose of the current study was to compare the clinical and radiological outcomes of high tibial osteotomy following subtotal or total medial meniscectomy versus the outcomes in knees with a virgin medial meniscus.

2. Methods

From a multi-centre database, a total of 82 patients were involved in the study. Patients were categorized into two groups; group I ($n = 41$) included the patients who underwent HTO and had no previous history of surgery in the ipsilateral knee. And group II ($n = 41$) were matched in age (± 3 yrs), gender, and preoperative global WOMAC scores (± 5 pts), who underwent HTO and had a previous history of either total or subtotal meniscectomy.

2.1. Clinical evaluation

All patients were evaluated with regard to the history of the onset of symptoms. Preoperative and postoperative assessment of flexion range in degrees, presence of flexion contracture in degrees, and presence or absence of knee effusion were noted. Preoperative clinical evaluation is demonstrated in Table 1. Additionally, the preoperative and postoperative patient-reported outcome measures (PROMs) were reported. This included the visual analogue scale (VAS) scores, Tegner activity scores, and Western Ontario and Macmaster University scores (WOMAC) for stiffness, function as well as global WOMAC scores. The preoperative and postoperative PROMs are demonstrated in Tables 2 and 3.

2.2. Radiological evaluation

All patients had a preoperative radiographic evaluation for the degree of osteoarthritic changes based on the Ahlbäck grade, and Kellgren–Lawrence grade. Preoperative and postoperative radiological geometrical parameters were assessed including hip-knee-ankle angle (HKA), femoral mechanical angle (FMA), medial proximal tibial angle (MPTA), joint line convergence angle (JLCA), proximal posterior tibial angle (PPTA), as well as limb length discrepancy (LLD). The radiological characteristics and geometrical parameters are demonstrated in Table 4. Additionally, Delta values for the main geometrical parameters were calculated; Δ HKA, Δ JLCA, Δ PPTA, Δ MPTA (Postop – Preop), Δ MPTA (Postop – Target). Delta values are demonstrated in Table 5.

2.3. Operative details

Seventy patients (85.36%) underwent opening wedge high tibial osteotomy (OWHTO); 33 patients (40.24%) were in group I and 37 (45.12%) patients were in group II. And 12 patients (14.63%) underwent closed wedge high tibial osteotomy (CWHTO); 8 patients (9.75%) in group I, and 4 patients (4.87%) in group II. A conventional free-hand osteotomy technique was followed in 41.46% of the cases ($n = 34$). Patient-specific instrumentation was used in 25.60% ($n = 21$), and navigation was used in the remainder of 32.92% of the patients ($n = 27$). The osteotomy gap in OWHTO was filled with autograft in 15.85% of the cases ($n = 13$), allograft in 36.56% ($n = 30$), and synthetic materials in 46.34% of the cases ($n = 38$). Postoperatively, 14.63% ($n = 12$) of the patients were allowed full weight-bearing, 24.39% ($n = 20$) were allowed partial weight-bearing at 3 weeks, and 59.75% ($n = 49$) were allowed partial weight-bearing at 6 weeks. Operative details and postoperative protocol are demonstrated in Table 6. Postoperative complications and their management are reported in Table 2.

2.4. Statistical analysis

Data that are descriptive statistics are presented as mean $\pm$ SD. Statistical analysis was performed with SPSS™ 12.0 (IBM Corporation, Somers, NY, USA). Student's paired *t*-tests and Fisher tests were planned for intragroup comparison. Two-sample *t*-tests and Fisher tests were planned for intergroup comparisons. Non-parametric tests were used for parameters with non-gaussian distribution.

Statistical significance was assumed at *p*-values of < 0.05.

A post-hoc sample size analysis exhibited that our series allowed the comparison of lower-limb morphological parameters, clinical scores and demographic parameters with a statistical power > 80%.

3. Results

The study population comprised 82 patients, of which 90.24% were males with a mean age of 51.18 ± 8.64 (27–68). Patient characteristics are demonstrated in Table 7.

Patients with previous meniscal surgery had a longer history of symptoms when compared to the patients with no previous history of surgery, 43 ± 41 months versus 38 ± 36 months, respectively ($p = 0.01$). However, there was no significant difference in the clinical evaluation of both groups. Details are demonstrated in Table 1.

A greater proportion of the patients demonstrated moderate preoperative osteoarthritic changes (KL grade 2 or 3): 78% in group I and 70% in group II ($p = 0.02$). Preoperative and postoperative radiographic parameters and delta values were almost similar which are demonstrated in Tables 3 and 4.

Table 1
Clinical evaluation, all values were applicable are presented as mean ± standard deviation [95% confidence interval].

Variable assessed	Total	Group I	Group II
The onset of symptoms (months)	38.07 ± 36.11	43.34 ± 41.03	12.80 ± 10.01
Preoperative effusion (number of patients)	33	16	17
Preoperative flexion contracture (degrees)	0.54 ± 1.53 [0.21, 0.88]	0.63 ± 1.69 [0.09, 1.17]	0.46 ± 1.36 [0.03, 0.89]
Preoperative flexion (degrees)	136.15 ± 10.57 [133.83, 138.48]	135.73 ± 10.22 [132.50, 138.05]	136.58 ± 11.03 [133.10, 140.06]
Postoperative effusion (number of patients)	9	4	5
Postoperative flexion contracture (degrees)	0.51 ± 1.90 [0.08, 0.94]	0.65 ± 2.07 [−0.02, −0.18]	0.37 ± 1.74 [−0.18, 0.93]
Postoperative flexion (degrees)	136.53 ± 9.51 [134.39, 138.68]	136.71 ± 9.88 [133.46, 139.95]	136.37 ± 9.26 [133.41, 139.33]

Table 2
Postoperative complications and management.

Complication	Group I	Group II	Management
Superficial infection	1	0	Oral antibiotics
Deep infection	0	1	Open washout + antibiotics course
Sciatic nerve neuropraxia	1	0	Observation (completely resolved at 3 months)
Compression syndrome	0	1	Revision
Postoperative hematoma	0	1	Observation (resolved)

Table 3
Preoperative PROMs mean ± standard deviation [95% confidence interval].

PROMs Score Preoperative	Total	Group I	Group II
Pain VAS	77.67 ± 25.22 [71.79, 83.56]	76.31 ± 24.45 [68.39, 84.24]	79.23 ± 26.35 [70.04, 88.43]
Tegner score level	Number of patients		
0	2	1	1
1	5	4	1
2	5	2	3
3	17	8	9
4	15	7	8
5	27	15	12
6	8	2	6
7	0	0	0
8	3	2	1
WOMAC			
Stiffness	48.43 ± 22.78 [43.03, 53.79]	46.95 ± 26.58 [38.09, 43.75]	50.0 ± 18.19 [43.75, 56.24]
Function	56.02 ± 21.17 [51.31, 60.73]	52.79 ± 24.02 [45.11, 60.48]	59.25 ± 17.58 [53.62, 64.87]

PROMs: patient-reported outcome measures; VAS: visual analogue scale; WOMAC: Western Ontario and Macmaster University index.

Preoperative pain VAS scores were slightly higher in group II vs. group I, 79.23 ± 26.35 vs. 76.31 ± 24.45, respectively. However, postoperatively, the pain scores significantly improved in group I vs. group II, 22.84 ± 3.65 vs. 41.69 ± 17.33, respectively.

Preoperative Tegner activity scores between 3 to 5 were reported in 30 patients in group I and 29 patients in group II. Postoperatively, Tegner activity scores between 3 to 5 were reported again in 30 patients in group I and 26 patients in group II.

Preoperative WOMAC scores were better for both stiffness and function in group II patients when compared to group I patients. Group II reported 50.0 ± 18.19 for stiffness and 59.25 ± 17.58 for function. Whereas, patients in group I reported 46.95 ± 26.58 for stiffness and 52.79 ± 24.02 for function. However, postoperatively, WOMAC scores between both groups were similar for stiffness, and global scores, group I reported 29.48 ± 31.86, and 27.75 ± 30.55, respectively. Whereas, group II reported, 29.41 ± 38.66, and 28.11 ± 35.19. However, the WOMAC function scores were better in group I when compared to group II, 26.13 ± 25.84 versus 20.01 ± 17.98. All patients returned to work at an average of 0.82 ± 0.38 months. The preoperative and postoperative PROMs are demonstrated in Tables 3 and 8.

4. Discussion

The most important finding in the presented study is the confirmation of our hypothesis that HTO will result in equivalent effective clinical outcomes regardless of a previous history of subtotal or total meniscectomy. In the presented study, all patients in both groups underwent similar surgical procedures with almost equivalent variables and achieved corrections. And all patients reported postoperative equivalent clinical improvement as reflected by the patient-reported outcome measures (PROMs). Slightly better VAS pain scores were reported in group II versus group I, 79.23 ± 26.35 versus 76.31 ± 24.45, respectively. And WOMAC function scores were better in group I versus group II, 26.13 ± 25.84 versus 20.01 ± 17.98, respectively.

Table 4
Radiological characteristics and geometrical parameters. All results were applicable are presented as mean ± standard deviation [95% confidence interval].

Radiological parameter	Total patients	Group I	Group II
Preoperative radiological OA	Number of patients		
Ahlbäck grade			
1	15	8	7
2	50	27	23
3	17	6	11
Kellgren–Lawrence grade			
1	7	4	3
2	21	11	10
3	40	21	19
4	14	5	9
Preoperative radiological geometrical parameters			
HKA	173.99 ± 3.01 [173.32, 174.65]	173.73 ± 2.96 [172.79, 174.69]	174.24 ± 3.08 [173.27, 175.22]
FMA	91.13 ± 1.94 [90.70, 91.57]	91.21 ± 1.60 [90.69, 91.73]	91.06 ± 2.24 [90.34, 91.78]
MPTA	84.80 ± 2.75 [84.18, 85.42]	84.43 ± 2.70 [83.55, 85.31]	85.16 ± 2.79 [84.26, 86.05]
JLCA	8.69 ± 32.29 [1.55, 15.83]	10.71 ± 37.05 [−0.98, 22.40]	6.63 ± 26.87 [−1.96, 15.22]
PETA	4.75 ± 2.89 [4.10, 5.40]	4.58 ± 2.32 [3.83, 5.33]	4.92 ± 3.39 [3.82, 6.02]
PPTA	4.64 ± 3.16 [3.76, 5.51]	4.66 ± 2.91 [3.57, 5.75]	4.60 ± 3.53 [3.07, 6.13]
LLD	−0.06 ± 0.98 [−0.28, 0.14]	−0.13 ± 1.30 [0.54, 0.27]	0.007 ± 0.48 [−0.16, 0.14]
Postoperative radiological geometrical parameters			
HKA	181.40 ± 3.20 [180.69, 182.11]	180.86 ± 3.45 [179.75, 181.96]	181.95 ± 2.87 [181.03, 182.86]
FMA	90.94 ± 2.40 [90.40, 91,47]	91.57 ± 1.92 [90.96, 92.18]	90.31 ± 2.68 [89.45, 91.16]
MPTA	90.45 ± 10.51 [88.10, 92.79]	90.82 ± 2.73 [89.95, 91.69]	90.07 ± 14.70 [85.37, 94.77]
JLCA	3.37 ± 9.89 [1.16, 5.57]	2.39 ± 2.83 [1.48, 3.30]	4.35 ± 13.72 [−0.04, 8.74]
PETA			
PPTA	4.88 ± 3.28 [3.97, 5.79]	5.10 ± 2.88 [4.0, 6.19]	4.60 ± 3.77 [2.97, 6.24]
LLD	0.15 ± 0.85 [−0.14,0.45]	0.23 ± 1.09 [0.25, 0.02]	0.02 ± 0.08 [−0.02, 0.07]

HKA: hip-knee-ankle angle; FMA: femoral mechanical angle; JLCA: joint line convergence angle; PETA: proximal epiphyseal tibial angle; PPTA: proximal posterior tibial angle; CI: confidence interval.

Table 5
Delta Δ values of the radiological geometrical parameters.

Δ radiological parameter	Total patients	Group I	Group II
Δ HKA (Postop – Preop)	7.42 ± 3.67 [6.59, 8.24]	7.19 ± 4.14 [5.86, 8.52]	7.65 ± 3.16 [6.62, 8.67]
Δ JLCA (Postop – Preop)	2.38 ± 2.40 [1.69, 3.07]	2.81 ± 2.88 [1.67, 3.95]	1.85 ± 1.53 [1.17, 2.52]
Δ PPTA (Postop – Preop)	1.13 ± 1.29 [0.77, 1.49]	1.06 ± 1.09 [0.65, 1.48]	1.21 ± 1.53 [0.55, 1.88]
Δ MPTA (Postop – Preop)	7.29 ± 19.89 [2.84, 11.75]	6.86 ± 19.99 [0.46, 13.25]	7.74 ± 20.03 [1.24, 14.23]
Δ MPTA (Postop – Target)	3.63 ± 2.71 [3.01, 4.35]	3.51 ± 3.07 [2.50, 2.98]	3.75 ± 2.34 [2.98, 4.52]

HKA: hip-knee-ankle angle; JLCA: joint line convergence angle; MPTA: medial proximal tibial angle; PPTA: proximal posterior tibial angle; CI: confidence interval.

The notable role of the meniscus in preserving the joint chondral surfaces is well-reported in the literature [25]. Amongst the primary functions of the menisci are load distribution and stability. The medial meniscus transmits 50% of the medial knee compartment load in extension, which increases to 85% in flexion. After medial meniscectomy, contact stresses increase to 100% [2,26–31]. Additionally, several studies have reported post-meniscectomy remarkable deterioration of the soft tissues, chondral surfaces, and subchondral bones, both radiographically and with magnetic resonance imaging (MRI) evaluation [8,32–34].

There is scarce evidence in the literature on the non-operative management of symptomatic post-meniscectomy knees [35]. Few studies demonstrated the lack of significant clinical benefits following either personalized physiotherapy programs or viscoelastic supplementation [36,37].

Table 6
Operative details and postoperative protocol, all values where applicable are presented as mean ± standard deviation [95% confidence interval].

	Total	Group I	Group II
Osteotomy type			
OWHTO	70	33	37
CWHTO	12	8	4
Planning technique			
Conventional	34	16	18
PSI	21	14	7
Navigation	27	11	16
Targeted level of correction			
HKA	182.26 ± 1.91 [181.84, 182.68]	182.69 ± 1.27 [182.29, 183.09]	181.84 ± 2.31 [181.10, 183.57]
MPTA	90.84 ± 13.32 [87.84, 93.85]	91.21 ± 13.45 [86.85, 95.57]	90.47 ± 13.35 [86.14, 94.80]
Δ MPTA	8.26 ± 3.13 [7.56, 8.96]	8.98 ± 3.27 [7.93, 10.03]	7.52 ± 2.83 [6.60, 8.44]
Gap filling in OWHTO	Number of patients		
Autograft	13	8	5
Allograft	30	13	17
Cement	38	20	18
Postoperative weight-bearing status	Number of patients		
FWB	12	6	6
PWB (at 3 weeks postop)	20	10	10
PWB (at 6 weeks postop)	49	25	24

OWHTO: open wedge high tibial osteotomy; CWHTO: closed wedge high tibial osteotomy; PSI: patient-specific instrumentation; HKA: hip-knee-ankle angle; MPTA: medial proximal tibial angle.

Table 7
Patient characteristics, all values where applicable are presented as mean ± standard deviation (range).

Variable	Total	Group I	Group II
Gender			
Male	74	37	37
Female	8	4	4
Age	51.18 ± 8.64 (27–68)	51.39 ± 7.53	50.98 ± 9.71
BMI	27.30 ± 3.58 (18.92–43.69)	28.15 ± 3.93	26.45 ± 2.99
Side			
Right	38	17	21
Left	44	24	20
Professional activity level	Number of patients		
Sedentary	18	10	8
Light	27	17	10
Moderate	28	10	18
Arduous	9	4	5

HTO: high tibial osteotomy; BMI: body mass index; OA: osteoarthritis.

On the contrary, there are multiple studies on a variety of surgical options for the management of symptomatic post-meniscectomy knees [30,38–41]. Meniscal scaffolds have demonstrated satisfactory clinical outcomes whether isolated or combined with other surgical procedures [42–44]. However, in a metanalysis of clinical outcomes following polyurethane meniscal scaffolds, Shin et al. [45] reported deterioration of the articular cartilage at the last follow-up despite clinical improvements.

Meniscal allograft transplantation (MAT) has been demonstrated to have a high clinical failure rate at midterm follow-up, with Lysholm scores < 65 points. Especially, in females and when a combined procedure is required such as cartilage surgery or ACL reconstruction. [46]. Moreover, a meta-analysis has shown the medial MAT to have lower survival compared to the lateral MAT at the midterm follow-up (5–10 years) 85.8% vs. 89.2% respectively, and at the long-term follow-up > 10 years, 52.6% vs. 56.6%, respectively [47]. Furthermore, a relatively high reoperation rate, up to 30–46% was reported in another study [48].

The real challenge presents in cases of post-meniscectomy with associated varus malalignment, as it has been shown that the combination expedites cartilage degeneration and development of osteoarthritic changes [5,49]. On the long-term (10–22 years), post-meniscectomy degenerative changes were demonstrated to be significantly higher in maligned limbs [5]. Even on a shorter term, following meniscectomy with varus malalignment, Covall and Wasilewski [49] reported that at 5.4 years, 50% of the patients developed grade 1 Fairbank changes [50], and 43% developed changes greater than grade 2.

In a biomechanical study, Van Thiel et al. [30], demonstrated that peak pressures significantly increased in the meniscectomized state in every degree of varus/valgus ($p < 0.05$). Whereas, HTO improves the peak pressures in the medial compartment at all degrees of varus/valgus alignment, with a significant drop ($p < 0.001$) between neutral and 3 degrees of valgus. Nha et al. [51] in a second-look arthroscopic study following open wedge HTO, demonstrated a high healing rate of the unrepaired posterior root tear of the medial meniscus, despite no improvement in the clinical outcomes.

The ideal target in managing post-meniscectomy patients is to prevent osteoarthritis progression. In addition to providing symptomatic relief in daily activities, and improving function [35]. In a systematic review, Harris et al. [52] evaluated the survival and clinical outcomes of isolated HTO versus combined biological knee reconstructions. They concluded that isolated HTO can potentially

Table 8
Postoperative PROMs mean ± standard deviation [95% confidence interval], and satisfaction level.

PROMs score postoperative	Total	Group I	Group II
Pain VAS	39.48 ± 20.43 [34.71, 44.25]	22.84 ± 3.65 [30.15, 44.96]	41.69 ± 17.33 [35.64, 47.74]
Δ Pain VAS	38.19 ± 27.88 [31.68, 44.70]	38.76 ± 30.67 [28.81, 48.70]	37.54 ± 24.74 [28.90, 46.17]
Tegner score level	Number of Patients		
0	4	2	2
1	3	1	2
2	2	2	0
3	16	11	5
4	20	9	11
5	20	10	10
6	6	2	4
7	0	0	0
8	2	2	0
WOMAC			
Stiffness	71.91 ± 24.80 [66.12, 77.70]	72.75 ± 25.94 [64.34, 81.16]	70.95 ± 23.78 [62.65, 79.25]
Function	78.81 ± 20.28 [74.08, 83.55]	78.98 ± 20.84 [72.23, 84.74]	78.62 ± 19.92 [71.66, 85.57]
Global	73.72 ± 24.08 [68.10, 79.34]	73.65 ± 25.32 [65.45, 81.86]	73.79 ± 22.96 [65.78, 81.80]
Δ WOMAC			
Stiffness	29.45 ± 34.94 [21.29, 37.60]	29.48 ± 31.86 [19.15, 39.81]	29.41 ± 38.66 [15.92, 42.90]
Function	23.28 ± 22.58 [18.01, 28.55]	26.13 ± 25.84 [17.76, 34.51]	20.01 ± 17.98 [13.74, 26.29]
Global	27.92 ± 32.56 [20.32, 35.52]	27.75 ± 30.55 [17.85, 37.66]	28.11 ± 35.19 [15.83, 40.39]
Satisfaction level	Number of patients		
Dissatisfied	2	2	0
Mildly satisfied	13	6	7
Moderately satisfied	35	15	20
Enthusiastic	29	16	13
Missing data	3	2	1

PROMs: patient-reported outcome measures; VAS: visual analogue scale; WOMAC: Western Ontario and Macmaster University index.

slow cartilage progression in the malaligned post-meniscectomy knee. In the presented study, it has been demonstrated that these goals could be achieved through an isolated high tibial osteotomy with clinical and radiological results equivalent to those performed in knees with intact menisci.

5. Conclusion

Knee preservation with high tibial osteotomy is equally effective in managing unicompartmental degenerative changes in varus malaligned knees with either no previous history of meniscal surgeries or where a meniscal sacrifice was inevitable, either with subtotal or total meniscectomy.

Ethical approval

N/A.

Informed consent

N/A.

Disclosure of interest

Matthieu Ollivier, Jean-Marie Fayard: consultant Newclip.

Ahmed Mabrouk Cécile batailler, Nicolas Bougennec, Nicolas Tardy, Goulven Rochcongar declare that they have no competing interest.

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Authors' contributions

AM, MO drafted the manuscript and completed the necessary revisions.

JMF, GR edited the paper extensively.

JMF, GR, CB, NT, NB created initial dataset.

All the authors have reviewed and edited the manuscript.

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