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Knee joint preservation with combined neutralising High Tibial Osteotomy (HTO) and Matrix-induced Autologous Chondrocyte Implantation (MACI) in younger patients with medial knee osteoarthritis: A case series with prospective clinical and MRI follow-up over 5 years

S. Bauer [a,*], R.J.K. Khan [a], J.R. Ebert [b], W.B. Robertson [a], W. Breidahl [c], T.R. Ackland [b], D.J. Wood [a]

[a] School of Surgery and Pathology (Orthopaedics), The University of Western Australia, Perth, Australia
[b] School of Sport Science, Exercise and Health, The University of Western Australia, Perth, Australia
[c] Perth Radiological Clinic, Subiaco, Perth, Western Australia, Australia

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ABSTRACT

Purpose: There is no ideal treatment for younger patients with medial knee osteoarthritis (OA) and varus malalignment. We have investigated the first case series of combined neutralising high tibial osteotomy (HTO) and Matrix-induced Autologous Chondrocyte Implantation (MACI) with MRI. Treatment goals were clinical improvement and delay of arthroplasty.
Methods: Between 2002 and 2005 18 patients (Mean age 47 years) underwent surgery. Exclusion criteria were lateral compartment and advanced patellofemoral OA. The Knee Injury and Osteoarthritis Outcome Score (KOOS), six minute walk test (6MWT) and a validated MRI score were outcome measures.
Results: There were significant improvements ($p<0.05$) in all five KOOS domains. Four were significantly maintained to 5 years. The domain "symptoms" and results in the 6MWT dropped off at 5 years. MRI results were first significantly improved (24/12) but declined at 60 months. Good quality infill was found in 33% patients at the study endpoint ($n=5/15$). Histological investigation of one knee demonstrated full-thickness hyaline-like cartilage (20/12). After 2 early failures and one graft detachment graft fixation was changed (Smart nails instead of sutures in 14 cases). Graft hypertrophy requiring a chondroplasty occurred once. There were no other major complications. Specific minor complications included patellar tendinitis ($n=8$).
Conclusions: This combined procedure provides a safe treatment option for younger patients with medial knee OA and varus alignment with significant clinical improvement at 5 years. However, overall graft survival and cartilage infill were poor. Larger studies are needed to statistically verify predictors for longer term cartilage repair in these patients.

1. Introduction

Cartilage lesions of the knee are common. Grade IV lesions are most often located at the medial femoral condyle (MFC). In a review of over 30,000 arthroscopies 5% of patients were under the age of 40 and had a grade IV lesion [1]. Usually such lesions lead to progression of osteoarthritis (OA) [2,3]. Joint malalignment may contribute to this process due to overload of the affected compartment [4].

Young and active patients with medial OA are a treatment challenge, troubled by pain, loss of function and disability. Unicompartmental (UKA) and Total Knee Arthroplasty (TKA) fail early in younger patients with poor outcomes of revision surgery [5]. In the last few decades, arthroscopic lavage, debridement, marrow stimulating techniques and osteotomy have been used to address cartilage lesions [6]. To date, no gold standard treatment for medial knee OA in younger patients has been established [7]. More innovative techniques using the potential of hyaline chondrocytes have since been developed.

Matrix-induced Autologous Chondrocyte Implantation (MACI), the second generation of Autologous Chondrocyte Implantation (ACI), does not use a periosteal cover as used in the traditional technique [8]. Instead, chondrocytes are seeded directly onto a bio-absorbable membrane [9] and fixed in place with fibrin glue. Ideally, the indication of MACI is limited to focal cartilage lesions with healthy native cartilage borders, in normally aligned and stable knees with preserved menisci [10].

High Tibial Osteotomy (HTO) is indicated in young patients with large chondral lesions located on the medial femoral and tibial condyles associated with malalignment, to off-load the affected medial compartment and transfer load-bearing onto the healthy lateral compartment [11]. Traditionally, in these situations valgus

* Corresponding author. Tel.: +61 405368669.
E-mail address: stef11bau@yahoo.co.uk (Stefan Bauer).

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Table 1
Pre-operative characteristics of patients and follow up.

Age	Gen	BMI	ROM	Defect site; Ahlbäck stage	Defect size (cm^2)	Previous knee surgery	Tibia (Outerbridge)	Menisci	Ligament status	PF (Outerbridge)	f/u
34	M	24	147	LMFC; I	5	x 4 arthroscopies, including MF, C/P, PMM	Kissing lesion, II	PMM	Intact	II	SE1&2
47	F	24	122	RMFC, I	14	No previous surgery	Kissing lesion,III	Intact	Intact	II	SE1
51	F	28	133	LMFC; I	10	x 2 arthroscopies, including C/P and PMM	Kissing lesion, II	PMM	Intact	III	SE1&2
34	M	25	146	RMFC; I	2	x 2 arthroscopies, including C/P and PMM	Kissing lesion, II	PMM	Intact	II	5y clin/1y MRI f/u
56	M	27	137	LMFC; I	12	x 3 arthroscopies, including C/P and PMM	Kissing, lesion, II	PMM	Partial ACL-tear, no laxity	Intact	SE1
51	M	23	146	RMFC; I	5	x 2 arthroscopies, including C/P, PMM, and medial meniscal repair	Kissing lesion,III	PMM	Intact	II	SE1
54	M	33	143	LMFC; I	9	x 2 arthroscopies, including C/P and PMM	Kissing lesion, II	PMM	Intact	II	SE2
49	M	30	117	LMFC; I	6	x 2 arthroscopies, including C/P and PMM	Kissing lesion, II	PMM	Intact	II	SE1
58	M	28	128	RMFC; I	6	x 1 arthroscopy, including C/P and PMM	Kissing lesion, II	PMM	Intact	III	SE3
38	F	24	144	RMFC; I	2	x 2 arthroscopies, including C/P	Kissing lesion, II	Intact	Intact	II	SE1
48	M	27	149	LMFC; I	2	x 1 arthroscopy, including C/P and PMM	Kissing lesion, II	PMM	Intact	II	SE1
46	M	27	130	LMFC; I	8	x 3 arthroscopies, including C/P	Kissing lesion, II	Intact	Intact	II	SE1
55	M	28	130	LMFC; I	10	x 2 arthroscopies, including C/P and PMM	Kissing lesion,III	PMM	Intact	II	SE1
56	M	26	146	LMFC; I	3	x 1 arthroscopy, including C/P and PMM	I	PMM	Intact	Intact	SE1
57	M	27	127	RMFC; I	2	x 2 arthroscopies, including C/P and PMM	Kissing lesion, II	PMM	Intact	III	SE1
52	M	27	135	LMFC; I	7	x 1 arthroscopy, including C/P and PMM	Kissing lesion, II	PMM	Intact	II	5y clin/3y MRI f/u
56	M	28	125	LMFC; I	3	x 2 arthroscopies, including C/P and PMM	I	PMM	Intact	Intact	SE1
51	M	29	140	LMFC; I	3	x 1 arthroscopy, including C/P and PMM	I	PMM	Intact	II	5y clin f/u, SE2

(M = Male, F = Female, BMI = Body Mass Index, ACL = Anterior Cruciate Ligament, PMM = Partial Medial Meniscectomy, MF = Microfracture, C/P = Chondroplasty, PF = Patello-femoral, LMFC = Left Medial Femoral Condyle, RMFC = Right Medial Femoral Condyle, f/u = follow up, SE = Study Endpoint, SE1 = 5-year clinical and MRI f/u completed, SE2 = Graft failure after 2 years (MRI-score of 1), indication, planning or performance of total knee arthroplasty, SE3 = Death, clin = clinical, MRI = Magnetic Resonance Imaging).

overcorrection has been recommended [12]. Factors which are suggested to influence outcome of HTO include extent of deformity correction, age, gender, muscle strength, Body Mass Index (BMI), knee range of movement (ROM) and lateral thrust [13,14,15]. HTO has been described in combination with marrow stimulating repair procedures such as abrasion arthroplasty and microfracture [16,17,18], but these results have limited relevance to our study. HTO in combination with MACI is considered to have an increasing role for chondral lesions associated with malalignment [19]. So far only one case series of combined HTO and MACI with assessment of clinical outcomes only has been published [20,21].

We have conducted the first prospective MRI follow-up of a case series with combined neutralising HTO and MACI in young patients with medial knee compartment arthritis associated with varus malalignment. The aim was to assess whether this combination provides a safe treatment option with acceptable interim clinical and radiological outcomes.

2. Methods and materials

2.1. Inclusion criteria

Younger patients below the age of 60 with knee joint cartilage lesions of the medial compartment and varus malalignment were considered for inclusion.

2.2. Exclusion criteria

Exclusion criteria were total loss of medial joint space on weightbearing views, full thickness lateral or patellofemoral chondral lesions (Outerbridge IV), previous infection or total meniscectomy and ligament laxity.

2.3. Patients

Eighteen patients fulfilled the inclusion criteria and participated in this study between 2002 and 2005 undergoing HTO combined with MACI. Pre-operatively, patients underwent long leg alignment radiographs (Maquet views) and high-resolution magnetic resonance imaging (MRI) of the affected knee. During the same time period 33 patients underwent isolated MACI in our institution. The latter patients showed no indication for HTO. They had smaller defects and no evidence of OA or malalignment on plain x-rays. No isolated HTO procedures were carried out during the study period.

Table 1 shows the pre-operative patient characteristics. There were 15 males and 3 females with a mean age of 47 years (Range: 34–58) and BMI of 27 (Range: 23–33). All patients presented with chronic knee problems, with a median duration of symptoms of 5 years (Range: 2–10 years), while 17 patients had undergone previous surgery (Median: 2, range: 0–4, see Table 1). These patients had previous chondroplasties and one patient had a microfracturing

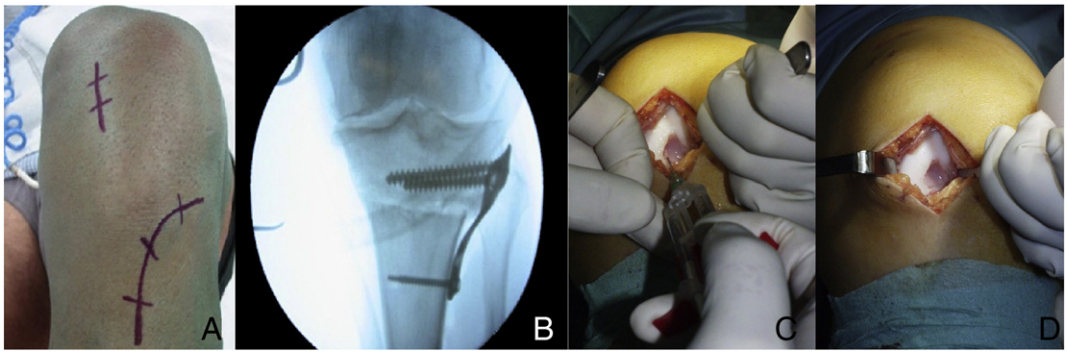

Fig. 1. Dual surgical approach: Medial parapatellar and "inverted hockey stick" incision (A). Intra-operative fluoroscopy of a lateral closing wedge HTO (B). MAC implantation (C/D).

Table 2
Progression of post-operative weight-bearing, knee range of motion and exercise rehabilitation after MACI in combination with HTO.

Postop timeline	Rehabilitation progress
Week 1-3	• Weight-bearing status: ≤ 20% BW • Ambulatory Aids: 2 crutches used at all times • Knee ROM: active ROM from 0-30º (week 1) to 0-60º (week 3) • Knee Bracing: 0-30º (week 1–2) to 0-45º (week 3) • Rehabilitation: circulation and isometric exercises, passive and active knee flexion exercises, remedial massage, soft tissue & patella mobilisation, continuous passive motion, cryotherapy and hydrotherapy
Week 4-6	• Weight-bearing status: ≤ 20% BW (week 4) to 30% BW (week 6) • Ambulatory Aids: 2 crutches used at all times • Knee ROM: active ROM from 0-90º (week 4) to 0-125º (week 5) • Knee Bracing: 0-75º (week 4) to 0-90º (week 5) • Rehabilitation: straight leg exercises, introduction of calf raises, weighted hip adduction and abduction, trunk strengthening, recumbent cycling
Week 7-12	• Weight-bearing status: 50% BW (week 7) to 100% (week 11–12) • Ambulatory Aids: 1 crutch (week 6–7) to no crutches (week 8) • Knee ROM: active ROM from 0-125º (week 6) to full range (week 7) • Knee Bracing: Full knee flexion • Rehabilitation: introduction of proprioceptive/balance activities, cycling, walking, resistance and CKC activities
3-6 months	• Rehabilitation: introduction of more demanding OKC and CKC (ie. leg press), upright cycling, rowing ergometry and elliptical trainers
6-9 months	• Rehabilitation: increase difficulty of proprioceptive/balance, OKC & CKC exercises (ie. modified squats), introduction of controlled mini trampoline jogging
9-12 months	• Rehabilitation: increase difficulty of CKC exercises (ie. squat activities on unstable surfaces), introduction of sport specific agility drills, return to competitive activity after 12 months

ROM = range of motion; BW = body weight; CKC = closed kinetic chain; OKC = open kinetic chain.

procedure. Three patients had intact menisci, whilst a partial meniscectomy with preservation of at least the peripheral third of the meniscus had been undertaken in 15 patients. All knees showed evidence of full thickness cartilage loss over the MFC. The median defect size was 6 cm^2 (Range: 2-14 cm^2) and the median varus deformity was 6º (Range: 5º- 8º). Partial thickness ("Kissing") lesions of the opposite medial tibial plateau were present in 15 patients (Grade II to III). Three patients had intact patellofemoral compartments. Patellofemoral cartilage lesions were found in 15 knees (Grade II to III). One knee showed a partial anterior cruciate ligament (ACL) tear on MRI, however clinical testing showed no laxity.

2.4. Procedures

Initially, a day-case arthroscopy was undertaken to harvest cartilage and, following surgery, chondrocytes were isolated, cultured and seeded onto the collagen membrane (ACI-Maix Matricel GmbH, Germany). This was undertaken according to previously published protocols [9].

MACI in combination with HTO was performed approximately six weeks after the biopsy. All surgery was performed by the senior author (DJW). MACI was performed via a short medial parapatellar arthrotomy (Fig. 1A). The defect site was prepared by removing all damaged cartilage down to, but not through, the subchondral plate. The lesion was circumscribed with a scalpel to reveal the borders of adjacent healthy cartilage. The graft was then measured and cut to fit the defect, and was fixed in place with fibrin glue (Fig. 1C/D). Glue fixation was augmented with sutures in 4 cases (6.0 Prolene) and with bioabsorbable smart nails in 14 cases (Conmed/Linvatec, Tampere, Finland, ∅ 1.5 mm, length: 16 mm, 20 mm and 25 mm). Finally, firm and even pressure was applied over the graft for 30 seconds while the glue set. The knee was put through 10 full range of motion manipulations to confirm graft stability.

Seventeen knees were treated with a lateral closing wedge HTO, while the remaining one knee underwent a medial opening wedge osteotomy to address leg shortening and mal-union associated with a previous tibial plateau fracture. The degree of correction was calculated on pre-operative Maquet views according to the method described by Miniaci [22]. The aim was neutral alignment (0–3 degrees of valgus) to restore physiological joint forces.

HTO was performed through an inverted "hockey stick" incision (Fig. 1A). The tibialis anterior muscle was detached from the anterolateral border of the proximal tibia. The proximal tibiofibular joint was disrupted with an osteotome. The patella tendon was identified and protected. Using the Sulzer HTO system a lateral closing wedge osteotomy was performed. The osteotomy cutting guide was positioned and pinned parallel to the joint line under fluoroscopy control and the first osteotomy cut was made parallel to the joint line falling short of the second cortex. Then a second jig set at the required degree of correction was used and a wedge of bone was removed with osteotomes and bone nibblers. The proximal pins were removed and replaced with screws and a distal compression hole was drilled. Gradual compression (1 minute intervals) was carried out until the osteotomy site was fully closed. This was verified with the image intensifier before the plate (Non-locking HTO compression plate, Sulzer Orthopaedics, Fig. 1B) was fixed distal to the compression site. The final position was checked again with fluoroscopy. The plates were removed nine months after surgery.

The mean duration of combined surgery was 82 minutes (range: 70–100 min).

2.5. Outcome measures

2.5.1. Clinical Outcomes

Subjective outcome was assessed pre-operatively and at 3, 6, 12, 24, 36 and 60 months post-surgery using the Knee Injury and Osteoarthritis Outcome Score (KOOS) [23]. The KOOS was used to assess pain (P), symptoms (S), activities of daily living (ADL), sport and recreation (S&R) and knee related quality of life (QOL). Functional outcome was assessed using the six-minute walk test (6MWT) [24].

2.5.2. Maquet views

All patients had their osteotomy correction checked 2–6 months post surgery with long leg Maquet weight bearing views.

2.5.3. Magnetic Resonance Imaging (MRI)

All patients were scanned on a GE (Gradient Echo) 1.5 Tesla Signa Excite platform using an 8 channel knee coil. Sagittal and coronal proton density weighted sequences were obtained with a FOV (Field Of View) of 14 cm, slice thickness of 3 mm with a 1 mm gap, a matrix of 512 x 384, 2 NEX (Number of Excitations), and a TR (Repetition

Table 3
Outcome parameters over 5 years compared to baseline. Means, 95% CI's and p-values.

		KOOS Pain	Symptoms	ADL	Sports	Kqol	6MWT	MRI
Baseline	Mean	55	64	64	15	18	545	1.06
	n	18	18	18	18	18	18	18
	95%CI	46-65	55-73	55-72	7-23	14-24	475-618	1.02-1.1
6/12	Mean	69	79	80	19	34	589	————————
	n	18	18	18	18	18	18	————————
	95%CI	60-79	72-86	78-87	8-28	26-41	538-638	————————
	p-value	0.013*	0.015*	0.002*	0.232	<0.001*	0.032*	————————
12/12	Mean	75	80	85	39	43	588	2.42
	n	18	18	18	18	18	18	18
	95%CI	66-83	73-87	75-95	25-54	32-55	537-638	2.22-2.68
	p-value	0.001*	0.009*	0.003*	0.001*	<0.001*	0.041*	<0.001*
24/12	Mean	79	83	88	48	48	600	2.46
	n	14	14	14	14	14	14	14
	95%CI	67-91	75-90	80-94	28-68	33-65	533-668	2.24-2.69
	p-value	<0.001*	0.007*	<0.001*	<0.001*	<0.001*	0.031*	<0.001*
36/12	Mean	84	81	90	53	53	636	2.13
	n	14	14	14	14	14	14	14
	95%CI	77-91	71-91	83-99	31-71	33-71	552-720	1.57-2.69
	p-value	<0.001*	0.007*	<0.001*	<0.001*	<0.001*	0.021*	0.022*
60/12	Mean	80	74	83	46	45	564	2.01
	n	17	17	17	17	17	13	13
	95%CI	71-88	63-85	75-93	35-56	30-59	497-630	1.58-2.44
	p-value	<0.001*	0.055	0.006*	<0.001*	0.004*	0.257	0.031*

$p<0.05$ considered statistically significant*.

Time) of 3100 ms and a TE (Echo Time) of 30 ms. Sagittal and coronal T2w sequences with fat suppression were obtained with the same FOV, slice thickness and NEX, a matrix of 256 x 224, a TR of 3300 ms and a TE of 85 ms.

Cartilage specific MRI was performed at 3, 12, 24, 36 and 60 months. An independent, leading musculoskeletal radiologist (WB) assessed the grafts based on criteria previously described by Marlovits [25]. A previously defined and validated composite score was used [26]. Eight MRI criteria with different weighting factors (WF) were assessed: signal intensity (WF 0.3), defect infill (WF 0.2), border integration (WF 0.15), surface contour (WF 0.1), structure (WF 0.1), subchondral lamina (WF 0.05), subchondral bone (WF 0.05), and effusion (WF 0.05). Each criterion was scored from 1 to 4 and the score multiplied by the weighting factor. Summation of the 8 scores gives a score ranging between 1 and 4 (1 = poor, 2 = fair, 3 = good, and 4 = excellent).

2.5.4. Histological assessment

The complete knee of one patient who died following a mountain bike accident 20 months after MACI was assessed macroscopically and histologically. Standard staining methods using alcian blue proteoglycan staining and haematoxylin-eosin were used to reflect the proteoglycan content and demonstrate cartilage architecture.

2.6. Rehabilitation

Patients underwent an intensive 3 months postoperative, specialised rehabilitation program. The underlying principle for this program was to initially protect the tibial osteotomy, then encourage and maximise the chondrocyte maturation process, whilst minimising the risk of graft failure through graft overload [26,27].

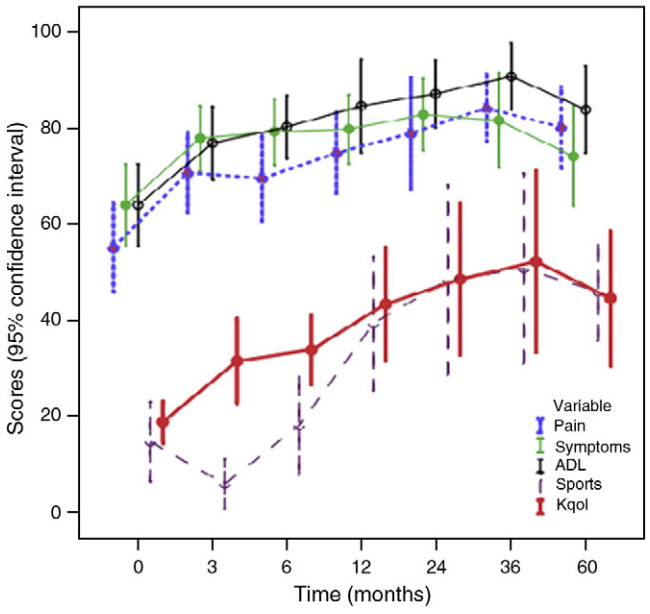

Fig. 2. KOOS-score means with 95% CI's. Significant improvements ($p<0.05$) throughout in all domains compared to baseline (0 months) apart from 'Symptoms' at 60 months.

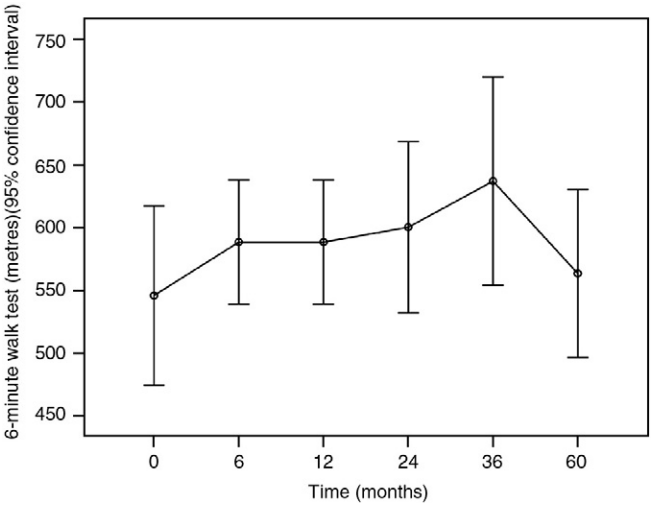

Fig. 3. 6MWT means with 95% confidence intervals. Significant improvement ($p<0.05$) to 36 months compared to baseline (0 months) and drop-off at 60 months.

Table 4
Complications, events, osteotomy correction, MRI-results and surgical opinion on graft outcome.

Age	Gen	Graft fixation	Complications	Events and compliance	Corr/Insall-I/Slope	Postop-ROM	MRI- score-result	Surgical opinion on graft outcome
34	M	Glue + suture	DVT, warfarin treatment	Early failure	0°/1.05/7° slope	2/150	Failure:1.3 at 6 and 12/12	Multiple operations with MF's, ? Insufficient fixation without pegs leading to early failure
47	F	Glue + suture	Anterior knee pain, PF arthritis, Patellar tendinitis	Nil	3° valgus/1.08/6° slope	4/120	Good: 2.9 at 5 yrs	Low BMI (<28), no adverse factors, middle aged (40–49)
51	F	Glue + suture	Graft failure at 3-6/12	Early failure	2° valgus/1.0/3° slope	0/120	Failure:1.3 at 3-6/12	? Insufficient fixation without pegs leading to early failure, advanced age (>49)
34	M	Glue + suture	Haematoma drained, Sf wound infection, effusion after fall	Consistent with rehab and follow up	2° valgus/1.0/4° slope	0/150	Good: 3.3 at 1 yr (5 yrs*)	Low BMI (<28), young (<40), no adverse factors
56	M	2nd op: Glue + s. nail	Graft detachment at 2/52, revision + peg fixation	Early failure/graft detachment.	2° valgus/1.05/4° slope	0/146	Good: 3.3 at 5 yrs	Low BMI (<28), initial graft detachment, then robust fixation with pegs
51	M	Glue + s. nail	Nil	Nil	1° valgus/1.0/3° slope	0/143	Fair: 2.0 at 5 yrs	Fair result: Low BMI (<28) but advanced age (>49)
54	M	Glue + s. nail	Early graft failure at 1 year, ITB tendinitis	Post-op weight gain, Early heavy farm work	0°/1.1/3° slope	0/143	Failure:1.0 at 1 yr	? failure influenced by high BMI (>28), advanced age (>49) and non-compliance
49	M	Glue + s. nail	Patellar tendinitis	Heavy manual working early on	0°/1.1/3° slope	0/130	Fair: 2.2 at 5 yrs	? fair result influenced by high BMI (>28) and early heavy work
58	M	Glue + s. nail	Death after accident, Patellar tendinitis, Sf wound infection	Consistent with rehab and follow up	1° valgus/1.05/4° slope	4/132	Good: 2.6 at 1 yr	Good histological graft result after 18 months, boarderline BMI, consistent rehab
38	F	Glue + s. nail	Slow ROM regain, Pes tendinitis, synovitis at 1 yr (aseptic; rheumatologically neg.), steroid injections + synovectomy. MCL, MM, LM tear: Arthroscopic PMM, LFC chondroplasty + bracing, Graft delamination	Fall on knee 13/52 with admission. Wrong rehab in rural area with squatting and lunging before 10/52 post surgery	8° valgus/1.23/3° slope	0/146	Fair: 2.2 at 5 yrs	Synovitis (? Graft sensitivity) and collateral knee trauma postoperatively with 2 further knee arthroscopies: Further analysis of factors therefore not meaningful
48	M	Glue + s. nail	Patellar tendinitis. Skiing accident with MCL rupture after 3 yrs, (Graft poor before: 1.85)	Active builder & vigneron, early heavy work, limited compliance	4° valgus/1.01/1° slope	2/140	Failure:1.8 at 5 yrs	? failure influenced by heavy manual work with limited focus on rehab instructions
46	M	Glue + s. nail	Nil	Inconsistent with rehab and follow up plan	2° valgus/1.00/3° slope	3/133	Fair: 2.1 at 5 yrs	? fair result influenced by fair rehab compliance
55	M	Glue + s. nail	Patellar tendinitis	Consistent with rehab and follow up	1° varus/1.06/2° slope	3/128	Good: 2.7 at 5 yrs	Despite advanced age (>49) and borderline BMI (28) good result after consistent rehab
56	M	Glue + s. nail	Graft hypertrophy with debridement after 5 yrs, Paget's disease post-op (femur, pelvis,? tibia)	Truck driver, back to work early on	6° varus/1.32/2° slope	0/143	Good: 3.6 at 5 yrs	Low BMI (<28). Good result despite advanced age (>49), early work and residual varus deformity
57	M	Glue + s. nail	Popliteus and patellar tendinitis	Nil	2° valgus/1.02/4° slope	3/130	Good: 2.9 at 3 yrs	Low BMI (<28). Good result despite advanced age (>49)
52	M	Glue + s. nail	Nil	Heavy farm work and lifting early on	3° valgus/1.04/4° slope	0/135	Failure:1.3 at 6/12 (1 yr, 5 yrs)	? failure influenced by heavy manual work, non-compliance, and advanced age (>49)
56	M	Glue + s. nail	Patellar tendinitis	Nil	3° valgus/1.18/4° slope	0/136	Failure:1.8 at 1 yr, 1.3 (5 yrs)	? failure influenced by advanced age (>49), borderline BMI (28)
51	M	Glue + s. nail	Patellar tendinitis	Nil	1° varus/1.11/3° slope	2/130	Failure:1.0 at 5 yrs: no graft	? failure influenced by advanced age (>49) and high BMI (>28)

(Gen = Gender, BMI = Body Mass Index, s. nail = smart nail, Op's = previous operations, Corr = Correction angle, Insall-I = Insall-Salvati Index, ROM = Range Of Movement, M/F = Male/Female, DVT = Deep Vein Thrombosis, MF's = Microfractures, Sf = Superficial, PF = patellofemoral, ITB = Iliotibial Band, MCL = Medial Collateral Ligament, MM = Medial Mensicus, LM = Lateral Meniscus, LFC = Lateral Femral Condyle, PMM = Partial Medial Meniscectomy, *followed up in Boston, US at 5 years).

Post-operative inpatient rehabilitation initially consisted of: continuous passive motion (0–30 degrees) within 12–24 hours after surgery to reduce the chance of intra-articular adhesions, active dorsi- and plantar-flexion of the ankle to encourage lower extremity circulation, isometric contraction of lower limb musculature to maintain muscle tone and minimize muscle loss, and cryotherapy for edema control. To protect the repaired cartilage surface, a range of motion (ROM) control brace was worn post-operatively for up to 24 hours per day.

Following these early post-operative stages, patients participated in a structured, supervised out-patient rehabilitation program over a 3 month period, while further activity guidelines and advice were provided to patients up until 12 months post-surgery (Table 2). These protocols were individually modified for each patient dependent on the presentation of clinical signs throughout the post-operative period reflective of overload such as pain and swelling.

2.7. Study completion

The study endpoint (SE) was determined by completion of clinical and radiological follow up at 5 years (SE1), definitive graft failure after 2 years on MRI (Composite score of 1 = no infill), the indication, planning or performance of TKA (SE2) or death of the patient (SE3) (Table 1).

2.8. Statistical analysis

Descriptive statistics (mean, 95% CI) were used to describe outcome variables of the KOOS, the 6MWT and the MRI composite score over the study period. Two-factor ANOVA-tests were used to determine differences between clinical and MRI outcome parameters pre-operatively (baseline) and at follow-up time points. P-values of less than 0.05 were considered statistically significant.

Multivariate analysis with binary logistic regression for MACI-graft success/failure (MRI-result) was carried out. Binary values (1 = favorable, 2 = adverse) were ascribed to age (<50 = 1), defect size (<6 cm^2 = 1), PMM (no = 1), BMI (<28 = 1), previous operations (<2 = 1) PF OA (<II Outerbridge = 1), medial tibia OA (<II Outerbridge = 1), rehab compliance (yes = 1), slope (>2º = 1), valgus correction angle (0º-3ºvalgus = 1), patella norma (ISI<1.1 = 1) and gender also (Female = 1) and assessed as independent variables against good MACI graft results (MRI score >2.5 = 1) as dependent variable. Patella norma (ISI<1.1 = 1) was also assessed against knee ligament tendinitis (No = 1).

The StatPlus® statistic software package for Microsoft excel 2008 for Mac and SPSS 17.0 for Mac were used.

3. Results

Fifteen patients (83%) were followed up clinically and by MRI to SE1, SE2 or SE3, as defined above. A total of 17 patients were followed up with clinical outcomes at 60 months (94%). Thirteen patients were followed up to 60 months with MRI (SE1). One further patient was investigated by MRI up to 36 months post surgery (clinically to five years). At 24 months, two patients showed MRI evidence of graft failure (No infill; SE2). One patient died 20 months post surgery (SE3).

3.1. Clinical outcomes

Patients experienced a significant improvement ($p<0.05$) in all KOOS subscales from pre-surgery to 24 months post-surgery (Table 3, and Fig. 2). These benefits were maintained at 36 months, but dropped off at 60 months, though statistically significant improvement was maintained when compared to pre-surgery scores. Sixteen patients (89%) had significant improvement in the KOOS score at 60 months. Only the subscale 'symptoms' was not significant at 60 months when compared with pre-surgery scores. The initial decrease in the sport and recreation subscale at 3 months can be explained by the limitations placed upon patients at this point in the post-operative period.

Patients demonstrated a significant improvement ($p<0.05$) in the 6MWT up to 36 months post-surgery when compared with the pre-operative status (Table 3, and Fig. 3). At 60 months the mean walking distance decreased.

Two patients were listed for TKA. One of these patients had MRI evidence of graft failure, with no infill of the defect.

3.2. Maquet views

Postoperative Maquet views showed a mean correction angle of 2.3º valgus (Median: 2.0º valgus, 95%CI: 1.0º valgus - 3.5º valgus, range: 6º varus - 8º valgus). Individual correction angles and ISI's are listed in Table 4. Two patients showed over correction (8º and 4º of valgus) and 3 patients under correction (6º, 1º, 1º of varus). 89% of patients were corrected (n = 16/18) to a range between 1º varus and 4º valgus and 78% (14/18) to a range between 0º and 3º of valgus. The mean postoperative Posterior Tibial Slope (PTS) was 3.5º (Median: 3º, 95%CI: 2.66º - 4.34º, range: 1º - 7º). The mean Insall-Salvati Index (ISI) was 1.08 (Median: 1.05, 95%CI: 1.02 - 1.13, range: 1.0 – 1.32º). Two patients showed postoperative ISI's above 1.2 (Patella alta).

3.3. Magnetic Resonance Imaging (MRI)

A statistically significant improvement in the MRI composite score was seen after 12 (Mean 2.37 = fair) and 24 months (2.45 = fair to good) though this decreased at both 36 and 60 months, with larger 95% CI's (Table 3 and Fig. 4). The overall MRI-results at 60 months were unsatisfactory. Of the 15 knees which reached a SE five scored a good (33%), five a fair (33%) and five a poor radiological result (33%). A poor and good MRI outcome is illustrated in Fig. 5 (A-D).

3.4. Multivariate analysis

Age (<50 = 1), defect size (<6 cm^2 = 1), PMM (No = 1), BMI (<28 = 1), previous operations (<2 = 1) PF OA (<II Outerbridge = 1), medial tibia (<II Outer-bridge = 1), rehab compliance (Yes = 1), slope (>2º = 1), correction angle (0º-3º = 1), Patella norma (ISI<1.1 = 1) and gender (Female = 1) were all non-significant as predictors for a good MACI graft result (MRI score >2.5 = 1) and patella norma was non-significant for knee ligament tendinitis ($p>0.05$). Table 4 gives a descriptive overview of indicators and the surgical opinion on their influence. Glue and suture fixation of MACI grafts for large defects onto sclerotic bone or soft adjacent cartilage was believed to have contributed to early graft failure in 3 of the first 5 grafts (60%). This was salvaged in one case and 14 consecutive grafts were fixed with smart nails into the bone. From the surgeons point of view the 11 graft failures/fair results were influenced by poor fixation (no smart pins), multiple operations with microfractures, high BMI combined with non-compliance and early heavy work, advanced age and postoperative knee injury. Neither of these factors were statistically significant as predictors.

3.5. Macroscopic and histological assessment

One patient died 20 months after combined HTO and MACI (Table 1). At the time of macroscopic graft assessment, there was evidence of white graft infill at the MFC site (Fig. 6). The grafted area proved rich in proteoglycan with preserved cartilage architecture and chondrocyte distribution, without fibrillation in comparison to the adjacent arthritic cartilage (Figs. 7 and 8). Histology demonstrated a successful cartilage implantation within arthritic surroundings.

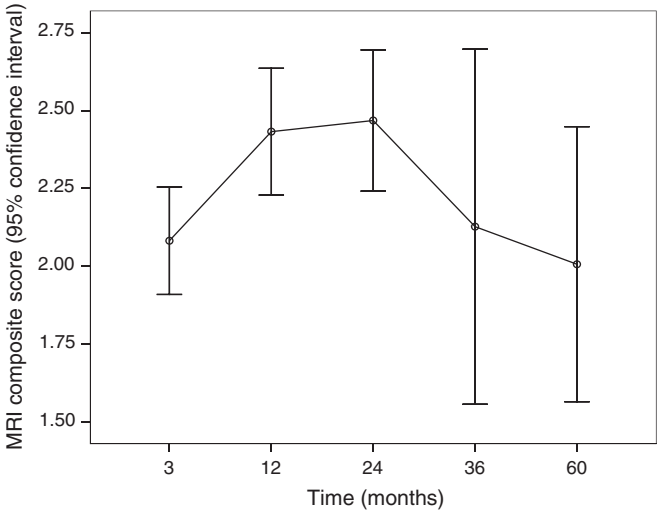

Fig. 4. MRI composite scores means with 95% confidence intervals. Significant ($p<0.05$) improvement in score results throughout compared to baseline (0 months) with best results at 12 and 24 months.

3.6. Complications and adverse events

Table 4 gives an overview about complications, adverse events and outcomes. The first 5 patients had a graft fixation with glue and sutures. Early failure during the first year occurred in 2 of these patients. The 5th patient had a graft detachment within 2 weeks after surgery and the graft had to be reattached with glue and smart nails to secure adequate fixation into the bone. Only one further patient showed graft failure within 1 year after regular smart nail fixation. Two patients were over corrected (8º and 4º valgus) and 3 patients were under corrected (6º, 1º, 1º of varus). Three patients had a PTS of less than 3º (1º, 2º, 2º). Two patients showed a ISI of more than 1.2 (Patella alta). Postoperative patellar tendinitis occurred in 8 patients and ITB tendinitis, pes anserinus tendinitis and popliteus tendinitis in one patient respectively. The tendon morbidity settled in all patients after 12 to 26 months. Postoperative patellofemoral OA with anterior knee pain became the leading symptomatology in one patient. Prolonged acute synovitis (Aseptic and rheumatologically negative) occurred in one patient requiring steroids and arthroscopic synovectomy. Later on, this patient sustained a further injury with extensive collateral knee damage. Graft hypertrophy requiring arthroscopic debridement occurred in one patient. Compliance issues with the rehab requirements were recorded and interfered with the rehab protocol and recommendations in 39% of patients (7/18). One patient died after a bicycle accident.

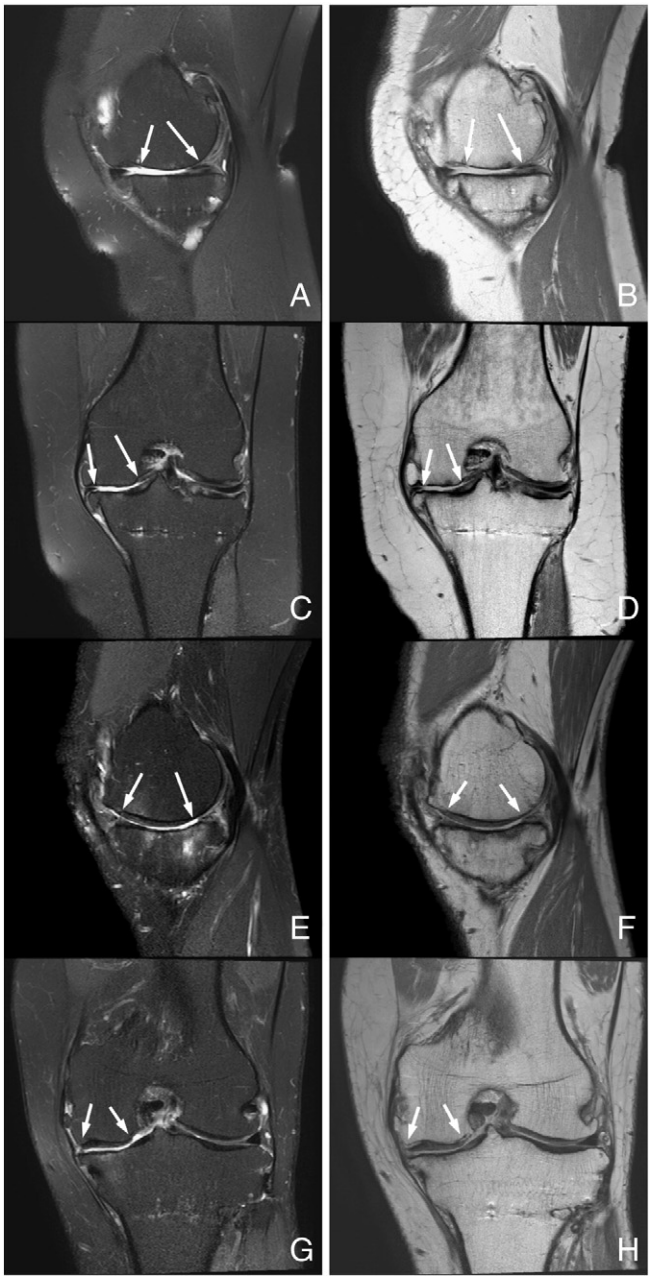

Fig. 5. Examples of a poor (A-D, Proc. ID 3) and good outcome (E-H, Proc. ID 5) evidenced by magnetic resonance imaging after 5 years. Complete loss of graft in the centre of the defect (between arrows) on sagittal and coronal imaging (A/C: T2; B/D: PD). Nearly iso-intense cartilage regenerate in the centre of the lesion (between arrows) on sagittal and coronal imaging (E/G: T2; F/H PD).

Fig. 6. The MACI grafted defect (inside dashed line) appeared white and smooth in texture macroscopically, as seen with healthy cartilage, whereas the surrounding knee surface was yellow and appeared fibrillated as with osteoarthritic cartilage. From deceased patient.

4. Discussion

This cohort consisted of younger patients with medial femorotibial knee OA and associated joint malalignment. We have combined neutralising HTO with bio-engineered cartilage implantation into the MFC. In this group of patients, MACI was performed in the relatively hostile environment of an arthritic medial compartment, often without stable adjacent cartilage borders requiring bio-absorbable nail fixation. The clinical outcome was overall good: 89% of patients (n = 16) had significant improvement in the KOOS score at 5 years. MRI analysis showed significant postoperative improvements but poor results at the study end point with only 33% good infill (n = 5/15) and a mean composite score of 2.01 (95%CI 1.58-2.44).

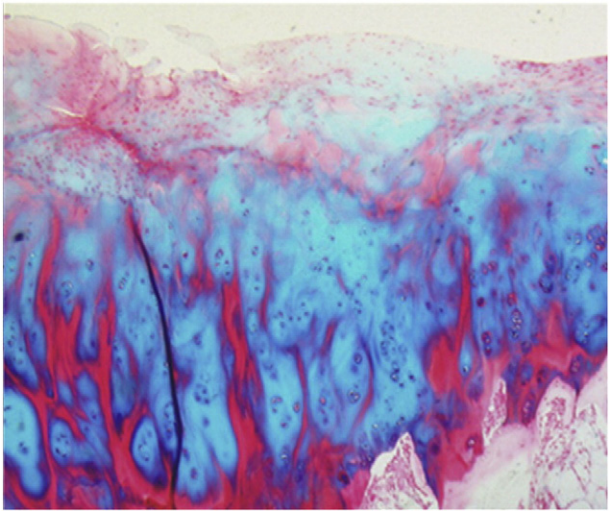

Fig. 7. Cartilage immediately adjacent to the MACI grafted defect with characteristic fibrillation of the articular cartilage surface, chondrocyte clustering, and negligible matrix proteoglycan staining superficially in keeping with osteoarthritis (Acian blue stain 40x magnification).

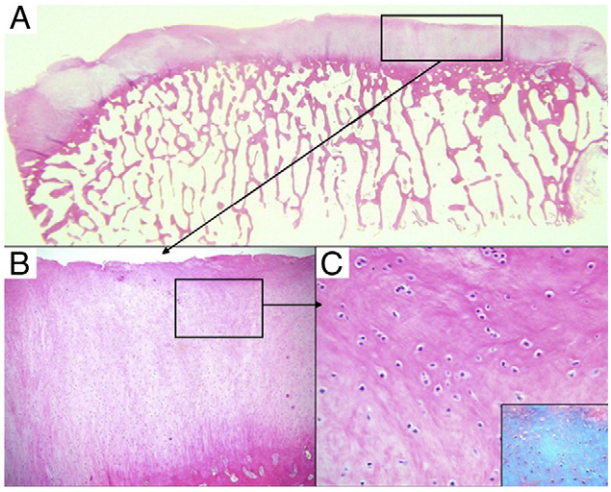

Fig. 8. The MACI grafted area showed good restoration of osteochondral architecture (A & B), and regenerative tissue was characterized as hyaline-like cartilage with homogenous chondrocyte distribution (C) rich in proteoglycan (C insert), (A: H&E stain 4x magnification (mag); B: H&E stain, 40x mag; C: H&E stain, alcian blue stain (insert), 200x mag).

Good quality MRI based studies evaluating isolated MACI grafting at 3 to 5 years are uncommon. Three studies have been identified which report better mean composite scores than in our series at 3 and 5 years [28,29,30]. In these studies all MRI-features of the cartilage repair such as intensity, infill, integration, contour, structure, subchondral bone and effusion showed to be good or excellent in most patients at 3 and 5 years.

Reasons for this discrepancy to our MRI outcomes may be due to differences in patient characteristics. Our patients had larger defects (Mean: 6 cm^2 compared to 2.6 cm^2, 3.0 cm^2 and 4.2 cm^2 in the respective studies), were older (Mean age 47 compared to patients with a median age of less then 39 respectively) and had more previous operations.

With our limited number of cases we could not identify a statistically significant indicator for a good or poor MRI outcome. However on critical analysis of every case insufficient graft fixation (No smart nails), non-compliance and further joint injury seemed to be associated with graft failures and low BMI with good graft results. Age is likely to have a negative impact on outcome but we were not able to demonstrate that with the numbers involved.

A traditional goal of HTO is overcorrection to valgus [12]. Physiological alignment is a trend followed in recent years to restore a normal joint [21]. We were aiming for correction to neutral alignment with cartilage repair, firstly to recreate physiological forces across the knee joint and secondly to avoid possible compromise to any future knee arthroplasty caused by a valgus deformity, loss of proximal tibial bone stock or grossly altered patellofemoral mechanics. This goal was achieved in 89% (n = 16) of our patients (Correction between 1º of varus and 4º of valgus). In isolated HTO with overcorrection to valgus, 10 year post-operative knee survival prior to the onset of moderate to severe pain ranges from 28% to 66% of patients [12,31,32] and from 51% to 93% of patients before TKA is undertaken [15,33,34,35,36]. Recent publications report 5-year survivorship of 89.5% and 95% [19,37] with best survivorship achieved by overcorrection to 10º of valgus [37]. This compares to good clinical outcomes in 89% of our patients with neutralising HTO and MACI and 100% survivorship (2 patients were offered a TKA) at 5 years. How much MACI or HTO have contributed to the good clinical results at 5 years and whether the combined procedures with neutralisation are mutually beneficial cannot be answered with our data. However, neutralisation and lack of overcorrection did not lead to early failure as previously suggested [12,37] and this might have been influenced by the added MACI.

The complication of loss of graft fixation could be successfully addressed during the study. With our experience in these cases we recommend graft fixation with bioabsorbable nails in arthritic surroundings. Graft hypertrophy occurred only once. Stiffness was no postoperative issue. Tendon problems proofed to be common but settled in all patients with physical therapy and NSAIDs after 12 to 36 months.

A limitation of our series is the presence of confounding variables. Patients with medial knee joint arthritis and large cartilage lesions presented to us with the wish for improvement in their quality of life and the aim to postpone knee arthroplasty. We included all patients who underwent a medial meniscectomy that preserved at least the peripheral third of the meniscus being aware that meniscal deficiency decreases the contact area and increases the load in the compartment [38,39]. We also included kissing lesions of the medial tibial plateau and associated partial-thickness patello-femoral cartilage lesions. They are highly prevalent in younger patients and difficult to treat. Further limitations of our series are the small number of cases and the lack of a control group.

Treatment options for younger patients with medial compartment OA and malalignment are limited. Based on our series, combined neutralising HTO and MACI provides a safe treatment option for patients with medial knee osteoarthritis. Patients showed significant clinical improvement at five years. However overall graft survival at 5 years was unsatisfactory and significant improvement in MRI scores could only be maintained in a third of patients who reached a study end point (N = 5). Larger prospective studies with MRI follow-up are needed to demonstrate longer lasting cartilage repair after combined procedures in specific patients.

5. Conflict of interest statement

I herby confirm on behalf of all co-authors that neither of us have received anything else than basic financial support to carry out and finance this research.

There is nothing else to be declared other than mentioned in the acknowledgement of this paper and neither of us have any conflict of interest to declare.

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