Implementing one standardized rehabilitation protocol following autologous chondrocyte implantation or microfracture in the knee results in comparable physical therapy management

Dieter Van Assche PT, PhD, Danny Van Caspel PT, Filip Staes PT, PhD, Daniel B Saris MD, PhD, Johan Bellemans MD, PhD, Johan Vanlauwe MD & Frank P Luyten MD, PhD

To cite this article: Dieter Van Assche PT, PhD, Danny Van Caspel PT, Filip Staes PT, PhD, Daniel B Saris MD, PhD, Johan Bellemans MD, PhD, Johan Vanlauwe MD & Frank P Luyten MD, PhD (2011) Implementing one standardized rehabilitation protocol following autologous chondrocyte implantation or microfracture in the knee results in comparable physical therapy management, Physiotherapy Theory & Practice, 27:2, 125-136, DOI: 10.3109/09593981003681046

To link to this article: http://dx.doi.org/10.3109/09593981003681046
RESEARCH REPORT

Implementing one standardized rehabilitation protocol following autologous chondrocyte implantation or microfracture in the knee results in comparable physical therapy management

Dieter Van Assche, PT, PhD,1 Danny Van Caspel, PT,2 Filip Staes, PT, PhD,1 Daniel B Saris, MD, PhD,2 Johan Bellemans, MD, PhD,1 Johan Vanlauwe, MD,1 and Frank P Luyten, MD, PhD1

1Division of Rheumatology and Department of Orthopedics, University Hospitals Leuven, Leuven, Belgium
2Department of Physiotherapy, Central Military Hospital, Utrecht, Netherlands

ABSTRACT

Objective: The major aim of the study was (1) to compare the physiotherapy management in patients treated with autologous chondrocyte implantation (ACI) versus microfracture (MF) at the knee using a standardized rehabilitation protocol; and (2) to investigate the effect of activities in low-load conditions after surgery on the functional recovery was explored. Design: 95 physiotherapists received a standardized rehabilitation protocol that was used in a randomized controlled trial. A secondary analysis on patients’ outcome was studied in a cohort design. Outcome measures: An electronic report form including 18 physiotherapy variables was used to compare physiotherapy management. Patients’ functional outcome was assessed using the KOOS (Knee Injury Osteoarthritis Outcome Score) and the pooled symmetry index (SI) based on one strength and three hop tests. Both subjective and objective outcomes were evaluated pre-surgery, and at 1 and 2 years post-surgery. Results: 65 physiotherapists adhered very consistently to the protocol during the first 3 months and showed a similar preference and timing for the physiotherapy modalities in both treatment groups. Patients with high amount of low-load activities (LLA+, n=21) post-surgery performed significantly better compared to patients with low amount of LLA (LLA−, n=17). At 24 months the mean pooled SI of LLA+ cohort was 92.4 compared to 78.2 for LLA− cohort (95% confidence interval [CI] 1.8 to 26.2). Conclusion: Overall, the compliance post-surgery with the rehabilitation protocol was excellent and the applied rehabilitation was comparable in both treatment groups. A high amount of low-load activities post-surgery appears beneficial for the objective functional outcome.

INTRODUCTION

As the natural healing capacity of damaged articular cartilage is poor, joint surface injuries are a prime target for regenerative medicine. Microfracture (MF), a marrow stimulating technique in an arthroscopic procedure, and autologous chondrocyte implantation (ACI) in an open knee procedure are currently most frequently used for cartilage repair (Cole, Pascual-Garrido, and Grumet, 2009; Jakobsen, Engebretsen, and Slauterbeck, 2005; Smith, Knutsen, and Richardson, 2005). After ACI, the patient remains hospitalized for approximately 3 to 5 days compared to 1 day for MF (Derrett et al, 2005; Steadman, Rodkey, and Rodrigo, 2001). Since the physical abilities of patients following these diverse surgical procedures differ, one might expect that rehabilitation management will vary accordingly (Ferruzzi et al, 2008; Noyes, Mangine, and Barber, 1987).
The existing rehabilitation programs following cartilage repair procedures are primarily based on the clinical experience of physiotherapists and opinion leaders (Gillogly, Myers, and Reinold, 2006; Hambly et al, 2006; Reinold et al, 2006). In their assessment of the limited evidence concerning rehabilitation following ACI, Hambly et al (2006) noted “a consensus of opinion that weight bearing and range of motion should be restricted in early rehabilitation, but that there is considerable variation across cartilage repair centers as to the extent and duration of these restrictions.” Publications on MF rehabilitation by Rodrigo, Steadman, Silliman, and Fulstone (1994) and Steadman, Rodkey, and Briggs (2002) provide details about rehabilitation programs, which include results from a retrospective comparative study of rehabilitation with or without continuous passive motion. Surgeons and physiotherapists highlight the need to protect the graft during the first 3 months following surgery for both cartilage repair techniques, as the repair site is ‘mechanically’ at its most vulnerable during that period (Brittberg et al, 1994; Irgang and Pezzullo, 1998; Roberts et al, 2001). Furthermore, it is known that a lengthy rehabilitation period is necessary to guarantee the return to optimal functioning (Brittberg, 2008; Gillogly, Myers, and Reinold, 2006; Hambly et al, 2006; King, Bryant, and Minas, 2002; Steadman, Rodkey, and Briggs, 2002; Wilk et al, 2006). Different authors have suggested guidelines, but little is known about the content or relation of physiotherapy management and objective outcome after cartilage repair (Jakobsen, Engebretsen, and Slauterbeck, 2005; Peterson et al, 2000; Smith, Knutsen, and Richardson, 2005; Steadman, Rodkey, and Briggs, 2002). Numerous in vitro studies have been conducted on the mechanical stimulation of cartilage repair tissue (Carter et al, 2004; Huselestein et al, 2008; Jackson, Lalor, Aberman, and Simon, 2001; Smith, Carter, Schurman, and Smith, 2004). In animal models mechanical stimulation may enhance tissue repair in cartilage defects in vivo (Hunziker, 2003; Jackson, Lalor, Aberman, and Simon, 2001; Salter, 1989). However, the effect of low-load activities on the objective functional outcome in humans after cartilage repair surgery has not been previously investigated.

For the present study, a standardized program for rehabilitation after MF or ACI was developed. The aims of the present study were to examine the compliance of physiotherapists with this standardized rehabilitation program and to analyze the effect of the amount of low-load activity levels post-surgery on patients’ functional outcome at 1- and 2-year assessments.

We hypothesized that the rehabilitation management is influenced by the type of surgery and that a high amount of low-load activities post-surgery is related to better functional performance at 2 years.

METHODS

Setting and design

The implementation of the standardized rehabilitation protocol was evaluated within a randomized controlled trial (RCT). The setting was the multicenter RCT conducted by Saris et al (2008). Patients enrolled in the RCT had a symptomatic cartilaginous defect of the femoral condyle and were randomized to ACI with characterized chondrocytes (N = 57) (ChondroCelect; TiGenix N.V., Haasrode, Belgium) or to MF (n = 61). To analyze the effect of the amount of low-load activities (LLA) post-surgery and patient’s objective outcome, two cohorts were created in a subgroup of the original RCT study. Patient characteristics at baseline are summarized in (Table 1).

Participants

A total of 95 Dutch-speaking physiotherapists met the inclusion criteria of this study, namely having a licensed qualification of physiotherapy with advanced knowledge of musculoskeletal rehabilitation, a private practice with sufficient infrastructure, and the consent to report weekly on the treatment modalities they used. The informed consent of all 95 participating physiotherapists was obtained prior to the surgery. The study protocol was approved by the ethics review board at University Hospitals Leuven and University Medical Center Utrecht. Of the 118 patients, 67 were enrolled in the two major recruiting centers and were followed up with objective and subjective outcome measures up to 2 years.

Study procedure

Before surgery, surgeons and study team personnel were trained extensively in the standardization of both surgical procedures and each patient provided the contact information of his/her physiotherapist to the coordinator of the rehabilitation program. The physiotherapist received an explanation of the study and instructions from the coordinator for implementing and reporting on the standardized rehabilitation protocol. Each physiotherapist treated one randomized participant. The physiotherapist, who reported weekly as agreed, received no additional training on the rehabilitation protocol and no contact was taken by the coordinating physiotherapist. Informed consent was obtained from all participants and the study protocol was approved by the ethics review board at each center.
All patients started the standardized rehabilitation protocol on the day following hospital discharge (Table 2). During hospitalization, the ACI-treated patients received relative bed rest with continuous passive motion for 2 to 3 hours each day and quadriiceps setting exercises in full extension. The rehabilitation protocol (Appendix 1) was based on guidelines for rehabilitation following MF and ACI and on the different phases of wound healing, with special focus on graft protection and wound control (Irrgang and Pezzullo, 1998; Minas and Chiu, 2000; Peterson et al, 2000; Steadman, Rodkey, Briggs, and Rodrigo, 1999; Steadman, Rodkey, and Rodrigo, 2001).

Outcome measures

The report rate was defined as the percentage of physiotherapist reporting weekly during the first 3 months. The physiotherapy management was based on the responses on 18 physiotherapy modalities in the report form (Table 2). The modalities were defined and included in the report form. For each modality, two variables were explored: (1) the time spent in minutes on the modality (time); and (2) the number of sessions per week that the modality was performed (number). For modalities performed by the participant at home, the variables explored were the ‘time spent’ or the ‘number of repetitions’ per week. Eleven modalities were defined as ‘active’ and seven were defined as ‘passive’ because they involved respectively a physically active and passive patient (Table 2).

In 67 patients (two major centers) the objective functional outcome was assessed. Therefore two independent physical therapists were instructed and trained. The objective functional outcome was based on four performance tests: (1) concentric knee extension strength at 60°/s; and three one-leg hop tests: (2) the single hop; (3) the crossover triple hop; and (4) the 6-m timed hop (Barber et al, 1990; Impellizzeri et al, 2008; Mattacola et al, 2002; Noyes, Barber, and Mangine, 1991). These one-leg hop tests are designed to mimic the greater demands imposed on the knee in

<table>
<thead>
<tr>
<th>TABLE 1 Characteristics of patients in treatment groups and in LLA cohortsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized in multicenter RCT (Saris et al, 2008)</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Gender: male/female, n (%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Pre-injury activity level (ARS score)</td>
</tr>
<tr>
<td>Cartilage repair: ACI/MF, n (%)</td>
</tr>
<tr>
<td>Concomitant lesions treated (ACL and ML), n (%)</td>
</tr>
<tr>
<td>Knee condition at baseline</td>
</tr>
<tr>
<td>Duration since onset (years)</td>
</tr>
<tr>
<td>Defect size on femur condyle (cm²)</td>
</tr>
<tr>
<td>Normal opposite knee, n (%)</td>
</tr>
<tr>
<td>No previous knee surgery, n (%)</td>
</tr>
<tr>
<td>Functional outcome at baseline</td>
</tr>
<tr>
<td>KOOS (score)</td>
</tr>
<tr>
<td>Pooled Symmetry Index (% score)</td>
</tr>
</tbody>
</table>

aValues are mean ± SDs (unless stated otherwise).

bMedian two-samples test and Fisher’s exact test analyses were used to compare groups respectively for continuous and categorical variables, significance level set at 0.05. *No significant differences between cohorts for all variables, except stratification variable, p < 0.001.

ARS=Activity Rating Scale; High LLA and Low LLA=cohorts with high and low amount of low-load activities during 3 months postsurgery; ACI=autologous chondrocyte implantation with characterized chondrocytes; MF=microfracture; ML=meniscus Lesion; ACL=anterior cruciate ligament; KOOS=Knee Injury and Osteoarthritis Outcome Score.
the everyday environment. Since the one-leg hop tests offers the benefit of providing between-leg and within-subject comparisons, these tests are used widely as clinical benchmarks for establishing normal versus abnormal one-leg hop performance. Accordingly, the symmetry index (SI) of each test was calculated by dividing the result for the operated leg with the nonoperated leg, multiplied by 100. To evaluate the overall objective functional outcome for each patient, the SI of the four tests were pooled (Reid et al., 2007). Therefore, for each participant at each time point the mean of four SI scores was calculated (Reid et al., 2007). The subjective functional outcome was assessed by the Knee Injury and Osteoarthritis Outcome Scale (KOOS) (Table 3) (Roos et al., 1998). Both functional outcomes were measured pre-surgery and at 1 and 2 years post-surgery. At 2 years in 80% of patients (n=54) the objective functional outcome could be assessed (Table 4).

Data analysis

To examine possible differences in compliance of physiotherapists guiding patients treated with microfracture or ACI to the standardized rehabilitation program, the percentage of physiotherapists reporting, the percentage of physiotherapists using a particular modality, and the mean minutes spent per session on each modality were calculated and analyzed. Therefore descriptive statistics (mean, SD) were calculated for the minutes spent per session on each of the 18 modalities (dependent variables). The mean time that was spent on a modality was compared between both treatments groups (independent variables) with a Mann-Whitney U test for each of the first 12 weeks and the significance level set at p < 0.05. Additionally, the number of protocol violations during the first 3 months and the overall withdrawal rate of participants over 1-year period were calculated.

To examine the effect of the amount of low-load activity levels post-surgery on patients’ functional outcome at 1- and 2-year assessments, descriptive statistics (mean, SD) were calculated for objective and subjective outcome measures. Preceding two cohorts were created according to the amount of low-load activities post-surgery. The low-load activities of participants were calculated for a subgroup of 38 participants using rehabilitation compliance data that were reported weekly by the physical therapists during the first 3 months after surgery. All modalities with repetitive movements in low-load conditions (8 of 11 active modalities) were taken into account. These were totaled for each participant and the average time spent in 1 day calculated. Modalities included muscle training, active mobilization exercises, functional exercises at home, neuromuscular control and neuromuscular coordination exercises, gait re-education, general mobilizations, and functional joint stability exercises. Participants in the high (low-load) activities cohort (LLA+, N=21) were highly active in post-surgery low-load modalities (>12 minutes/day) and participants in the low (low-load) activities cohort (LLA−, N=17) had low levels of activity in low-load modalities post-surgery (≤12 minutes/day). The cut-off score of 12 minutes was determined before cohort

---

**TABLE 2** Summary of the standardized rehabilitation protocol

**Goals & Restrictions on mobility and weight bearing:** Only non-weight-bearing exercises were allowed during the first 2 weeks. After 2 weeks, weight bearing could start with 10 to 15 kg. Subsequently, an increase of 10 to 15 kg loading per week was allowed. All participants wore a custom-made unloader brace (unloader XT®; Generation-II Orthotics, Canada) during the first 8 weeks (Matsuno, Kadowaki, and Tsuji, 1997; Roberts et al., 2001).

Crutches were used during the first 5 weeks and participants were allowed to reduce the use of crutches gradually from week 6 if the gait pattern was normal and swelling, pain and propioception were optimal.

Joint circulation exercises, such as heel slides, stationary cycling, or rowing without resistance, were recommended to be performed for up to 1 hour each day as soon as motion was permitted. Stationary bicycle training as well as static and dynamic bilateral closed chain exercises was introduced at 6 weeks. The duration, frequency and intensity of specific exercises were not strictly imposed, but could be adapted to the participant’s needs.

Strength training in the first 2 weeks consisted of isometric m. quadriceps settings in varied knee positions for muscle re-education. No open chain exercises were allowed. Proprioception and neuromuscular control were the primary goals for strength training during weeks 3 to 6. Progressive closed chain exercises were started. After 3 months, strength training was intensified by an increase in work load and after 6 months, by increasing resistance and decreasing the number of repetitions. High impact activities, such as jumping, landing, or pivoting on one leg or fast accelerating or decelerating, was not allowed before 3 months. Between 3 and 6 months moderate impact exercises (bipodal jumping and landing) started in short sets on a soft underground. After 6 months, unipodal landing and push off was initiated under the same conditions.

Return to sports: During the final phase of the rehabilitation (10 months after surgery), impact training was initiated, as were heavier weight training and sport-specific exercises. During the final phase, low-impact activities could be started depending on sports discipline and sports level of the participant. High-impact activities were allowed at 16 months and after approval of a medical specialist.
TABLE 3 Active and passive modalities with the percentage of physiotherapists reporting the modality, the minutes (mean and SD) per session each modality was applied, and the number of weeks with differences in time spent on a modality between ACI and MF physiotherapists

<table>
<thead>
<tr>
<th>Modality (first 3 months)</th>
<th>% of physiotherapists reporting the modality</th>
<th>Minutes per session</th>
<th>Mean (SD)</th>
<th>Number of weeks with differences in time spent between ACI and MF physiotherapists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active modalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle training (general)</td>
<td>47%</td>
<td>14.4 (9.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Active mobilizations (active ROM exercises, e.g., heel slides)</td>
<td>40%</td>
<td>10.9 (8.9)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Functional exercises at home (stationary cycling or rowing)*</td>
<td>37%</td>
<td>19.5 (14.4)*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Proprioception (exercises on positioning and movement sense)</td>
<td>35%</td>
<td>9.4 (6.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>General exercises (to increase active activity in the limb)</td>
<td>29%</td>
<td>14.0 (19.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gait re-education (with or without crutches)</td>
<td>26%</td>
<td>9.2 (6.1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular control (local muscle control exercises)</td>
<td>25%</td>
<td>11.9 (10.9)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Neuromusc. coordination (muscle control during specific skills)</td>
<td>22%</td>
<td>12.5 (10.5)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Postural balance (maintaining balance in different conditions)</td>
<td>19%</td>
<td>6.1 (3.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Functional joint stability (during landing/pushing)</td>
<td>17%</td>
<td>10.6 (7.5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Myofeedback (to enhance local muscle control)</td>
<td>2%</td>
<td>7.6 (7.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Average for active modalities</strong></td>
<td></td>
<td>27%</td>
<td>10.6*</td>
<td></td>
</tr>
<tr>
<td><strong>Passive modalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anamnesis and/or clinical examination</td>
<td>29%</td>
<td>8.3 (7.8)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Soft tissue mobilization (for scar tissue, muscles, etc.)</td>
<td>25%</td>
<td>8.3 (5.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Coaching (goal setting, education on exercise planning)</td>
<td>21%</td>
<td>16.0 (22.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thermal applications at home (use of icepacks)*</td>
<td>16%</td>
<td>22.4 (20.2)*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Traction and/or translations (manually applied)</td>
<td>6%</td>
<td>4.4 (3.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Electrotherapy (to externally stimulate specific muscles)</td>
<td>4%</td>
<td>7.0 (4.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Manual therapy (techniques others than those above)</td>
<td>2%</td>
<td>2.5 (1.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Average for passive modalities</strong></td>
<td></td>
<td>15%</td>
<td>7.7*</td>
<td></td>
</tr>
</tbody>
</table>

*Mann-Whitney U test with a significance level of p<0.05.
ACI=autologous chondrocyte implantation with characterized chondrocytes; MF=microfracture; ROM=range of motion.
*Performed by the participant at home.
1Modalities performed at home were not taken into account for the average time spent by the physiotherapist.

TABLE 4 Objective and subjective outcomes of patients at 2 year post-surgery

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MF (n=26)</th>
<th>ACI (n=28)</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee extension strength, peak torque at 60°/s (Nm)</td>
<td>214 (60)</td>
<td>196 (70)</td>
<td>21 (−53 to 17)</td>
</tr>
<tr>
<td>Single Hop for distance (cm)</td>
<td>163 (44)</td>
<td>137 (57)</td>
<td>26 (−53 to 1)</td>
</tr>
<tr>
<td>Crossover triple Hop for distance (cm)</td>
<td>442 (138)</td>
<td>400 (153)</td>
<td>42 (−120 to 36)</td>
</tr>
<tr>
<td>Timed Hop over 6 m (s)</td>
<td>2.6 (0.6)</td>
<td>3.2 (1.1)</td>
<td>0.6 (0.1 to 1.1)*</td>
</tr>
<tr>
<td>Pooled SI (%)</td>
<td>96 (15)</td>
<td>85 (17)</td>
<td>11 (−23 to 1)</td>
</tr>
<tr>
<td>Change from baseline for pooled SI (%)</td>
<td>6.5 (14)</td>
<td>1.6 (12)</td>
<td>4.9 (−13 to 3)</td>
</tr>
<tr>
<td><strong>Subjective outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline overall KOOS (%)</td>
<td>13.1 (17)</td>
<td>15.1 (17)</td>
<td>−2 (−10 to 6)</td>
</tr>
</tbody>
</table>

*Values are mean±SD.
MF=microfracture; ACI=autologous chondrocytes implantation with characterized chondrocytes; SI=symmetry index; CI=confidence interval; KOOS=Knee Injury and Osteoarthritis Outcome Score.
*Significant difference between group means for variable 6-m timed hop with CI set at 95%.
creation and data analysis, and was based on the estimated time spent on low-load activities, if the patient attended the surgeon prescribed physical therapy sessions (3 to 5 sessions/week of 30 minutes with 75% active participation in low-load activities). The analysis on functional outcomes relied on a mixed linear model, with subjects as random variables, cohorts and visit as dependent categorical variables. The mixed linear model was used to account for dependence of repeated outcome measures on the same subject and missing data. The confidence interval (CI) was set at 95%. Contrast analyses were performed to test consecutive time points within each treatment group (Littell, Henry, and Ammerman, 1998; Molenberghs et al, 2004). To compare cohorts at one time point, a Wilcoxon sum rank tests was used with the significance level set at \( p < 0.05 \). The authors had full access to the dataset and take responsibility for its integrity.

**RESULTS**

**Physiotherapy management**

**Report rate of physiotherapists**
All physiotherapists reported on their management during the first 3 months. Eighty of the 95 (85%) physiotherapists provided a monthly report, of which 65 (81%) physiotherapists reported spontaneously once a week on the treatment modalities they applied.

The physiotherapists \((n=30)\) who were not reporting spontaneously every week were identified and contacted by the coordinating physiotherapist (Figure 1). In order to maximize protocol adherence, explanation was given. Since communication occurred and report rate was insufficient, their data were not analyzed for this study. Many of these physiotherapists mentioned that they considered reporting to be too much of an administrative task, but the protocol greatly facilitated communication with these physiotherapists.

**Physiotherapy management during the first 3 months**
The 65 physiotherapists reported a mean of four modalities per session for both surgical treatment arms. The ACI physiotherapists performed a mean of 3.6 sessions per week and the MF physiotherapists a mean of 3.1 sessions per week during the first 3 months.

General muscle training was the most frequently reported active modality during the first 3 months (47% physiotherapists) and was performed on average 14.4 minutes/session \((SD 9.9)\). Anamnesis/clinical examination (29%), soft tissue mobilizations (25%), and coaching (21%) were the most frequently reported passive modalities (Table 2). In general, few differences were observed between the two groups for the total time spent on individual active and passive modalities during

![Flow chart of physiotherapists in implementation study. ACI=autologous chondrocyte implantation with characterized chondrocytes; MF=microfracture; RCT=randomized clinical trial.](image-url)
the first 3 months. Details are provided in Table 3. More physiotherapists reported the use of active than passive modalities (27% versus 15%). In addition, the time spent on active modalities (mean: 10.0 minutes/session) was more than the time spent on passive modalities (mean: 7.7 minutes/session; Table 3).

Compliance with the rehabilitation protocol during the first 3 months
All but one physiotherapist achieved the goals for range of motion. A single physiotherapist reported an extension deficit of 20° for a participant in the MF group. The rehabilitation protocol specified stationary cycling for up to a total of 1 hour a day between 6 and 12 weeks after surgery. All physiotherapists were compliant on the timing to start stationary cycling at week 5, as a range of motion of more than 90° flexion was permitted at that time (Figure 2A). Only during week 7 did ACI patients cycle significantly more than MF participants (p=0.028; Figure 2A). Some physiotherapists started with postural balance training within weight-bearing limits at week 3 (Figure 2B).

Rehabilitation protocol violations
One MF-treated patient took full weight without the brace at week 4. This patient was excluded from the RCT. This was the only withdrawal from the RCT due to a lack of compliance with the physiotherapy program. Overall, there were no withdrawals due to physiotherapy ‘mismanagement’ in the RCT by Saris et al (2008).

Functional outcome following ACI and MF at 2 years
Both treatment groups had comparable objective and subjective outcomes at 2 years (Table 4). When taking the minimal detectable change into account of 7.05% for pooled tests based on Reid et al (2007) the changes from baseline for the pooled SI (symmetry index) are not significant over the 2 years. Additionally, the mean change from baseline in overall KOOS was 13.1 and 15.1, respectively, for the MF and ACI groups. These changes can be interpreted as clinically significant for both groups because the change was more than the minimal perceptible clinical improvement of 10 points suggested by Roos and Lohmander (2003) (Table 4).

Effect of patient’s activity level post-surgery on the overall functional recovery
The effect of patient’s activity level post-surgery on the functional outcome at the 1- and 2-year assessments was examined using two cohorts: (1) Participants in the high-LLA cohort (n=21) were highly active in low-load modalities post-surgery (>12 minutes/day); and (2) participants in the low-LLA cohort (n=17) were low active in low-load modalities post-surgery (≤12 minutes/day). The mean time spent per day on LLA was 45.9 minutes (SD 29.0) in the high-LLA cohort and 6.8 minutes (SD 4.0) in the low-LLA cohort. Both LLA cohorts did not differ on any baseline characteristics at baseline, except for the stratification parameter LLA (95% CI 25 to 52.9; Table 1).

At baseline the high-LLA cohort had a mean pooled SI of 87.5% (SD 18.0) and the low-LLA cohort 85.5% (SD 16.0; Figure 3). The objective functional outcome in the low-LLA significantly decreased between baseline and 1 year (95% CI 3.9 to 22.7). In contrast, the high-LLA cohort improved slowly over the 2 years, which resulted in a significant difference between both cohorts over the 2 years (95% CI 0.4 to 24.9). At 24 months, the functional outcome of the high-LLA cohort with mean pooled SI of 92.4% (SD 8.0) was significantly better than in the low-LLA cohort (mean pooled SI: 78.2% SI [SD 22.0]) (95% CI 1.79 to 26.21, p=0.04; Figure 3).
over time, significance level was set at 0.05. LLA participant with a low body mass index (Mithoefer participant, whereas it may not be harmful for the repair site in the overweight participant, whereas it may not be harmful for the repair site in the overweight participant. Progress to resumes full weight bearing significantly later than a participant with a low body mass index. Although all participants were required to wear a custom-made unloader brace during the first 8 weeks, permitting. As a result, an overweight participant resumes full weight bearing significantly later than a participant with a low body mass index. Progress to full weight bearing on exactly the same timeline could be harmful to the repair site in the overweight participant, whereas it may not be harmful for the participant with a low body mass index (Mithoefer et al, 2005). Therefore we encourage the implementation of specific training parameters to maximize the individual approach.

Although the applied protocol was based on literature, it still was experience based (Irrgang and Pezzullo, 1998; Minas and Chiu, 2000; Peterson et al, 2000; Steadman, Rodkey, Briggs and Rodrigo, 1999; Steadman, Rodkey, and Rodrigo, 2001). As all new treatment protocols, optimization is possible. For example, the protocol suggested 60 minutes of cycling each day between weeks 6 and 12; however, physiotherapists in our study reported an overall average daily cycling time of 33.4 (SD 22.4) minutes for the ACI group and 26.5 (SD 19.2) minutes for the MF group. So based on our results, this time commitment of 60 minutes seems to be unrealistic for the majority of participants. As unrealistic goal setting is one of the most important factors in decreasing motivation, it is important that future protocols recommend realistic time progression, depending on the participant’s characteristics (Nothwehr and Yang, 2007; Senko and Harackiewicz, 2005).

Participating physiotherapists could individualize their management to the needs of the patients and the goals set. This resulted, irrespective to patient’s pre-injury activity levels, in a large variation in the time spent on low-load activities (Table 1). The total group mean time spent on LLA was 23 minutes/day (SD 23.0). This variation is noteworthy as patients who were highly active in LLA post-surgery (n=21, high-LLA cohort) showed significant better functional performance at 1 and 2 years after surgery. At 2 years, the mean pooled symmetry index was 92.4% in the high-LLA cohort. In contrast, the low-LLA cohort (n=17) had a mean pooled symmetry index of 78.0%. Knowing that a symmetry index higher than 90% is considered as normal, the low-LLA cohort showed insufficient functioning to start high impact sports (Barber et al, 1990; Hambly et al, 2006). The study participants in the high-LLA cohort were active in many different low-load modalities such as heel slides, stationary cycling, and rowing. Numerous in vitro studies on mechanobiology showed the importance of a variety of mechanical stimuli on chondrocytes and cartilage tissue adaptation (Carter et al, 2004; Huselstein et al, 2008; Jackson, Lalar, Aberman, and Simon, 2001; Smith, Carter, Schurman, and Smith, 2004). In animal models, mechanical stimulation appears to contribute to remodeling and homeostatic processes. So mechanical stimuli may enhance tissue repair in cartilage defects in vivo (Jackson, Lalar, Aberman, and Simon, 2001; Wakitani and Yamamoto, 2002). Clinical cartilage repair studies in humans frequently report the use of continuous passive motion (CPM), as it has been shown to improve healing in

![Functional Performance in Low vs High LLA cohorts](image_url)

**FIGURE 3** Functional performance (pooled symmetry index) post-surgery in low- and high-LLA cohorts (respectively low and high amount of low-load activities during the first 3 months post-surgery). Groups are significantly different: *: at 24 months (Wilcoxon test) and **: within groups over time, ***: between groups over time (linear mixed models). Significance level was set at 0.05. LLA=low-load activities.

**DISCUSSION**

To our knowledge we are the first to report on the implementation of a standardized rehabilitation protocol in a controlled randomized trial comparing two cartilage repair procedures. We hypothesized that the physiotherapy management would be influenced by the type of surgery. As only a few small differences in timing and time spent on 18 physiotherapy modalities were observed between treatment groups, we conclude that the type of surgery did not lead to major differences in physiotherapy management during the first 3 months following surgery. In the standardized rehabilitation protocol the duration, frequency and intensity of specific exercises were not strictly imposed, whereas goals and limits for range of motion and weight bearing were strictly prescribed. Several authors emphasized the need to adapt physiotherapy programs to participants’ characteristics (Gillogly, Myers, and Reinold, 2006; Hambly et al, 2006; Reinold et al, 2006). Implementing the standardized rehabilitation protocol, however, did not mean that all participants experienced the same training stimuli. Although all participants were required to wear a custom-made unloader brace during the first 8 weeks, the standardized protocol allowed an individual approach within preset limits (Matsuno, Kadowaki, and Tsuji, 1997). For example, a gradual increase in weight bearing by 10 to 15 kg each week was permitted. As a result, an overweight participant resumes full weight bearing significantly later than a participant with a low body mass index. Progress to full weight bearing on exactly the same timeline could be harmful to the repair site in the overweight participant, whereas it may not be harmful for the participant with a low body mass index (Mithoefer et al, 2005). Therefore we encourage the implementation of specific training parameters to maximize the individual approach.

Although the applied protocol was based on literature, it still was experience based (Irrgang and Pezzullo, 1998; Minas and Chiu, 2000; Peterson et al, 2000; Steadman, Rodkey, Briggs and Rodrigo, 1999; Steadman, Rodkey, and Rodrigo, 2001). As all new treatment protocols, optimization is possible. For example, the protocol suggested 60 minutes of cycling each day between weeks 6 and 12; however, physiotherapists in our study reported an overall average daily cycling time of 33.4 (SD 22.4) minutes for the ACI group and 26.5 (SD 19.2) minutes for the MF group. So based on our results, this time commitment of 60 minutes seems to be unrealistic for the majority of participants. As unrealistic goal setting is one of the most important factors in decreasing motivation, it is important that future protocols recommend realistic time progression, depending on the participant’s characteristics (Nothwehr and Yang, 2007; Senko and Harackiewicz, 2005).

Participating physiotherapists could individualize their management to the needs of the patients and the goals set. This resulted, irrespective to patient’s pre-injury activity levels, in a large variation in the time spent on low-load activities (Table 1). The total group mean time spent on LLA was 23 minutes/day (SD 23.0). This variation is noteworthy as patients who were highly active in LLA post-surgery (n=21, high-LLA cohort) showed significant better functional performance at 1 and 2 years after surgery. At 2 years, the mean pooled symmetry index was 92.4% in the high-LLA cohort. In contrast, the low-LLA cohort (n=17) had a mean pooled symmetry index of 78.0%. Knowing that a symmetry index higher than 90% is considered as normal, the low-LLA cohort showed insufficient functioning to start high impact sports (Barber et al, 1990; Hambly et al, 2006). The study participants in the high-LLA cohort were active in many different low-load modalities such as heel slides, stationary cycling, and rowing. Numerous in vitro studies on mechanobiology showed the importance of a variety of mechanical stimuli on chondrocytes and cartilage tissue adaptation (Carter et al, 2004; Huselstein et al, 2008; Jackson, Lalar, Aberman, and Simon, 2001; Smith, Carter, Schurman, and Smith, 2004). In animal models, mechanical stimulation appears to contribute to remodeling and homeostatic processes. So mechanical stimuli may enhance tissue repair in cartilage defects in vivo (Jackson, Lalar, Aberman, and Simon, 2001; Wakitani and Yamamoto, 2002). Clinical cartilage repair studies in humans frequently report the use of continuous passive motion (CPM), as it has been shown to improve healing in
osteoarticular defects in rabbits (Salter, 1989). The use of CPM is suggested for 6 to 8 hours a day for up to 6 weeks (Steadman, Rodkey, and Briggs, 2002; Steadman, Rodkey, Briggs, and Rodrigo, 1999). However, it is questionable if this time investment is realistic and preferable (Brosseau et al, 2004; Hambly et al 2006). Many protocols on the use of CPM after cartilage repair have been described, with no studies reporting on the additional effect of different patient activity levels (Brosseau et al, 2004; Steadman, Rodkey, and Briggs, 2002; Steadman, Rodkey, and Rodrigo, 2001). As such, the level of beneficial low-load mobilizations to enhance cartilage healing in humans remains unclear. With regard to our second hypothesis, our results may support the advice of intense mobilizations in low-load conditions following cartilage repair. In contrast to studies using CPM, the modalities used in our study were heel slides, stationary cycling, and rowing. To confirm the significant results of our study and to define dose-response effects, future studies are warranted and should investigate larger samples of patients.

ACKNOWLEDGMENTS

The authors acknowledge and thank Bracing Center (Belgium) and Spronken (the Netherlands) for supplying and adapting the custom-made GII braces for each participant professionally. The authors also thank Martine Thomis for her contributions and all physiotherapists for their active cooperation. This work was supported by a grant from the Fund for Scientific Research, Flanders, Belgium.

Declaration of Interest: Danny Van Caspeland Filip Staes declared no competing interests, Dieter Van Assche, Johan Vanlauwe, Johan Bellemans and Frank P Luyten own Tigenix Stock; Johan Vanlauwe and Daniel B Saris received reimbursement for educational activities from Tigenix and declared a potential conflict of interest.

REFERENCES

Brittberg M 2008 Autologous chondrocyte implantation—technique and long-term follow-up. Injury 39: S40–S49
Hunziker EB 2003 Tissue engineering of bone and cartilage. From the preclinical model to the patient. Novartis Foundation Symposium 249: 70–78

Physiotherapy Theory and Practice


Reid A, Birmingham TB, Stratford PW, Alcock GK, Giffin JR 2007 Hop testing provides a reliable and valid outcome measure during rehabilitation after anterior cruciate ligament reconstruction. Physical Therapy 87: 337–349


Roos EM, Lohmander LS 2003 The Knee injury and Osteoarthritis Outcome Score (KOOS): From joint injury to osteoarthritis. Health and Quality of Life Outcomes 1: 64


Salter RB 1989 The biologic concept of continuous passive motion of synovial joints. The first 18 years of basic research and its clinical application. Clinical Orthopaedics and Related Research 242: 12–25


Steadman JR, Rodkey WG, Briggs KK, Rodrigo JJ 1999 The microfracture technique in the management of complete cartilage defects in the knee joint. Orthopade 28: 26–32


Wakitani S, Yamamoto T 2002 Response of the donor and recipient cells in mesenchymal cell transplantation to cartilage defect. Microscopy Research and Technique 58: 14–18

APPENDIX 1. GUIDELINES FOR REHABILITATION AFTER CARTILAGE REPAIR ON 
THE FEMORAL CONDYLE OF THE KNEE

(Original for RCT: in Dutch on 4 pages, 2000)

Goals for range of motion (ROM)

Weeks 0–4: 0° to max. 90° active flexion.
Week 5: 0° to max.110° active flexion.
Weeks 6–8: 0° to max.130° active flexion.
Full ROM progressively by 8 weeks.
Weeks 0–8: the unloader brace is worn day and night. Subsequently, wean off gradually, starting at night.

Goals for weight-bearing

Weeks 0–2: non-weight-bearing.
Week 3: weight-bearing control with 10 to 15 kg for all activities.
Weekly: increase by 10 to 15 kg every week.
Still always use 2 crutches and progress to normalization of gait.

Goals for strength and function

Weeks 0–2: isometrics in varied knee positions, pain free; use of myofeedback for muscle reeducation; no open chain exercises with resistance below the knee; joint circulation exercises.
Weeks 2–6: closed chain exercises, within weight-bearing restrictions; weight-shifting activities (isometric) with a focus on proprioception and neuromuscular control; aquatic therapy for general conditioning.
Weeks 6–12: stationary bike 1 hour every day; bilateral closed chain exercises (concentric and eccentric); progression in proprioceptive exercises; all within limits of weight-bearing control.
Months 3–6: increase workload of the knee in functional activities; stepping within ROM; cycling with light resistance; short repetitions of bipodal landing on a shock-absorbing surface (e.g. a mini trampoline).
Months 6–10: gradually increase resistance through increase of repetitions and a decrease of sets; start with intense jogging (low average speed, high moving frequency over short distances, lots of sets)
Months 10–24: impact training; heavier weight training; sport-specific exercises and return to sports vary according to: sport, the level of the patient and the medical guidelines; high-level activities such as basketball and football can begin at 16 months or sooner if pain free, no swelling and consistent with medical advice.

General guidelines on joint circulation exercises

Joint circulation exercises are a necessity. They are needed for nutrition and stimulation of the transplanted cells at every stage of the rehabilitation; without nutrition, no cell or tissue adaptations can be expected. If nutrition is provided daily, the cells can develop properly and integrate optimally.
The exercises need to be:
- repetitive, with a large ROM
- pain free, performed daily and over an extended time, i.e. 60 minutes a day
- easy to perform, safe and preferably active, and last but not least, without substantial loading.

General guidelines on progressive ROM increase

The exact location of the implant should always be obtained, and for an increase in ROM:
- exercises are performed after active circulation exercises,
- with respect to glide-arthrokinematics
- only local pain during stretch in the region is normal
- exercises are long, static and with minimal stress, no adverse muscle tension is allowed.
Implement circulation exercise over the full range, stationary cycle can start if active 100° flexion has been obtained.

General guidelines on weight-bearing progression

To start progression in weight-bearing use:
- short loading times in functional weight-bearing positions
- perform lots of short sets to aim for lots of repetitions in total
- objective feedback of the weight–balance control in different exercises
Loading in slow movements can induce shear stress with deformation of the repaired surface and thus damage the graft site. Therefore, avoid slow, static loading movements
- in extension zone, if tibia/femur graft site is more anterior
- in > 45° of flexion, if tibia/femur graft site is more posterior
- within 0°–40° range, if graft site is patellar inferior
- within 0°–40° range, if graft site is trochlear superior
- in > 45° of flexion, if graft site is patellar middle or superior
- in > 45° of flexion, if graft site is trochlear inferior
If the repair site is small, progression in weight-bearing control can be more easily increased, with respect to the joint circulation exercises and the use of 2 crutches. It is normal to experience local swelling and pain in the month following the operation. Pain and swelling may not occur during or after the exercises!

General guidelines on strength and function

Every new exercise is a proprioception exercise. Position sense (reference to contact surface or body part) and movement sense (direction, speed and force) should be addressed. Isolated muscle control (isometric, concentric and eccentric) is needed for development and automatization of correct coordination.

**Postural balance** is optimized in a safe loading or weight-bearing position. The following adaptations can be made for progression using:
- an exercise surface that is stable, to less stable ground (within patient limits)
- eyes open to eyes closed
- equal bipodal balance to partial or shifted bipodal balance
- bipodal to unipodal balance.

**Strength training is functional training**, as much as possible. Normalization of open kinetic chain functions is needed, without the use of external force. External force might induce shear stress over the repaired site causing subsequent damage.

**Closed kinetic chain exercises are preferable** to train stability in functional weight-bearing positions.

To gain specific maximal power output an example is (where 1RM = one repetition maximum, “= minute, “=second, set=exercises repeated without stopping):
- starting at endurance: > 25 RM, rest 3' in between sets, 5 sets
- to low-intensity: > 20 RM, rest 2', 3 sets
- high intensity: 10 to 15 RM, rest 1’, 2 sets
- strength/maximal power: 3 to 8 RM, rest 30”, 1 to 2 sets

The number of sessions a week depends on the patient’s recuperation time and the performed exercises. This is different for individuals; nevertheless 3 exercise sessions a week are often possible and are recommended. **Movement speed** during exercises should be functional speed. Learning a movement is easier and safer at low speed. To prevent shear stress on the repaired site, weight-bearing adaptation is necessary.

General guidelines on recreational sport activities

Sports that are characterised by repetition of movement cycles, with low joint impact forces, are preferable.

In the rehabilitation program they are placed under joint circulation exercises. Safety precautions are always essential.

**Cycling**: Getting on and off the bicycle should be practiced once with the physiotherapist to ensure good control of stability. Cycling with a ‘recumbent’ bicycle (an inclined seating position) is possible as soon as an emergency stop can be performed safely. Using any bike (mountain or race), it is recommended to reduce peak force. This can be achieved by: performing lots of moving cycles per minute, using clip-in paddles, staying in the saddle and choosing a good easy road.

**Aquatic sports**: Safety precautions for getting in and out of the pool are recommended. Aqua therapy, such as aqua jogging, is recommended as soon as the movement cycle can be performed and the wound has healed. Breaststroke will place the knee joint under stress and lots of flexibility is required. It is allowed to start at 4 months after the operation when it is pain free. Crawl is allowed as soon as the movement cycle can be performed safely (starting after 6 weeks). Caution must be taken for the turns. Often peak force is generated. Turns are taken with the uninvolved leg for landing and push-off.

**Inline or ice-skating** is allowed after 4 months. Previous experience and competence is required. Motor control for an emergency stop should be practiced on a safety mat before starting. Artistic or acrobatic movements are best avoided.

**Cross-country skiing** is allowed after 4 months. Previous experience and competence is required. Motor control for an emergency stop should be practiced on a safety mat before starting.

**Sports like diving, golf, indoor climbing, tai chi...** do not specifically enhance joint circulation, although they are advisable. The variation in motor control and joint protection can be relatively easily managed within these sports.

**Sports characterized by movement reaction time, high-velocity and high-impact during landing or push-off are not advisable**. For example football, basketball, volleyball, tennis, paragliding, track and field, surfing, skiing, snowboarding etc. are all not advisable. The resulting force impact can damage the repaired site. This can occur initially without any symptoms. Therefore, sport-specific exercises and return to sports vary according to: the specific sport, the level of the patient and the medical guidelines. High-level activities can begin at 16 months or sooner if the patient’s knee is symptom free and following medical advice.