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Cartilaginous tibial eminence fractures in children: which recommendations for management of this new entity?

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Abstract

Purpose Cartilaginous tibial eminence fracture (CTEF) is a new pattern of ACL rupture in children under the age of nine. MRI signs have been recently reported, but no series gave information about outcomes. It was hypothesized that primary treatment gave better results than delayed management due to frequent misdiagnosis.

Method This retrospective study focused on 15 patients, managed acutely (\(n=7\)) or delayed (\(n=8\)). The patients’ median age at the time of initial injury was 6.5 years (range 5–9). Lysholm, IKDC 2000 subjective scores, and the measurement of the residual laxity by a side-to-side difference with a KT-1000 junior arthrometer were used at the time of revision.

Results After a mean follow-up of 9.8 years (range 1–18.5), the mean Lysholm and IKDC subjective scores were, respectively, 97.7 ± 2.6 and 97 ± 3.4. The median residual laxity was 2 mm (range 0–4). Non-operative treatment lead to 2 failures: intermeniscal ligament entrapment and combined avulsion fracture at the femoral site. Suture fixation of the avulsed fragment allows regularly good results when performed acutely or even 4 years after the injury. The hypothesis that primary treatment gives better result than delayed treatment tends to be wrong as 2 failures were reported in each group. An ACL reconstruction was performed in 3 out of the 4 treatment failures. Progressive resorption of the avulsed fragment was noticed in 3 of the 4 failures suggesting an associated ACL resorption.

Conclusion CTEF has a good prognosis even after misdiagnosis and treatment at the time of non-union; this could be due to low-energy mechanism of injury and low rate of associated lesion. Orthopaedic treatment for acute minimally displaced fractures is only indicated under strict MRI control, and suture fixation is the recommended strategy in other situations. Conservative management of non-union could expose to ACL involution and cannot be recommended.

Level of evidence Retrospective case series, Level IV.

Keywords Anterior cruciate ligament · Tibial eminence fracture · Children · Misdiagnosis · Cartilaginous avulsion

Introduction

Tibial eminence fracture is a frequent pattern of ACL rupture in skeletally immature patients [5, 6, 21]. Traditionally, it occurs between 8 and 14 years of age and is rare under the age of 8 [2, 16, 21].

A new entity has been recently reported in very young children, with purely cartilaginous avulsions of
the ACL insertion on either the femoral [4, 12, 17] or more commonly on the tibial site [7, 18, 28]. The latter are frequently misdiagnosed even after MRI examination because classical primary and secondary MRI findings after ACL injury can be negative [7]. A fluid signal underneath the cartilaginous fragment reaching up to the ossified epiphysis on T2 sequences or a double PCL sign may orient the diagnosis [7]. Despite a better knowledge about the diagnostic principles, no series reported the management and results of these rare injuries. The aim of this study was to focus on these 2 items through a multicentre series. The authors hypothesized that primary treatment of cartilaginous tibial eminence fractures (CTEFs) gave better results than delayed management due to misdiagnosis.

**Materials and method**

Out of 161 consecutive tibial eminence fractures treated in our department between 1994 and 2012, eleven patients with CTEF of ACL insertion were identified. Seven children were referred to our department as a tertiary referral hospital because of misdiagnosed injury, and 4 had primary treatment in our hospital. After a survey in the French Society of Paediatric Orthopaedics (SOFOP), 4 more patients were diagnosed and treated in two other institutions.

This retrospective study focused on 15 patients (8 right and 7 left knees) who had different regime of management: acute management \(n=7\), delayed management \(<6\) months \(n=2\), and delayed management \(>6\) months \(n=6\). The patients’ median age at the time of initial injury was 6.5 years \(\pm 1.4\) (range 5 to 9). The main cause of injury was a low-energy domestic accident \(n=7\), bicycle fall \(n=3\), or sports accident \(n=4\). All patients had immediate joint effusion at the time of injury. Other individual findings at the time of injury are summarized in Table 1 and Fig. 1 shows their management algorithm.

A retrospective analysis of the patients’ chart, traumatic history, conventional radiograph, and MRI was performed. Lesions were classified according to Meyers and McKeever as well as Zifko and Gaudernak [24, 31]. ACL reconstruction was considered as a management failure of CTEF.

In the acute management group, the diagnosis was radiologically suspected after careful examination by a senior paediatric orthopaedic surgeon due to the presence of a very thin and hardly visible bone lamella. Five of these patients had an orthopaedic treatment with long leg cast. A simple cast in slight flexion without reduction was performed for patient no. 1, and cast in extension for fracture reduction was performed for the others. Non-weight bearing during 4–6 weeks was recommended.

In the delayed management group \(<6\) months, the initial diagnosis of midsubstance ACL tear performed on MRI was revised during radiographic follow-up because of ossifications of the avulsed fragment. One patient had suture fixation 2.5 months after injury. The other underwent a non-operative management chosen at the time of referral 4 months after injury because of moderate functional disability (limitation of hyperextension and occasional but rare instability) and non-acceptance of surgery by the parents (patient no. 7).

In the delayed management group \(>6\) months, the 6 patients were referred because of functional disability due to extension deficit and/or instability and a past history of knee injury. The median delay for referral after the accident was 30 months \(\pm 27.6\) (6–72). Initial knee radiographs were interpreted as normal from the referring centres as well as after a retrospective second lecture. Despite MRIs, the diagnosis of CTEF was only suspected in 1 patient. Patient no. 9 had misinterpretation of MRI that conducted to erroneous diagnosis of an avulsed lateral discoid meniscus which conducted to inappropriate partial meniscectomy 9 months following the accident.

Management at the time of referral included 5 cases of suture fixation. In 4 cases, a mixed arthroscopic and mini-open reduction with a modified Ahn pull-out suturing technique of the tibial eminence with transphyseal absorbable sutures was performed [1, 9]. After debridement of the fracture bed and the fragment, care was taken to optimize the ACL tension and compensate plastic deformation of the ligament by countersinking the tibial fragment moderately [21, 26]. For patient no. 9, a pull-out reattachment of the medial meniscus posterior root using a modified Kim method with transphyseal absorbable suture was associated after arthroscopic shaving of the posterior ossification [19, 23] (Figs. 2, 3). Patient no. 14 had an epiphyseal suture without countersinking through an open approach. Because of good tolerance of the non-union, patient no. 6 had a conservative treatment between the ages of 6 and 12.

**Evaluation**

At the final follow-up, all patients were evaluated with the Lysholm and IKDC 2000 subjective scores. The residual laxity was assessed by a side-to-side difference with a KT-1000 junior arthrometer (MEDmetric, San Diego, CA) [14]. Clinical final results were scored according to the IKDC classification. A specific attention was given to detect growth disturbances clinically (leg discrepancy using the graduated blocks method and axial deformity assessment) and radiologically. Growth arrest, but also overgrowth was assessed according to standard recommendations [10].
### Table 1  Detail of individual patient’s feature at the time of injury

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex/age at injury</th>
<th>Type of initial accident/mechanism</th>
<th>First radiograph</th>
<th>Misdiagnosed injury/ presumed diagnosis</th>
<th>MRI (delay after accident)</th>
<th>Retrospective diagnosis/type of displ#</th>
<th>Initial acute management</th>
<th>Management in referred centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/6.5</td>
<td>Fall from bicycle</td>
<td>Thin ossification</td>
<td>–</td>
<td>I-A or II-A</td>
<td>Cast in flexion 5 weeks</td>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F/5.5</td>
<td>Fall from bicycle</td>
<td>Ossification</td>
<td>–</td>
<td>II-A</td>
<td>Cast in extension/GA</td>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F/5</td>
<td>Crushing leg (motorcycle)</td>
<td>Thin ossification</td>
<td>–</td>
<td>IV-B</td>
<td>Suture fixation/tibia nailing</td>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>M/8.5</td>
<td>Fall from his height</td>
<td>Thin ossification</td>
<td>–</td>
<td>III-A and femur</td>
<td>Cast in extension/ needle aspiration/GA</td>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F/6.5</td>
<td>Fall from his height</td>
<td>Thin ossification</td>
<td>–</td>
<td>II-A</td>
<td>Cast in extension</td>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F/6</td>
<td>Ski twist</td>
<td>Normal</td>
<td>Sprain</td>
<td>W + 6</td>
<td>III-A</td>
<td>Splint</td>
<td>Non-union</td>
</tr>
<tr>
<td>7a</td>
<td>M/6</td>
<td>Fall from his height</td>
<td>Normal</td>
<td>Midsubstance ACL tear</td>
<td>W + 4</td>
<td>IV-B</td>
<td>Splint</td>
<td>Delayed M + 4</td>
</tr>
<tr>
<td>8a</td>
<td>F/5</td>
<td>Fall from his height</td>
<td>Thin ossification</td>
<td>Midsubstance ACL tear</td>
<td>W + 3</td>
<td>III-A</td>
<td>Splint</td>
<td>Delayed M + 2.5</td>
</tr>
<tr>
<td>9a</td>
<td>M/6</td>
<td>Fall from his height</td>
<td>Normal</td>
<td>Desinserted lateral discoid meniscus?</td>
<td>W + 6</td>
<td>IV-B</td>
<td>No immobilisation</td>
<td>Non-union</td>
</tr>
<tr>
<td>10</td>
<td>F/7.5</td>
<td>Fall from bicycle</td>
<td>Thin ossification</td>
<td>–</td>
<td>W + 1</td>
<td>IV-B</td>
<td>Cast in extension 5 weeks</td>
<td>Acute</td>
</tr>
<tr>
<td>11a</td>
<td>M/8.5</td>
<td>Ski/jump bad reception</td>
<td>Normal</td>
<td>Sprain/suspected CETF</td>
<td>W + 2</td>
<td>IV-B</td>
<td>No immobilisation</td>
<td>Non-union</td>
</tr>
<tr>
<td>12</td>
<td>M/8</td>
<td>Foot ball/knee hyperextension</td>
<td>Thin ossification</td>
<td>–</td>
<td>III-B</td>
<td>Suture fixation</td>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>13a</td>
<td>M/8.5</td>
<td>Judo twist</td>
<td>Normal</td>
<td>Midsubstance ACL tear/ lateral meniscus tear?</td>
<td>W + 4</td>
<td>IV-B</td>
<td>Splint</td>
<td>Non-union</td>
</tr>
<tr>
<td>14</td>
<td>M/5.5</td>
<td>NA</td>
<td>Normal</td>
<td>Sprain</td>
<td>M + 9</td>
<td>III-A</td>
<td>Splint</td>
<td>Non-union</td>
</tr>
<tr>
<td>15</td>
<td>M/9</td>
<td>Trampoline</td>
<td>NA</td>
<td>Sprain</td>
<td>M + 20</td>
<td>III-B</td>
<td>No immobilisation</td>
<td>Non-union</td>
</tr>
</tbody>
</table>

* Patients included in a previous study [7]. M Male, F female, L left, R right, delay for MRI is given in weeks or months (W and M); # classification according to [MM][Zifko]; GA general anaesthesia, NA not available
Due to the limited number of cases, no statistical analysis was performed.

Results

After a mean follow-up of 9.8 years ± 5 from the initial accident and 4.6 years (range 1–18.5) from the definitive treatment, the results of the series are presented in Table 2. The mean age at the time of last revision was 15 years (±5). A total of four failures out of the fifteen managed cases were noticed (Fig. 1). No failure was reported after suture fixations \( n = 8 \).

In the acute management group, non-surgical treatment failed in patient no. 4 and no 10 despite cast immobilization in extension for 5 weeks. Patient no. 4 had a combined second avulsion fracture at the femoral site that was diagnosed retrospectively. Complete resorption of the ossified fragment on the tibial side was noticed after a few months of conservative treatment.
Surgery, performed after skeletal maturity at the age of 15 because of instability, revealed an empty notch making suture fixation impossible, and an ACL reconstruction was performed. An associated stable and partial longitudinal tear of the posterior segment of the medial meniscus was treated by stimulation alone. Patient no. 10 had an intermeniscal ligament entrapment diagnosed retrospectively on radiographs under cast and MRI (Fig. 4). After cast immobilization, a rapid resorption of the ossified fragment was noticed. At the latest follow-up 2 years later, a non-operative treatment was still ongoing (stable knee after physiotherapy).

The 2 patients treated by suture fixation in emergency had an excellent result at follow-up.

In the delayed management group, 2 patients were managed by longstanding non-operative management. Patient no. 6 had a deficit of hyperextension due to avulsed ossified fragment during 3 years and a ski accident conducting to complete osseous resorption and required an ACL reconstruction with a modified Anderson procedure after 6 years [3]. Patient no. 7 had interstitial ACL fibres damage during specific ACL reconstruction [8] because of instability after 4 years of non-operative management.

**Discussion**

The most important finding of the present study was that suture fixation of the avulsed fragment allows regularly good results when performed acutely or even 4 years after the injury. At the contrary, the orthopaedic treatment without MRI support could expose to failure. The hypothesis that primary treatment gives better result than delayed treatment due to misdiagnosis tends to be wrong as 2 failures were reported in each group.

Cartilage tibial eminence fracture is a recent entity unknown before the 2 first cases reported in 2002 and 2008 [18, 28]. It should not be confounded with midsubstance ACL tears or peel-off injuries which are ligamentous soft tissue avulsions without any associated bony or cartilaginous fragment [13, 20]. CETF is involving children under the age of 9 and is usually due to domestic or low-energy injuries [7]. This may explain the low prevalence of associated bone bruises and meniscal tears in this series in opposition to classical bony tibial eminence fractures [27, 30]. Because traditional primary and secondary MRI findings after ACL injury are negative in CETF [7], the diagnosis is easily missed unless a thin bone lamella can be suspected on initial X-rays after careful examination. Unlike bony tibial eminence fractures, CTEF often extends far posteriorly lifting the entire intercondylar surface (9 types B of Zifko out of 15) giving a double PCL aspect on MRI. It could be argued that during this type of avulsion, the posterior hinge is preserved and that this lesion should be classified as a Meyers and Mc Keevers type II. This highlights the difficulties of using the latter classification for CTEF as it is exclusively based on the radiologic appearance of the bone fragment.

![Patient no. 9: 45 months after the injury, the lateral radiographs view in extension before suture fixation surgery reveals 2 separated ossifications (left). MRI with enlarged ossifications on posterior medial meniscus root avulsion under the PCL (right). The later avulsion was reinserted.](image)
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age at the time of definitive management</th>
<th>Definitive management/(Y + 6) delay after accident</th>
<th>Intraoperative observation</th>
<th>Follow-up/definitive TT/year</th>
<th>Lysholm score</th>
<th>IKDC 2000 subjective score</th>
<th>Observation/complain</th>
<th>Residual laxity different KT max(^a)</th>
<th>IKDC grade</th>
<th>Leg discrepancy (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.5</td>
<td>Cast in flexion/acute</td>
<td>–</td>
<td>18.5</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>A</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>5.5</td>
<td>Cast in extension/acute</td>
<td>–</td>
<td>13.5</td>
<td>94</td>
<td>91</td>
<td>Occasional slight pain</td>
<td>1</td>
<td>A</td>
<td>–10</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Suture fixation/acute</td>
<td>Anterior medical meniscus entrapment</td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>2</td>
<td>A</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>Secondary ACL after Y + 6.5</td>
<td>Empty notch/stable medical meniscus tear</td>
<td>5.5</td>
<td>95</td>
<td>100</td>
<td>Pivot shift: glide 4</td>
<td>Failure</td>
<td>IKDC B</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>6.5</td>
<td>Cast in extension/acute</td>
<td>–</td>
<td>1</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>2</td>
<td>A</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>Secondary ACL after Y + 6</td>
<td>NA</td>
<td>1.5</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>4</td>
<td>Failure</td>
<td>IKDC B-NoNA</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>Secondary ACL after Y + 4</td>
<td>Interstitial ACL lesion but no meniscus tear</td>
<td>3.5</td>
<td>94</td>
<td>92</td>
<td>Lachman grade 2/pivot shift: grade 1</td>
<td>4</td>
<td>Failure IKDC C-5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>Delayed suture fixation/after M + 2</td>
<td>No</td>
<td>3.5</td>
<td>99</td>
<td>97</td>
<td>0</td>
<td>1</td>
<td>A</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>Secondary suture fixation/after Y + 4</td>
<td>LMAH posteriorly displaced –PMMI avulsion</td>
<td>2</td>
<td>99</td>
<td>98</td>
<td>Slight deficit of full flexion/ difficult squat</td>
<td>3</td>
<td>B</td>
<td>+7</td>
</tr>
<tr>
<td>10</td>
<td>7.5</td>
<td>Cast in extension/failure conservative TT wait ACL r</td>
<td>–</td>
<td>–</td>
<td>Restricted activities/waiting period</td>
<td>–</td>
<td>Failure</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11.5</td>
<td>Secondary suture fixation after M + 30</td>
<td>LMAH on the fragment (discoid aspect)</td>
<td>1.5</td>
<td>95</td>
<td>94</td>
<td>Very occasional slight pain</td>
<td>1</td>
<td>A</td>
<td>+10</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>Suture refixation/acute</td>
<td>LMAH on the fragment</td>
<td>2.5</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>A</td>
<td>+5</td>
</tr>
<tr>
<td>13</td>
<td>9</td>
<td>Secondary suture fixation/after M + 6</td>
<td>Meniscal entrapment LMAH on the fragment</td>
<td>3</td>
<td>95</td>
<td>95</td>
<td>Very occasional slight pain</td>
<td>2</td>
<td>A</td>
<td>+7</td>
</tr>
<tr>
<td>14</td>
<td>6.5</td>
<td>Secondary suture fixation after M + 9</td>
<td>No</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>A</td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>Secondary suture fixation after M + 24</td>
<td>–</td>
<td>1</td>
<td>Wait further</td>
<td>NA</td>
<td>Wait further evaluation</td>
<td>Wait further evaluation</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*LMAH* lateral meniscus anterior horn, *PMMI* posterior medial meniscus root
An absence or an inappropriate immobilization of this lesion conducted regularly to delayed or non-union. The indication of non-surgical treatment with a long leg cast should be based on a careful MRI analysis allowing for a proper staging of the lesion and looking after associated lesions. If this treatment is initiated, a new MRI with the knee immobilized in the cast is recommended in order to assess the quality of closed fragment reduction and the absence of soft tissue interposition. As reported for osseous tibial eminence fracture [22], insertion of the anterior horn of the lateral meniscus on the avulsed fragment is a very consistent feature in CTEF (4 cases in this series). In 2 cases, it led to a confusing diagnosis of discoid lateral meniscus due to the posterior displacement of the anterior part of the meniscus.

When displacement is complete, arthroscopic suture fixation of CTEF is recommended. The management is similar to bony tibial eminence fractures, especially if a thin osseous layer is observed in the acute phase or at the time of secondary enlargement of the fragment. There are no data in this study suggesting that delayed treatment for few weeks is worth than acute management, and that is why the strategy of a new clinical examination with radiography after 2 or 3 weeks is a good alternative to MRI in all cases in the acute phase. In the case reported by Kim [18], a 5-year-old girl had successful treatment after a non-delayed pull-out suture under arthroscopy for a purely cartilaginous avulsion fracture, and there is no similar case in this series.

Long delay before surgical correction of CTEF with non-union is sometime justified in patients nearly asymptomatic, but parents must be aware that this option is potentially deleterious. The 2 patients in this series managed by conservative treatment for non-union failed after 4 and 6 years and eventually need ACL reconstruction. Voce et al. [28] reported a good result in a 9-year-old boy treated conservatively after misdiagnosis, but follow-up was only limited to 1 year. During the waiting period, a progressive osseous resorption of the fragment avulsed is possible. It was noticed in 3 of the 4 failures reported in this study and could be an indirect sign of ACL involution. This is a plea to avoid prolonged conservative management of non-union.

Suture fixation procedures must be encouraged as it bears a low complication risk and good final results (7 IKDC A and 1 IKDC B). These very good results contrast with some moderate objective results reported after long term of displaced osseous tibial eminence fracture [15, 29]. This difference could be attributed to higher-energy mechanism and higher rate of associated ACL fibre damage at the time of injury for bony avulsions compared to CTEF [26, 30].

This study highlights arthroscopic transphyseal pull-out method of suture fixation as it is the technical option of our institution, but open and epiphyseal pull-out suture was also performed with success. Because the cartilaginous fragment is fragile and sometimes very thin, a suture through the ACL could be more appropriate than screw.

Fig. 4 Intermeniscal ligament entrapment seen on MRI could explain failure of orthopaedic treatment (patient no. 10). Double PCL sign is noticed on the middle figure.
or wire. Prior to fixation, curettage of the fracture bed is encouraged to facilitate the best placement of the fragment and to obtain countersinking and restitute appropriate tensioning of the ACL. No ACL retraction was reported neither bone graft required when fixation was performed for non-unions, not even with long surgical delays after injury. The anterior fixation of the fragment must be the priority even with a CTEF extending posteriorly (Zitko type B) (Fig. 5). But care must be taken because a posterior ossification can be due to tibial avulsion of the medial meniscus posterior root and can require a specific associated procedure for meniscal fixation.

Growth arrest after transphyseal screw fixation for osseous tibial eminence fracture was reported [25]. This complication was not noticed in our series despite transphyseal fixation. The material used (thread) and the young age of patients could be argued, as the risk of growth arrest (type A according to Chotel's classification) is lower for very young children compared to adolescents [10, 11]. On the contrary, a slight overgrowth process (type B) was regularly noticed (Table 2). Similar observations were reported by Ahn following pull-out arthroscopic treatment for tibial osseous eminence fractures in an 11-year-old male and a 6-year-old female. Both patients displayed a 1-cm length increase in the affected limb at follow-up [1].

To our knowledge, this retrospective multicentre study reports the largest series of CTEF so far, but the number of patients is still low. The management of this rare injury was very heterogeneous which do not provide strong evidence-based treatment guidelines, but only recommendations based on a single-centre experience. Further multicentre studies on this probably underreported entity are necessary.

The clinical relevance of this study is to recommend the suture fixation of the avulsed fragment as the gold standard in the management of displaced CTEF.

**Conclusion**

Because of diagnosis difficulties for half of the patients, the management of CTEF was heterogeneous in this series. CTEF has a good prognosis even after misdiagnosis and treatment at the time of non-union. This could be due to low-energy mechanism of injury and low rate of associated lesion. Orthopaedic treatment for acute minimally displaced fractures is only indicated under strict MRI control, and suture fixation is the recommended strategy in other situations. Conservative management of non-union could expose to ACL involution and cannot be recommended.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.
References


