Donor site morbidity after articular cartilage repair procedures :
A review

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In order to perform an Osteochondral Autologous Transplantation (OAT) or an Autologous Chondrocyte Implantation (ACI), the integrity of healthy intact articular cartilage at a second location needs to be violated. This creates the possibility for donor site morbidity. Only recently have any publications addressed this issue. The aim of this manuscript is to review the current knowledge on donor site morbidity after an OAT or an ACI.

Reports were identified by searching Medline and Pubmed up to March 2010. Donor site morbidity was described mostly considering a clinical outcome, both in a qualitative (parameters in history or physical examination) and/or quantitative way (knee status reported by means of a numerical score). An increasing rate of problems is noted when using quantitative instead of qualitative parameters, and when donor site morbidity is the focus of attention, affecting up to more than half of the patients, in particular for an OAT procedure.

The decision to harvest an osteochondral or cartilage biopsy to perform a repair procedure should therefore be taken with caution. This also underscores the need for further research to identify safe donor sites or to develop techniques that eliminate the need for a formal biopsy ccompletely.

Keywords : articular cartilage ; repair ; donor site ; morbidity.

INTRODUCTION

It has been known since ancient times that damaged articular cartilage has no tendency to heal.

In 1743 William Hunter wrote : "*If we consult the standard chirurgical writers from Hippocrates down to the present age, we shall find, that an ulcerated cartilage is universally allowed to be a very troublesome disease ; that it admits of a cure more difficultly than a carious bone ; and that, when destroyed, it never recovered*" (*18*). In a comprehensive review of the literature, Campbell concluded that most of the earlier investigators observed that injuries of the hyaline cartilage did not heal with restoration of the native tissue, but mainly with fibrous tissue and fibro-cartilage (*9*). Three subsequent independent reviews confirmed the conclusions of Campbell (*2,19,22*).

Focal lesions of the knee and the tibiotalar joint are very frequent, in particular in sports injuries (*7,11,12,36,37*). Joint surface defects are a common cause of pain and disability and may cause chronic

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symptoms. For those patients who do not sufficiently benefit from a conservative approach, surgical treatment is an option. Best long-term results can be expected using a treatment procedure that restores the integrity of hyaline articular cartilage.

During the last decade, increasing experience has been gained with Osteochondral Autologous Transplantation (OAT) or Autologous Chondrocyte Implantation (ACI). Promising results have been reported with both techniques, not only in the knee, but also in other joints such as the ankle (5,32,36,39). However, both procedures need to violate the integrity of healthy, intact articular cartilage at a second location to obtain the cartilage-bone cylinders to be transplanted, or the cartilage to start the cell expansion procedure (8,16). This creates the possibility for donor site morbidity, especially if another healthy joint is involved ; it even introduces potential ethical concerns. Nevertheless, until the beginning of this century donor site morbidity was hardly reported or even mentioned. Only recently have an increasing number of papers addressed this issue. We performed a literature search to review the current knowledge on donor site morbidity after an OAT or an ACI.

METHODS

Literature search

Papers were identified by searching Medline and Pubmed up to March 2010. The search strings "chondrocyte AND donor", "chondrocyte AND morbidity", "osteochondral AND donor", "osteochondral AND morbidity", "cartilage AND donor" and "cartilage AND morbidity" were used in all fields. Papers were included when involving treatment of a (osteo-)chondral lesion by OAT or by ACI in humans, reporting on donor site morbidity, and published in a peer-reviewed journal. Additional relevant papers were identified by manually searching the reference lists of papers identified from electronic searching. Some papers contained duplicate results ; in these cases only the paper with the most detailed information was considered. The available data were extracted and analyzed concerning the type of treatment performed, the type of

outcome reported (anatomical-histological outcome, radiological outcome or clinical outcome), and the way the results were analyzed (quantitatively or qualitatively).

Parameters used to report the outcome

The issue of donor site morbidity can grossly be addressed from three points of view : the anatomical-histological outcome, the radiological outcome and the clinical outcome. The anatomical-histological outcome is reported based on gross inspection at repeat-arthroscopy or histological examination of slides stained in various manners. The radiological outcome is reported using magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT-CT) evaluations. The clinical outcome is reported in both a qualitative and quantitative way. Qualitatively, both subjective parameters at history as pain, limited function, locking and "complaints", and parameters reported at physical examination as crepitus and swelling, are reported. Quantitatively, the knee status and function are reported by means of a (validated) knee score as the Lysholm score, the Bandi score, the Cincinnati score, the International Knee Documentation Committee score (IKDC) or the Hospital for Special Surgery score. Pain was reported also quantitatively by use of a visual analogue scale (VAS).

RESULTS

OAT and morbidity

To our knowledge, Ahmad et al (1) were first to address specifically the intrinsic healing response at a donor site after an OAT procedure. They reported on the gross and histological appearance of the tissue found at a donor site in the intercondylar notch of the knee, one year after the procedure. Grossly, the donor site contained fibrous tissue, extending above the surrounding native cartilage. Histologically, they found dense fibrous tissue with some areas of bone and cartilage-appearing tissue. Subsequent papers confirm the gross repair process of the donor sites after osteochondral transfer with

exuberant fibrous or fibro-cartilaginous tissue (*17, 23,25*).

Valderrabano *et al* (*33*) focussed on the radiological outcome (MRI and SPECT-CT) in 12/21 patients after OAT in the ankle, using the knee as donor joint. Cartilage changes, joint space narrowing and cyst formation at the donor site were found in all patients. Focal radioisotope uptake was found in 7/12 patients. However, no preoperative examinations to compare with seemed to be available.

Concerning the clinical point of view, contrasting results are reported. Three of five papers using qualitative parameters or just mentioning "donor site morbidity" reported an absence of donor site morbidity (*4,6,15*). LaPrade and Botker (*25*) reported on two patients suffering of persistent knee pain, swelling and occasional catching that was resolved by shaving the fibrous hypertrophy at the donor sites or filling them with fresh osteoarticular allografts. Jakob *et al* (*23*) reported a patello-femoral crepitus and moderate to severe functional limitation in 3/7 patients at a minimum follow up (FU) of 24 months. Quantitative parameters were used in nine papers. Miura *et al* (*28*) reported on the fixation of osteochondritis dissecans lesions with osteochondral plugs harvested at the same knee. Although the knee score did not reach an excellent result in some patients at a FU ranging 2.8-5.9 years, no problems arising from the donor sites were observed ; and MRI at three month FU showed a signal intensity of these sites homogeneous with the surrounding cancellous bone. Eight papers reported on donor sites in a knee not being the joint to be treated. Valderrabano *et al* (*33*) reported a significant increase in the mean VAS pain score for the knee. Initially all patients had knee pain post operatively, but in five patients it completely resolved within the first year. Unfortunately, no information on a possible correlation with the radiographic outcome was mentioned. The other papers found a decreased knee score at various FU intervals. Gautier *et al* (*14*) reported a decreased mean IKDC score (range, 95.2-97.5) in 3/11 patients at a FU of 13-38 months. Lee *et al* (*26*) reported a decreased Kujala score of 85 and 90 in 2/17 patients with complaints of mild soreness, mild aching and some crepitus. However, both former reports mention

explicitly that no functional limitations were present. Al-Shaikh e*t al* (*3*) reported 7/19 patients having a decreased Lysholm score ranging 82-97 at a mean FU of 15 months. All these patients experienced pain during severe exertion, one reported giving-way and knee swelling, and none reported locking of the knee. Kircher *et al* (*24*) reported 1/8 patient to be lost to FU due to problems involving the donor site at the knee, requiring two additional operations. At a mean FU of 32.8 month 2/7 patients followed had a Lysholm score of 87 and 91 that normalised to 100 at 9.8 and 9.0 years FU respectively. One patient showed at latest FU a reduced Lysholm score of 95 at 8.8 years FU. Reddy *et al* (*31*) were the first to address the issue of donor site morbidity specifically and reported the highest rate. Nine of eleven patients showed a decreased Lysholm score ranging from 49 to 99 at FU (range, 28-77 month), while having a history of asymptomatic knees before graft harvest. Three patients still had a score higher than 94 (= excellent), two were rated as good (range, 84-94) and four as poor (scored 64 or less). Although subjective complaints were cited for the patients rated good or poor, nothing was reported concerning the other patients. No correlation was found between the number of grafts harvested and donor site morbidity. Paul *et al* (*30*) reported extensively on a cohort of 200 patients. All patients had asymptomatic knees before the procedure. At short-term FU a clear reduction in the Lysholm score was recorded, that did improve continuously at longer FU. However, at a minimum FU of two years still more than half of the patients did not report an excellent result, and at a FU of more than 30 months an increasing number of outliers towards an inferior score was noted. The number of harvested grafts had no influence on the outcome, neither had the size of the donor grafts or the age of the patient, but the body mass index was a negative prognostic factor. The aforementioned absence of an increasing probability for donor site morbidity as more cylinders are harvested is not universally reported by all other papers. Iwasaki *et al* (*20*) reported on the treatment of elbow lesions in 19 patients (apparently including almost all patients previously reported (*21*)), using on average a limited number of

smaller sized cylinders. At a minimum FU of 24 months all donor knees were graded as excellent on the Lysholm score (mean 99.6 ± 5), all except two patients returned to their previous competitive sports level and only one patient experienced continuing anterior knee pain when ascending stairs. All knees evolved into "normal" according to the IKDC. The authors concluded that unfavourable effects at the donor knee were not observed.

ACI and morbidity

No anatomical-histological data are available on the repair process of the donor site after an ACI (i.c. at the knee), although MRI follow-up does not seem to identify a "problem area", and in many cases the biopsy site is not identifiable on MRI on the middle or long term (Marlowitz, Van Breuseghem and Luyten, 2010, personal communication, up to 5 years FU). Other papers describing MRI findings after an ACI procedure do not seem to mention problems with the biopsy sites. However, in most reports it is unclear if an in depth assessment of the biopsy site was performed.

Concerning the clinical point of view, two studies are available, both addressing an ACI at the talar dome. Again, the study that only used qualitative parameters did not find residual knee symptoms at FU *(29)*. However, Whittaker *et al (38)* used the Lysholm score and did report a reduction ranging 5-43 points in 7/10 patients at a FU ranging from 12 to 37 months. Unfortunately they did not report on specific subjective complaints.

DISCUSSION

In this paper we reviewed the possibility of donor site morbidity after an Osteochondral Autologous Transplantation (OAT) or an Autologous Chondrocyte Implantation (ACI) procedure to treat joint surface defects. Only during the last decade have reports on donor site morbidity become available. Most papers have focused on the clinical outcome at the donor site, and an increasing rate of problems is noted when using quantitative instead of qualitative parameters, and when donor site morbidity is the focus of attention. It is obvious that the poten-

tial morbidity of harvesting osteochondral plugs for OAT appears to be different from the harvest of a cartilage biopsy for ACI, as is also noted from this literature review.

Several limitations to this review should be noted. The review suffers from methodological difficulties when comparing the results of the different studies, caused by differences in study design, methods, definitions and outcome parameters used, and in the joints involved. To compare the results as accurately as possible, we preferred to report them listed by type of procedure used and by type of parameter reported and we looked if a trend was present. Nevertheless, the comparison still has to be interpreted with caution as only a limited number of papers is currently available. Therefore, the major weakness of this review is the paucity of data available on the topic.

Intuitively it can be easily understood that it is difficult to assess donor site morbidity in those patients where lesion and donor site are located in the same (knee) joint. If problems in the joint persist during follow-up, it will be difficult to differentiate between residual symptoms from the original lesion and new symptoms due to the donor site. Indeed, only a few papers report on donor site morbidity in knees that served as their own donor site. More studies are available that report on donor site morbidity in knees that were instrumented to obtain grafts needed in the contra-lateral knee or in a joint at another position.

The anatomical-histological outcome of the donor site after AOT seems unfavourable as all studies report the presence of exuberant repair tissue, but unfortunately no clinical outcome to compare with is presented. No hard data on the anatomical-histological outcome of the donor site after ACI are available.

Concerning the clinical outcome, papers using only qualitative parameters did not report on persisting donor site morbidity. However, 6/10 papers using quantitative parameters did report persistent problems, especially when donor site morbidity was the main focus of the study. Clearly, the amount of evidence for donor site morbidity in the knee after an ACI procedure is weak as only two papers are available yet and their results are contrasted.

Conclusions in line with the trend observed after performing an autologous osteochondral graft procedure have to be made with caution since several variables need to be taken into account. First, in case of an OAT procedure, the total surface area of the various cylinders harvested is usually several times greater than the biopsy area for an ACI procedure, increasing the possibility for donor site morbidity in case of the former procedure. Second, in case of an ACI the subchondral plate is left intact when harvesting the biopsy and no healing even by fibrous tissue can be expected, although cartilage sliding and fibrocartilage filling has been seen. Third, as the OAT procedure harvests a cylinder deep into the subchondral bone, it severely violates the osteochondral junction. Restoration *ad integrum* of this junction and a perfect alignment with the neighbouring joint surface appears extremely difficult to achieve, as also seen in animal models (*34*), thereby potentially jeopardizing the load distribution across the joint surface, with possible long-term consequences.

Donor site morbidity will, among other factors, depend on the mechanical loading of the involved part of the joint. Lower contact pressures along the medial trochlea of the patellofemoral joint, compared to the lateral side have been reported (*13*). Therefore, one must bear in mind that the aforementioned reported donor site morbidity can depend on the particular location of the donor sites. Unfortunately, not all studies mentioned the exact location of their donor sites and therefore it is not possible to draw any conclusions on that issue.

Taken together, an increasing awareness of the existence of donor site morbidity seems to be present among clinicians, and an increasing number of cases is being reported. Therefore, the decision to harvest a cartilage biopsy to perform a joint surface defect repair procedure should be taken with caution. This also underscores the need for further research to determine sites as safe as possible for harvest. Additionally, standardization and optimization of the harvest with proper instrumentation appear of paramount importance. Finally, it remains a challenge to develop techniques that eliminate the need for a formal biopsy (*27*). Furthermore, the use of progenitor cells derived from other tissue sources such as synovium and fat pad is attractive as long as autologous material is used (*10,35*). Allogenic cell and tissue sources solve the issue of donor site morbidity altogether, but bring in a totally different set of challenges including safety issues.

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