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We do not have evidence based methods for the treatment of cartilage defects in the knee

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Abstract
Purpose The aim of this study was to perform a systematic review of studies concerning current treatment of chondral defects of the knee.
Methods The relevance for evidence based data and for successful surgical treatment of cartilage defects was evaluated. From 56,098 evaluated studies, 133 studies could be further pursued. These supplied data concerning microfracturing, the osteochondral autograft transplantation system (OATS), the autologous chondrocyte implantation (ACI) and the matrix induced chondrocyte implantation (MACI). The modified Coleman Methodical Score (CMS) and the Level of Evidence (LOE) were applied to evaluate the quality.
Results In these studies, a total of 6,920 patients were reviewed with a median of 32 patients per study and a mean follow-up of 24 months. The mean CMS was 58 of 100 points. No study reached 100 points in the CMS. Three studies reached a level above 90. Ten studies were Level I, five studies reached Level II. Seven studies reached Level III, 111 studies Level IV. MRI scans to verify the clinical data were used by only 72 studies. The means in the modified CMS were for the different procedures as follows: ACI 58 points, MACI 57 points, microfracturing 68 points and OATS 50 points. 24 studies applied the Lysholm Score (LS) for clinical evaluation of cartilage surgery. All operative procedures yielded comparable improvements of the LS (n.s.) meaning that no operative procedure proved superior.
Conclusion As the majority of studies evaluated by this review is insufficient for EBM purposes more coherent studies with LOE of I or II are needed. Co-relating the systems of CMS and LOE and validating the applied scores seems desirable.

Keywords Cartilage defects · Evidence based medicine · Knee injury · Repair

Introduction

Articular chondral defects find an increasing interest of orthopaedic surgeons because these lesions normally do not heal spontaneously and may predispose the joint to the development of secondary osteoarthritis.

This study was conducted to evaluate if any of today's most frequently applied and well documented articular resurfacing methods are evidence based. It is important for the funding health system to have objective criteria about the effectiveness of the respective methods as most decisions on funding are based on reliable data.

A number of different treatment options exist, none of which may be judged as the golden standard. Microfracturing, Osteochondral Autograft Transplantation System (OATS), Autologous Chondrocyte Transplantation (ACT) and Matrix Induced Chondrocyte Implantation (MACI) are the operative procedures for the treatment of articular defects which are very well documented by studies in the literature.There is much controversy to be found as to which treatment would be the most effective.

The multitude of studies treating this topic, the diversity of study designs and the high number of articles published

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are a reason for a comprehensive review with a systematic analysis. Some systematic reviews have been done on related subjects [59, 101].

Evidence Based Medicine (EBM) examines, evaluates and improves the quality of published data. It aims at creating scientifically sound standards for the physician. Important is the level of evidence with Level I and II studies yielding sufficient data from prospective randomised studies.

With articular resurfacing by the treatment of cartilage defects becoming increasingly popular and the public health system demanding evidence based facts especially for the different operative procedures existing in this field, a systematic review evaluating the existing material on the basis of evidence based medicine seems desirable.

Materials and methods

We performed a search strategy that involved clinical trials only. These should evaluate the treatment of cartilage defects in the human knee performing microfracturing, OATS, ACT and MACI, being currently the most commonly applied surgical techniques. A publication period from 2002 to 2007 was selected. The MEDLINE, EMBASE and Evidence Based Medicine Reviews were our databases. To extract the relevant articles, a search machine in the Ovid Linksolver was established. Online accessibility was one inclusion criterium. The other one was a text written in English, French or German. Abstracts in one of these languages were also included where the full paper was only available in a different language not meeting the selection criteria.

A total of 56,098 abstracts was screened by two independent scientists, 179 relevant publications could be selected by both. Of these, 133 studies could be extracted that met the following criteria: evaluating exclusively the operative techniques microfracturing, OATS, ACT and MACI, published between 2002 and 2007, available in the above databases, being online accessible, language in English, French or German, suitability for EBM evaluation.

Only papers evaluating the above operative procedures without any additional procedures werde considered as any additional procedure would influence the Level of Evidence.

Coleman Methodical Score (CMS)

The CMS as introduced first by Coleman et al. [21] was originally applied for grading clinical studies on patellar and Achilles tendinopathy. It was modified by Jakobsen et al. [59] changing the category of the postoperative rehabilitation protocol. The score has two parts and 10 criteria. A maximum score is 100 points, the minimum 0. A score of 100 means that the study excludes almost any bias, coincidence and other influences. Higher scores may support EBM.

Level of evidence (LOE) and lysholm score (LS)

The studies were also assessed by the use of the level-of-evidence-rating applied in the American Volume of The Journal of Bone and Joint Surgery since 2003. The Lysholm Score (LS) applied for cartilage injuries scores stair climbing, instability, squatting, limp, pain, support, locking and swelling. It was applied in 24 studies to compare clinical outcome of the different operative procedures as reflected in the studies.

Statistical methods

SSPS software version for Windows, version 17.0 (SSPS Inc, Chicago, Illinois) was applied to analyze the data. The continuous variables were reflected as medians. They were tested with the Shapiro-Wilkes-Test for their normal distribution. The Pearson correlation was used for normally distributed data. The Kruksal-Wallis-Test was used to test if the outcomes of different kinds of therapy differed significantly.

Results

56,098 articles corresponding to a MEDLINE, EMBASE and Evidence Based Medicine Reviews search conducted for the years 2002–2007 were reviewed.

133 relevant studies could be extracted. These reviewed 6,920 patients with a median of 32 patients per study and a mean follow-up of 24 months. There was an increase of 11% in the number of studies from 2002 to 2007 (Fig. 1). The most frequently described procedures in the single studies were ACI (36%), OATS (30%), MACI (14%) and microfracturing (10%). The combined studies compared ACI and OATS (4%), OATS and microfracturing (3%), MACI and microfracturing (1%), ACI and microfracturing (1%), ACI and MACI (1%) (Fig. 2).

Ten publications reached a LOA of I, five studies reached Level II. Seven studies reached Level III, 111 studies Level IV (Fig. 3).

The CMS as modified by Jakobsen et al. [59] yielded only ten studies with a score of 80 or above (Fig. 4). No study reached a score of 100. Three studies reached a score above 90. The mean CMS of all studies was 58 points. Applied to the operative techniques, microfraturing

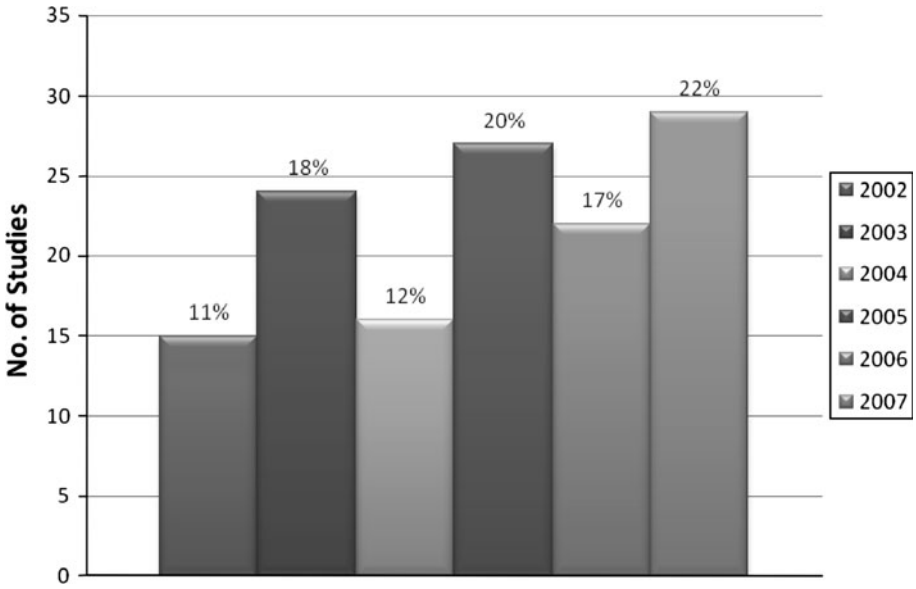

Fig. 1 The number of studies in relation to the years from 2002 to 2007. An increase of 11% was noted

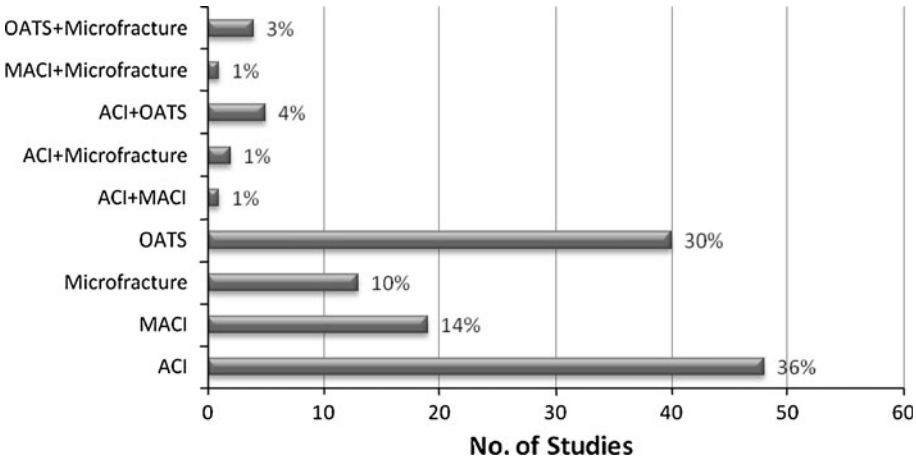

Fig. 2 Number of studies evaluating OATS, MACI, Microfracturing, ACI and a combination of procedures

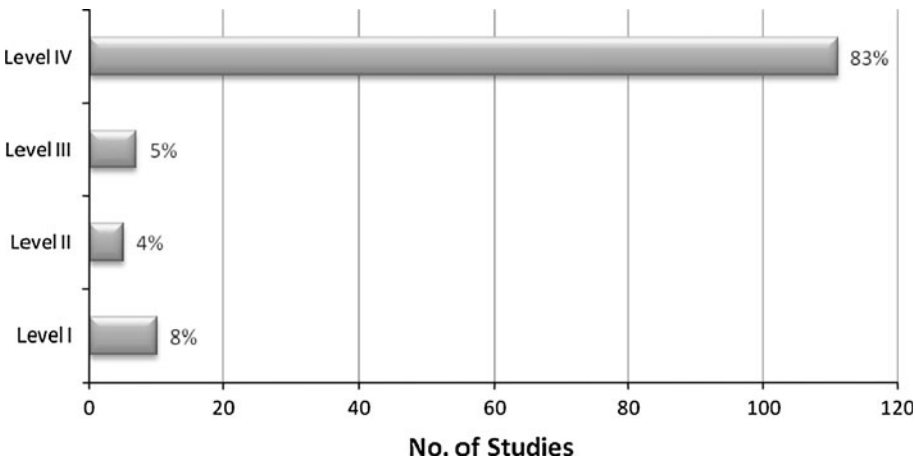

Fig. 3 Number of studies grouped by their level of evidence

reached the highest modified CMS (mean = 68), followed by ACI (mean = 58), MACI (mean = 57) and OATS (mean = 50) (Table 1). To evaluate the operative results, 24 studies applied the Lysholm Score (LS) for cartilage injury. An increase in the LS is related to the success of the procedure. The MACI reached the highest increase with a

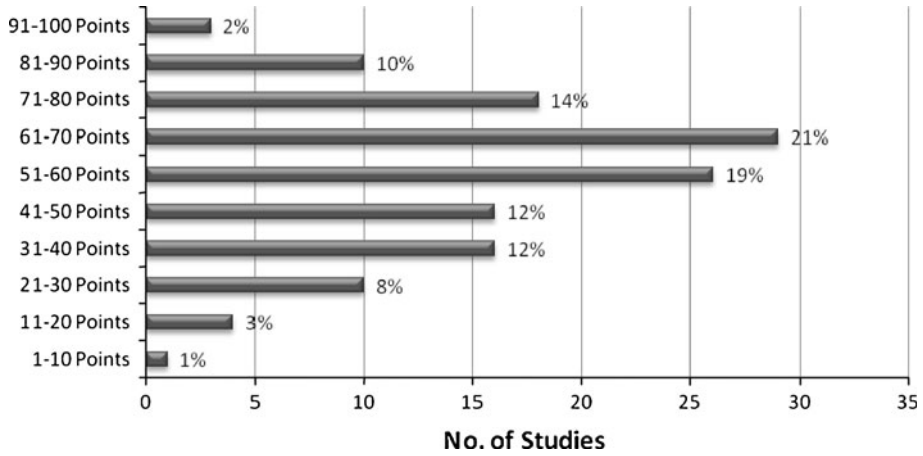

Fig. 4 The modified Coleman methodological score score as reached by number of studies

Table 1 Modified Coleman methodical score applied to the individual operative procedures

Type of therapy	Mean	SD	Median	Minimum	Maximum	*N*
ACI	58	18	60	20	97	56
MACI	57	18	63	20	84	21
Microfracture	68	22	73	14	97	20
OATS	50	19	52	10	85	49

median of 34 points, followed by OATS [32], microfracturing [32] and ACI [31]. There was no significant difference in the outcome of the procedures (n.s.) in the ONEWAY ANOVA).

Relating the studies applying the LS with their CMS yields a low correlation coefficient ($r = 0.129$) with high significance in the matched pair *t*-test ($P < 0.001$). MRI scans to verify the clinical data were applied in only 72 studies.

Discussion

The most important finding in this study was the following: although numerous studies examine results after cartilage surgery, no evidence based results could be clearly defined. The treatment of cartilage lesions is a problem in orthopaedic surgery as the self limiting of these lesions is not possible. Risks for developing a secondary arthritis are considerable, and for this reason the chondral lesions should be addressed. We have found that the general research about chondral lesions has increased by 11% from 2002 to 2007 which is not surprising giving the importance of this matter and its possible effects on lifestyle and activity. In order to help funding organisations such as insurance companies and public health systems to answer the following question: Is it possible to deduct from these studies the optimal treatment for the optimal patient? And is the Level of Evidence sufficient to underline this deduction?

The recommendation of the National Institute for Health and Clinical Excellence in London (NIHCE) from 2005 is based on four prospective randomised studies. Two compared ACI and OATS [11, 55], one compared ACI and microfracturing [67] and one compared different ways of ACI [13].

These studies demonstrated inconsistent and partially contradictory results which lead to discontinuation of funding of ACI by the British National Health System (NHS). This example shows the importance of Level I/II studies influencing public funding of a method.

Concerning the OATS technique, only 1 randomised controlled study by Bentley et al. [11] and the Level IV study by Hangody and Füles [47] were considered by the NIHCE as supportive in 2006. The Level I/II studies by Horas et al. [55] and Dozin et al. [25] were not considered. Studies comparing OATS and microfracturing like the prospective randomized one from Gudas et al. [39] were also not considered. More awareness should be raised to the funding boards about existing studies. This may be the future task of the respective medical boards.

One of the few studies comparing costs of articular resurfacing, Derrett et al. [23] reach the conclusion that average costs for ACI were lower than mosaicplasty. They recommend, however, more prospective studies to confirm this matter.

Generally, the MACI has a particulary poor data base: from 2002 to 2007, only one Level I study was found [8]. A prospective randomised study by Basad et al. [9] improves the data on MACI by comparing MACI to microfracturing.

Again, a difficult interpretation of the results due to different scores applied and partial incompatibility were noted, demonstrating that even Level I studies are difficult to compare and that the thorough review of the existing evidence based literature is important, even more so because these studies are comparatively scarce. The variance of the clinical tests applied is considerable: in the

analyzed 133 studies, 27 different clinical scores were applied impairing comparability.

A common flaw in many studies is the selection bias with drop outs being neglected. The variety of clinical scores applied makes the studies difficult to compare. The Lysholm score for example is applied in only 24 studies. Even in these cases, it is not decided which operative method is preferable. This diversity of applied scores makes it difficult to refer the outcomes to certain operative methods, often impairing the decision making by the funding organisations.

No study reached a CMS of 100, the average CMS was 58. This underlines the fact that most studies do not completely meet the criteria set by Coleman et al. [21] and Jakobsen [59].

Either these criteria are too strict to be applied for EBM in cartilage resurfing procedures or there are indeed too few studies that meet the criteria for EBM. The authors feel that the latter is more likely as the few studies reaching a higher CMS reach high LOEs.

The relationship between CMS and LOE has to the authors knowledge not yet been clearly established. It may be accepted that a CMS of 100 would support the highest LOE, and that a higher CMS would also support a high LOE. Our analysis looks at LOE and CMS as two different entities to evaluate the clinical significance of the screened studies. Not established is also the number of studies necessary to reach a strong EBM classification. For example, it remains uncertain if one study with a CMS of 100 and a LOE of I would suffice to support that the method is evidence based. This may be a serious flaw to the system of EBM. We could show in this study that decisions by health authorities and funding organisations are based on few EBM relevant studies, if at all. It is desirable that more prospective randomised studies are performed with comparable scores. This conclusion is supported by an article by Mithoefer et al. [101], where a similar conclusion regarding microfraturing alone is reached. We found that those studies applying the Lysholm Score for cartilage injuries could not provide a decision on a preferential method. There was also no co-relation between a higher Lysholm Score and the quality of a study, a fact also found by Jakobsen et al. [59]. Our results confirm that choosing and applying a commonly used score does not necessarily lead to a higher standard of EBM.

The studies researched in this review are quite heterogenous. For example, ACI is performed with a multitude of matrices and membranes, varying the original method. The OATS technique also varies quite considerably, in method and in definition. Even microfracturing as first introduced by Steadman is modified in many ways, using various membranes and matrices. It seems impossible to single out every factor that may influence the outcome of the respective research. In order to gain reliable EBM based data the methods of future studies should be coordinated and unified, preferably as suggested by their first author and his group, and performed by multi center research. As this is already standard for pharmaceutical research, the authors see no reason why this may not be applied in cartilage surgery.

Conclusion

There seems to be generally low methodical quality in the studies evaluated in this analysis. This may indicate that some caution is required when interpreting study results after surgical cartilage repair.

Definitive recommendations on which procedure to choose may not be given on the basis of the studies evaluated in this study. More attention should be paid to methodical quality when designing, performing, and reporting clinical studies. It is difficult to recommend a certain operative procedure because the pertaining literature is contradictory, prospective randomised trials are scarce in overall relation to the published literature and the applied scores are mostly unvalidated, too diverse and difficult to compare. This should change as decisions on funding by the public health system and the insurance companies tend to rely on prospective randomised studies.

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For the citation of the National Institute for Health and Clinical Excellence in London refer to www.nice.org.uk/TA089

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