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Review Article

The biology and clinical evidence of microfracture in hip preservation surgery

Chadwick John Green[1,*], Aswin Beck[2], David Wood[2] and Ming H Zheng[2]

[1]Department of Orthopaedic Surgery, Royal Perth Hospital, Perth 6000, Australia and [2]Centre for Orthopaedic Research, School of Surgery, University of Western Australia, Nedlands 6009, Australia
*Correspondence to: C. J. Green, PO Box 4078, Wembley 6914, WA, Australia . E-mail: cjgreen85@gmail.com
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ABSTRACT

The use of microfracture in hip arthroscopy is increasing dramatically. However, recent reports raise concerns not only about the lack of evidence to support the clinical use of microfracture, but also about the potential harm caused by violation of the subchondral bone plate. The biology and pathology of the microfracture technique were described based on observations in translational models and the clinical evidence for hip microfracture was reviewed systematically. The clinical outcomes in patients undergoing microfracture were the same as those not undergoing microfracture. However, the overall clinical evidence quality is poor in hips. This review identified only one study with Level III evidence, while most studies were Level IV. There were no randomized trials available for review. Repair tissue is primarily of fibrocartilaginous nature. Reconstitution of the subchondral bone is often incomplete and associated with poor quality repair tissue and faster degeneration. Subchondral bone cyst formation is associated with microfracture, likely secondary to subchondral bone plate disruption and a combination of pressurized synovial fluid and inflammatory mediators moving from the joint into the bone. There is a lack of clinical efficacy evidence for patients undergoing microfracture. There is evidence of bone cyst formation following microfracture in animal studies, which may accelerate joint degeneration. Bone cyst formation following microfracture has not been studied adequately in humans.

INTRODUCTION

Hip arthroscopy is an area under constant development, with a 6-fold increase in incidence from 2006 to 2010 [1, 2]. The indications for hip arthroscopy are also widening [3], and several publications on the use of microfracture in the hip have recently appeared in the literature. Although popular for the treatment of knee articular cartilage defects as a first line intervention to produce stem cell-based regeneration by bone marrow stimulation, we question the evidence for sustained clinical improvement following microfracture and have concerns about the potential harm caused by violation of the subchondral bone plate, the increased incidence of subchondral bone cyst formation and other pathology and adverse outcomes of autologous chondrocyte implantation following microfracture [4, 5].

Bone marrow stimulation was first presented to the British Orthopaedic Association in 1959 [6]. Pridie described the effects of drilling through the subchondral plate, making equally spaced holes to promote repair [6, 7]. Microfracture [8] and most recently the nanofracture technique [9, 10] are variations of an operation that breaches the subchondral bone plate to allow migration of stem cells and growth factors into a cartilage defect to form a 'super clot' and enhance repair. The reality seems to be coverage with a fibrocartilage scar of predominantly Type I collagen of variable quality in both the knee [11, 12], and hip [13], rather than the more durable Type II collagen of normal hyaline cartilage. Around 78 000 patients undergo microfracture annually in the United States [14, 15]. Microfracture is inexpensive and relatively easily performed arthroscopically, but more recent reports raise the concerns about the evidence to support the clinical technique traditionally in the knee and more recently in the hip [16, 17].

In light of a growing number of arthroscopic hip microfracture procedures for early cartilage loss [1, 2, 18], and the recent claim that this procedure is considered 'safe' and

'efficacious' for use in the hip [19], we have reviewed the biological, translational and clinical literature of this subject. Our objective is to critically appraise the available evidence and subsequently question whether arthroscopic microfracture is a valid treatment for full thickness chondral defects in the hip.

THE BIOLOGY OF MICROFRACTURE

The osteochondral unit of diarthrodial joints consists of hyaline cartilage and the subchondral bone. The articular cartilage consists predominantly of water (65–80%), and to a lesser extent chondrocytes, proteoglycans and collagen [20]. Most of the collagen is type II and highly organized in an arcade model [21], however cartilage is avascular, aneural and alymphatic [22], making intrinsic healing problematic. The articular cartilage is firmly attached to the subchondral bone via a calcified cartilage layer. This subchondral bone can be further subdivided in two distinct entities: the subchondral bone plate composed of cortical bone and the subchondral trabecular bone [23].

The 'superclot' and cartilage repair

Several animal studies have evaluated the temporal healing process following microfracture [24–27]. Penetration of subchondral bone enables marrow contents to enter the joint and synovial fluid to enter the marrow space. Pluripotential mesenchymal stem cells (MSCs) and blood enter the joint and may form a clot in the cartilage defect. Growth factors and MSC are purported to play a pivotal role in the repair process [28–31].

The fraction of mononuclear cells with trilineage potential and thus MSC phenotype obtained from bone marrow is ~0.02% [32, 33]. This low number of MSCs is concerning if we assume that tissue repair is based on engrafting and differentiating of these cells. Shapiro *et al.* [25] showed via ^{3}H-Thymidine labeling that osteochondral repair indeed occurred via differentiation of MSCs in a rabbit study. Besides the engrafting potential of MSCs, paracrine secretions and cell-to-cell contacts may also be involved in the repair process [34].

Although the timeline varies depending on the animal model investigated, the general repair events following fibrinous clot formation in a cartilage defect is similar across mammals. Initially, MSCs and capillary vessels infiltrate the fibrinous network from the periphery and fill the entire defect [25]. Differentiation of MSCs into chondrocytes and extracellular matrix formation are first evident around 10–14 days in rabbits [25, 27], but not until 6 weeks in horses [26]. The location of these initial chondrogenic foci varies from the more superficial layers of the defect [25], to below the top of the fracture hole [27, 35]. Repair tissue reaches the level of normal surrounding cartilage by around 2 weeks in rabbits [25]. The initial extracellular matrix consists of Type I collagen, with type II collagen and aggrecan increasing over time starting in the deep zone, and progressing toward the surface [26]. Over time collagen fibers in the superficial zone change from a perpendicular to a tangential orientation [26, 36]. The end result however is the formation of mixed tissue types consisting of fibrocartilage ($48 \pm 8\%$), fibrous tissue ($28 \pm 8\%$) and hyaline cartilage ($20 \pm 6\%$), which was not different from untreated defects in this horse model [26, 36]. Evaluation of the microfracture technique in rabbit [24, 37, 38], dog [39] and sheep models [40] has similarly reported repair tissue of predominantly fibrocartilaginous nature. Repair tissue is overall poorly integrated with the surrounding normal cartilage [25, 39] and the optimal repair achieved by microfracture appears to be ~8 weeks in rabbits [24, 25]. This is followed by progressive degenerative changes within the repair tissue starting as early as 10 weeks post-operatively [25, 41]. Persistence, but no improvement of tissue quality up to 6.5 months in rabbits, and up to 12 months in horses, has also been reported [26, 38].

There is some evidence that surgical technique could influence the quality of repair tissue. Although the number of MSCs in a cartilage defect is proportional to the total exposed area following penetration of the subchondral bone plate [42], increasing the diameter of drill holes (0.9 mm versus 0.5 mm) had no effect on cartilage repair in a rabbit model [38]. Conversely, drill holes with a diameter close to physiological subchondral trabecular distance (1 mm in a sheep model) resulted in better quality repair tissue compared with larger diameter drill holes (1.8 mm) in a sheep model [43]. This could suggest that subchondral bone integrity rather than the number of MSCs determine the quality of repair tissue.

Deeper drilling (6 mm compared with 2 mm) resulted in better cartilage repair in a rabbit trochlea model and there was no difference between drilling (2 mm) or microfracture (2 mm) [37]. On the contrary, Kok *et al.* [44] reported no effect of hole depth and diameter on repair in an acute osteochondral talus model in goats. Differences in animal species, technique (microfracture versus drilling) and defect location make generalization difficult.

Effect of microfracture technique on subchondral bone

It has been suggested that early stages of bone marrow-derived cartilage repair depend primarily on processes occurring in the subchondral bone [35]. The proposed normal healing of the subchondral bone following microfracture observed via histology is through a combination of intramembranous bone formation and endochondral

ossification, starting in the deeper parts of the defect and progressing toward the base of defect over time, followed by the replacement of woven bone with lamellar bone [25, 35]. The repair response of the subchondral bone is incomplete and extends to a region beyond the original surgical perforation [45]. In comparison to Pridie drilling, microfracture technique reportedly maintains the integrity of the subchondral bone [46]. The word 'integrity' deserves attention here. A 2-cm^2 defect treated with six microfracture holes, diameter 2.5 mm and placed 3–4 mm apart as described in the technique, effectively removes 14.7% of the subchondral bone plate surface. Although mechanical integrity may be largely maintained initially, the structure of the subchondral plate has been altered to allow the communication between the joint fluid and the subchondral bone.

Subchondral bone plate continuity is not restorred following microfracture for as long as 8 weeks to 6.5 months in animal models [25, 36, 38, 39, 41, 45, 47–49]. In addition, the repair processes following microfracture lead to a less dense subchondral bone plate, with a lower bone volume fraction, and thus increased porosity around 6 months in rabbits and sheep [38, 49]. Complete restoration however has also been observed around 18 weeks in a rabbit model [24]. These observations are important as incomplete reconstitution has been associated with more fibrous cartilage repair and increased degeneration of repair tissue [25, 48].

Surgical technique can influence the subchondral bone structure. Microfracturing with an arthroscopic awl has largely replaced drilling procedures as it produces no thermal necrosis of the bone [46]. Although thermal necrosis is indeed avoided, microfracture induced acute fracturing and compaction of bone surrounding the holes 24 h after creation in a rabbit model [50]. This sealed off the holes from the subchondral marrow and caused osteonecrosis [50]. Although it was suggested that the design of the custom-made awl could have contributed to the observation [50], compaction has also been reported using traditional arthroscopic awls [51].

Compared with drilling, microfracture lead to more residual holes and a coarser subchondral bone structure in a rabbit model [45]. Deeper drilling caused bone repair and remodeling over a greater region and restored the bone volume fraction to a greater extent than superficial drilling [45]. Drill holes with a diameter close to physiological subchondral trabecular distance (1 mm in a sheep model) resulted in improved restoration of the subchondral bone plate and subarticular spongiosa [43], an observation which has lead to the current clinical practice of nanofracture [9, 10].

Subchondral bone pathology

Bone tissue overgrowth into the chondral compartment is an important concern in marrow-stimulation procedures [4, 13, 52], and has also been observed in animal models [36, 41, 45, 49, 53–56]. Despite this observation, its recognition as pathology has been largely ignored [36, 53, 55]. For example, the current practice of removing the calcified cartilage prior to microfracture induced more bone formation in the chondral compartment in a horse model [53]. This observation was not further discussed, and the authors recommended removal of the calcified cartilage to achieve better integration of repair tissue with the subchondral bone [53].

Subchondral bone cyst formation

Bone cyst formation following microfracture in animal models is common [45, 47, 49, 53, 56]. Similar to bone overgrowth, this observation has received little attention and its significance has been questioned [47, 53]. The reported prevalence of subchondral bone cyst formation following microfracture in animal studies is as high as 92% [56], and appears to be more prevalent when the subchondral bone structure was specifically evaluated [45, 49, 56], suggesting a general underreporting of this important finding in the literature.

Besides creating a pathway for MSCs to migrate into the defect, penetration of the subchondral bone plate also allows synovial fluid to migrate into the subchondral bone space. Persistent communication between the joint and subchondral bone cysts via microfracture holes has been shown [56], and surgical penetration of the subchondral bone was essential to induce subchondral bone cyst formation in a horse model [57].

Both fluid pressure and flow have been shown to cause bone resorption in rat models of prosthetic loosening [58, 59]. Pressurized fluid can induce bone lysis either due to displacement of trabeculae directly by the fluid [60], or it may decrease perfusion and oxygen supply followed by osteocyte death and osteolysis [61]. Cox *et al.* [62] demonstrated via a computational model that fluid pressure resulted in an irregularly shaped cavity which became rounded and obtained a sclerotic bone rim after removal of the pressurized fluid. Cyst formation due to osteocyte death resulted in round cystic lesions surrounded by sclerosis [62]. Although the contribution of fluid pressure in cyst formation following microfracture technique has not been investigated specifically, in a recent sheep study we observed cyst formation with an irregular outline following microfracture technique [56], see Figs. 1. In the same study, we also observed high numbers of osteoclasts and Howship's lacunae at the periphery of the cystic lesions.

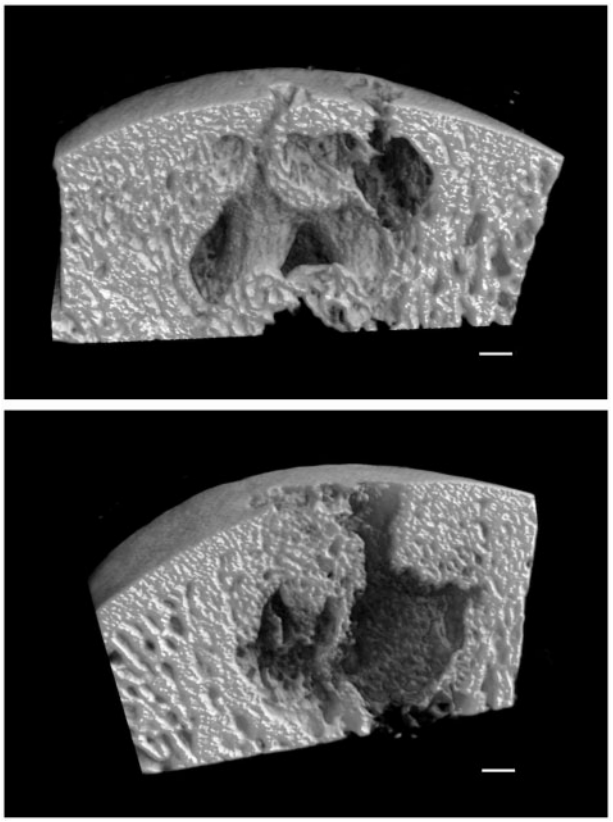

Fig. 1. Micro computed tomography 3D illustrations of subchondral bone cyst formation in the femoral condyle of sheep, 26 weeks following microfracture, with persistent communications with the microfracture hole (scale bar = 1 mm).

Von Rechenberg *et al.* [63] showed an upregulation of IL-1 and IL-6 mRNA in clinical cases of subchondral bone cysts in horses and concluded that both cytokines were associated with pathological bone resorption in cystic lesions. In an osteochondral autograft sheep model, Benazzo *et al.* [64] showed similarly an association between subchondral cyst formation and increased IL-1 and TNF-alfa levels in the synovial fluid. In addition, these cytokines have also been demonstrated within arthroplasty pseudomembranes in aseptic periprosthetic osteolysis [65], and their role in bone resorption has also been established via *in vitro* experiments [66, 67].

In summary of the preclinical evidence, marrow-stimulating techniques result in poorly integrated fibrocartilaginous repair tissue with deterioration occurring over time. Microfracture breaches the subchondral bone plate and leads to incomplete restoration of its structure at best. Smaller diameter drill holes seem to improve cartilage repair, possibly due to decreased disturbance of the subchondral bone structure. Microfracture weakens the trabecular bone structure and frequently leads to subchondral bone pathology including upward migration of the subchondral bone plate and subchondral bone cyst formation.

METHODS FOR CLINICAL REVIEW

To investigate the clinical evidence of microfracture, we identified original studies in humans looking specifically at arthroscopic hip microfracture, or patients that had microfracture as a treatment variable. Review articles were read, but not included in the analysis, as they were not original studies. Single case reports were excluded due to the high potential for bias. *In vitro* studies or studies not including humans were excluded.

On the 20th August 2015, a literature search was carried out using the MEDLINE and EMBASE databases with the following keywords: microfracture, marrow stimulation, hip, acetabulum and acetabular. There were 48 MEDLINE and 121 EMBASE hits, and after reading the abstracts and removing duplicate data we identified 12 original studies [13, 18, 68–77], of which there were 0 RCTs. A search of Cochrane Reviews for the keywords 'hip' and 'microfracture' returned zero results.

Reading through the reference lists of the review articles and the identified original studies manually identified three additional original studies, which involved microfracture for full thickness cartilage defects [78–80].

There were 15 original articles available for review. One cohort study (Level III evidence) [18], two case–control studies (Level IV evidence) and 12 case series (Level IV evidence). Studies with more than 10 microfracture patients [13, 18, 71, 72, 74–77, 79, 80] are presented in Table I and discussed below. Studies with less than 10 patients undergoing microfracture [68–70, 73, 78] are presented in Table II. We decided that these studies were grossly underpowered and have not discussed their results specifically in text.

THE CLINICAL OUTCOMES OF MICROFRACTURE

Microfracture in hips

A prospective cohort study by Domb *et al.* [18] found no significant difference in mean patient reported outcome (PRO) scores, between patients undergoing microfracture and those that did not at 2 years. However, PRO scores for both groups improved significantly from baseline—likely due to the confounding effect of the other procedures undertaken as indicated. The microfracture group had more pain on a 0–10 (10 being the worst) Visual Analogue Scale (3.63 versus 2.82, $P = 0.02$) and less satisfaction with their arthroscopy ($P < 0.05$). Patients undergoing

microfracture had full-thickness chondral defects in the hip (Outerbridge IV), compared with a matched control group without full thickness chondral defects (Outerbridge I–III), which is a potential source of bias for the results. In addition, patients in both groups underwent additional intra-operative procedures as indicated (e.g. acetabuloplasty, femoral neck osteoplasty, labral tear repairs or debridement). Though not the largest of the studies identified, Domb *et al.* had the greatest number of patients undergoing microfracture (baseline $n = 99$, follow-up $n = 79$). All patients underwent post-operative physiotherapy, continuous passive motion therapy, and a period of protected weight bearing (8 weeks for the microfracture group, 2 weeks for the control group).

A case–control study by McDonald *et al.* [74] looked at young male athletes and return to professional sports following hip arthroscopy. Return to sport was not significantly improved by microfracture at 36 months compared with no microfracture (77 versus 84%, respectively, $P > 0.05$) [74]. There were 39 patients in the microfracture group and 81 unmatched controls. There were many indications for the initial hip arthroscopy (e.g. labral tears, cartilage defects, loose bodies, femoroacetabular impingement, ligamentum teres or capsule pathology) and subsequently many confounding intra-operative procedures offered for both case and control groups; in addition to microfracture for Outerbridge IV defects in the case group.

A later case-control study by McDonald *et al.* [75], again in young male athletes, aimed to assess the level of function returning players achieved post-hip arthroscopy. The control group comprised other professional athletes from the league that were matched with cases based on pre-operative sports statistics (games played, wins, losses, performance statistics, etc). The controls did not undergo hip arthroscopy. Though the reported results were positive, with 82% of patients undergoing hip arthroscopy with microfracture returning to professional sports at the same level as matched controls [75], there was a significant loss to follow up of 47%. In addition, confounding intra-operative procedures were undertaken as part of the hip arthroscopy (femoral neck osteoplasty, acetabuloplasty, chondroplasty, labral tear repair, reconstruction or debridement, as indicated).

The largest two case series studies were by Byrd and Jones [79] and Haviv *et al.* [71]. Byrd and Jones [79] looked at 220 consecutive patients undergoing hip arthroscopy for cam impingement. Pre- versus post-operative modified Harris Hip Scores (mHHS) were recorded with a mean follow up of 16 months. All patients improved from baseline with a mean increase in the mHHS of +20, however there was no difference in improvement for patients undergoing microfracture ($n = 58$) and those who did not [79]. Similarly, Haviv *et al.* [71] looked at 381 consecutive patients undergoing hip arthroscopy for cam impingement. There was a 54% loss to follow up at 22 months for all patients, and only 29 patients available for review who had microfracture. The patients remaining in the study at 22 months all showed significant improvement from baseline on functional scores (mHHS and Non-Arthritic Hip Score—NAHS). Those having microfracture had better a mean NAHS at 22 months than those not having microfracture ($P < 0.05$), though were not significantly improved on the mHHS at 22 months [71]. Confounding intra-operative procedures were undertaken in both studies as indicated (femoral neck osteoplasty, correction of pincer impingement, chondroplasty, labral tear debridement or radio-frequency ablation) [71, 79].

No significant differences in post-operative functional scores between patients undergoing microfracture and those not undergoing microfracture were reported in the other Table I case series studies, due largely to their methodology and lack of a comparative group [13, 72, 77, 80]. Like Haviv *et al.*, they were also confounded by other intra-operative procedures, or different rehabilitation regimes, and had potential reporting bias from high losses to follow up.

In a second look arthroscopic study of 20 microfracture patients by Karthikeyan *et al.* [13] 19 out of 20 patients (95%) had a mean defect fill of 96% (89–100%). Two patients were biopsied, and their histology showed repair with predominantly fibrocartilage [13]. There was no statistical improvement in the NAHS for these 20 patients, from pre-original arthroscopy to 17 months post-original arthroscopy to post-second-look arthroscopy at 21 months (+55, +54, +73, respectively, $P > 0.05$).

Finally, a comparative case series by Fontana and de Girolamo [76], followed one series of cases undergoing microfracture and another series of cases undergoing autologous matrix-induced chondrogenesis (AMIC), for Outerbridge Grade III-IV chondral defects. Each series had statistical improvement in pre- versus post-operative mHHS scores, and the AMIC series was statistically better on mHHS at 5 years compared with the microfracture series (~82 versus ~72, $P = 0.001$) [76]. The lack of a control group and that patients were not randomly selected for each of the series limits the methodology and validity of the results seen. There were also confounding intra-operative procedures for both groups (femoral neck osteoplasty, acetabuloplasty, or labral tear repair, as indicated) and selection bias as the microfracture series included more men (71 versus 51%, $P = 0.017$) and had a higher incidence of cam lesions ($P = 0.034$).

Table I. Summary of original articles with greater than 10 patients undergoing microfracture for full thickness cartilage defects in the hip

Study (level of evidence)[a]	*Design (comparison group)*	*Patient numbers (hip numbers)*		*Mean age in years (%male) Athletes Only*	*Follow Up (mo)*	*Mean MFx Defect Size (mm^2)*	*Post op Limits*	*Outcome*[b]	*Comments*
		Baseline	*Follow-up*						
Domb *et al.* [18] (III)	Matched-Cohort (yes)	MFx 99 Control N/A	MFx 79 Control 158	44, in each group (59%) No	24	189 ± 98	Hip brace, variable protected weight bearing depending on group, physio-therapy & CPM	Mean PRO MFx versus Control (2 year) not significantly different Visual Analog Scale for Pain (0–10, 10 is most severe pain) - MFx (2 year) = 3.63 - Control (2 year) = 2.82 ($P = 0.02$) Patient Satisfaction - MFx (2 year) = 7.2 - Control (2 year) = 8.0 (P 0.05)	MFx patients had Outerbridge IV, and had 8 weeks of protected weight bearing Non-MFx patients had Outerbridge III or less, and had 2 weeks of protected weight bearing
McDonald *et al.* [74] (IV)	Case–control (yes)	MFx 39 (39) Control 81 (94)	MFx 39 (39) Control 81 (94)	29 (100%) Yes	36	162	MFx patients = physiotherapy, flat-foot 20-lb weight bearing and CPM for 8 weeks, and an Anti-rotation bolster 2 weeks	No significant difference in return to play post op: - MFx = 77% - Control = 84% ($P > 0.05$)	The control group is not matched to the case group. Non-MFx patients had only 2 weeks of protected weight bearing. MFx patients had Outerbridge IV grades, Non-MFx patients were Outerbridge I–III
McDonald *et al.* [75] (IV)	Case–control (yes)	MFx = 32	MFx = 17	31 (100%) Yes	24	119	As per above	- 82% of participants returned to professional sport - 18% (3 participants) did not return to professional sport. All had acetabular MFx, rim trimming, femoral neck osteoplasty and labral repair	MFx patients had Outerbridge IV grades. Players were excluded if they had previous ipsilateral hip surgery, or were retiring from professional sport. 'Matched-controls' did not undergo surgery

(continued)

Table I. Continued

Study (level of evidence)[a]	*Design (comparison group)*	*Patient numbers (hip numbers)*		*Mean age in years (%male) Athletes Only*	*Follow Up (mo)*	*Mean MFx Defect Size (mm^2)*	*Post op Limits*	*Outcome*[b]	*Comments*
		Baseline	*Follow-up*						
Byrd and Jones [79] (IV)	Case Series (no)	220 (227)	200 (207) MFx = 58	33 (69%) No	16	NR	WBAT with crutches, physio-therapy, impact loading avoided for 3 months. MFx Patients PWB 2 months	Mean mHHS improvement (range) - MFx: +20 (−17, +58) - Non-MFx: +20 (−17, +60) No difference in outcomes for MFx versus non-MFx	All patients with cam, or cam-pincer impingement included. 20 Patients with pincer-only impingement excluded. Microfractured patients had Outerbridge IV grades 1 patient converted to total hip arthroplasty, 8 months post arthroscopy.
Haviv *et al.* [71] (IV)	Case Series (no)	381 MFx = NR	166 (170) MFx = 29	37 (80%) No	22	<300	Weight bearing as tolerated, physio-therapy, Jog/Run 6weeks if non-MFx versus 14 weeks if MFx	Mean mHHS pre versus post-op - MFx: +73 -> 88 (P = 0.04) - Non-MFx: +70 -> 83 (P = 0.004) Mean NAHS pre versus post-op - MFx: +70 -> 90 (P < 0.001) - Non-MFx: +68 -> 81 (P = 0.003)	Patients with advanced arthritis (i.e. Tönnis grade 3) on preop radiography were excluded. Significant improvement in all groups compared with baseline. MFx significantly better that non-MFx on NAHS only at 22 months (P < 0.05)
Karthikeyan *et al.* [13] (IV)	Case Series (no)	Nb. 285 patients in original dataset	20 MFx patients had repeat arthro-scopy	37 (80%) No	17 ± 11	154	Immediate CPM 24–48 h, physio-therapy, Foot-flat non-weight bearing 6 weeks, full weight bearing by 8 weeks	At second look: - 19/20 pts (95%) had a mean defect fill of 96% ±7% - 2 athletes biopsied repair scar chiefly fibrocartilage - 4 patients had labrocapsular adhesions - 7 patients had catching sensation from cartilage	All patients had full thickness acetabular chondral defect in superior or antero-superior acetabular zones & a labral tear Indication for repeat scope was either persistent or reoccurring

(continued)

Table I. Continued

Study (level of evidence)[a]	Design (comparison group)	Patient numbers (hip numbers)		Mean age in years (%male) Athletes Only	Follow Up (mo)	Mean MFx Defect Size (mm^2)	Post op Limits	Outcome[b]	Comments
		Baseline	Follow-up						
								overgrowth at MFx site, requiring fibrochondroplasty NAHS pre versus post-MFx (17 months) versus post second-look (21 months) = +55 -> 54 -> 73 ($P > 0.05$)	symptoms of FAI. Possible selection bias. The authors acknowledge that the same surgeon did the MFx & also the assessment of defect fill on second look arthroscopy
Stafford *et al.* [72] (IV)	Case Series (no)	54	43 MFx = 43	24 (58%) No	28	NR	Physiotherapy, toe-touch weight bearing for 4 weeks with crutches post op.	Mean mHHS (pain) pre versus 28 months post-op (all patients) = 21.8 versus 35.8 ($P < 0.001$) Mean mHHS (function) pre versus 28 months post-op (all patients) = 40 versus 43.6 ($P < 0.001$) No significant difference in mHHS for 1 versus 3 years post op. ($P = 0.44$)	? MFx or fibrin as cause for significant improvement in pain and function scores. Areas of subchondral bone treated with MFx + Fibrin were still enclosed by 20% loss to followup
Philippon *et al.* [80] (IV)	Case Series (no)	122 MFx = 47	90 MFx = 25	41 (45%) No	27.6	NR	Physiotherapy, partial weight bearing and CPM for 6–8 weeks. Anti-rotation bolster for 10 days post op.	No difference in mean mHHS for MFx vs non-MFx patients (81 versus 86, $P = 0.2$). Mean mHHS improved from baseline for all patients ($P < 0.001$) 10 patients had undergone a THA at a mean of 16 months post arthroscopy – these patients were significantly older (58 versus 39 years), and had lower mean pre-op mHHS (47 versus 60, $P < 0.001$)	47% loss to follow up amongst microfracture patients. Only Charnley A, (see Charnley *et al.*, 1972) patients included in this study – i.e. patients where a single hip joint is the only cause of mobility debility. Subsequent selection bias. Patients undergoing MFx of both the acetabulum and femoral

(continued)

Table I. Continued

Study (level of evidence)[a]	Design (comparison group)	Patient numbers (hip numbers)		Mean age in years (%male) Athletes Only	Follow Up (mo)	Mean MFx Defect Size (mm^2)	Post op Limits	Outcome[b]	Comments
		Baseline	Follow-up						
									head were more likely to progress to THA and those who did not ($P < 0.001$)
Horisberger *et al.* [77] (IV)	Case Series (yes)	20 (drawn from a larger pool of 150 patients having arthroscopy for FAI)	19 (1 patient died from 'unrelated' causes) MFx = 15	47.3 (80%) No	36	NR	Physiotherapy 6–8 weeks. Non-MFx: full weight bearing. MFx: PWB 4–6 weeks	10/19 patients had undergone a THA at a mean of 1.4 years post index arthroscopy For nine patients without THA, mean NAHS pre-op versus 36 months 47.2 -> 78.3 ($P = 0.004$) (No significant difference between MFx and non-MFx groups)	The 20 selected patients had Outerbridge II or more Authors acknowledged confounding from associated surgery as likely cause for improvement from baseline for all patients
Fontana and de Girolamo [76] (IV)	Comparative Case Series (yes)	MFx = 77 AMIC = 70	3 years MFx = 70 AMIC = 70 5 years MFx=42 AMIC = 55	MFx 39 (71%) No AMIC 39 (51%) No	60	MFx 370 AMIC 350	Physiotherapy, CPM day 1, RoM exercises, non-weight bearing 4 weeks, partial weight bearing 7 weeks	mHHS pre-op. MFx = 47.1 AMIC = 44.7 ($P = 0.01$) mHHS 1 year MFx = ~82 AMIC = ~82 ($P > 0.05$) mHHS 5yr MFx = ~72 AMIC = ~82 ($P < 0.001$) All patients at 5 years improved compared with baseline ($P < 0.001$)	Included patients had: Outerbridge Grade III & IV chondral lesions, and less than Tönnis Grade II degenerative changes. Patients not randomized to groups. More males in MFx group ($P = 0.017$) Substantial loss to follow up at 5 years, more so in MFx group. 6 patients (7.8%) in MFx group required THA at a mean of 3.2 years post-op.

aBased on the Oxford Centre for Evidence-based Medicine - Levels of Evidence (see http://www.cebm.net/ocebm-levels-of-evidence/).

bAll papers included associated surgery; most papers had multiple associated surgeries in addition to microfracture. Associated surgeries as part of 'hip arthroscopy' included any of: femoral neck osteoplasty, acetabuloplasty, chondroplasty, labral tear repair or debridement, ligamentum teres debridement, capsule plication or release, fibrin glue use and/or loose body removal, as indicated

NR = not recorded; MFx = microfracture; PWB = partial weight bearing; CPM = continuous passive motion; PRO (Patient Reported Outcome Score) is the average of the following scores: Modified Harris Hip Score, Non-Arthritic Hip Score, Hip Outcome Score Activities of Daily Living Subscale, Hip Outcome Score Sport Specific Subscale [18]. mHHS = Modified Harris Hip; NAHS = Non-arthritic hip Score; THA = Total hip arthroplasty; AMIC = Autologous matrix-induced chondrogenesis; FAI = femoroacetabular impingement.

Table II.Summary of original articles with 10 or less patients undergoing microfracture for full thickness cartilage defects in the hip

Study (level of evidence)[a]	*Design (comparison group)*	*Patient numbers (hip numbers)*		*Mean age in years (% male) Athletes Only*	*Follow up (months)*	*Mean MFx defect size (mm^2)*	*Post-op. limits*	*Outcome*[b]	*Comments*
		Baseline	*Follow-up*						
Amenabar and O'Donnell [78] (IV)	Case Series (no)	36 (44)	16 (NR) MFx N = 8	22 (100%) Yes	49	NR	Full weight bearing as tolerated	mHHS pre vs post-op = +84 -> 98 ($P < 0.05$) NAHS pre- versus post-op = +86 -> 97 ($P < 0.05$)	Outcomes post microfracture not measured specifically
Singh *et al.* [70] (IV)	Case Series (no)	24 (27) MFx = 6	24 (27) MFx = 6	22 (100%) Yes	22	<300	NR Avoidance of impact loading for 6 weeks	Mean mHHS pre- versus 2 years post-op (all patients) = 86 versus 97 - *P* values not reported Mean NAHS pre- versus 2 year post-op (all patients) = 81 versus 99 - *P* values not reported All players satisfied with surgery. 23 out of 24 returned to professional AFL football	Participants were all Professional AFL football players, all with sub-acute groin pain, not-responding to conservative treatment. 1 player who did not return had most severe lesion found on arthroscopy – rim lesion with 40% cartilage loss, an unstable os acetabula, and cam impingement. Patient underwent femoroplasy, chondroplasty, excision of unstable os acetabula and labral tear, and MFx Microfractured patients had Outerbridge IV grades

(continued)

Table II. Continued

Study (level of evidence)[a]	Design (comparison group)	Patient numbers (hip numbers)		Mean age in years (% male) Athletes Only	Follow up (months)	Mean MFx defect size (mm^2)	Post-op. limits	Outcome[b]	Comments
		Baseline	Follow-up						
Boykin *et al.* [73] (IV)	Case Series (no)	21(23) MFx N = 9	17 (NR) MFx N = 8	28 (100%) Yes	41	NR	Hip brace, variable protected weight bearing and CPM depending on if MFx occurred, Physiotherapy, hydro-therapy	mHHS mean change (95%CI, *P* value) = +16.4 (2–30, $P < 0.05$) HOSs mean change (95%CI, *P* value) = +20.8 (6–35, $P = 0.01$) No difference in improvement for those undergoing MFx versus those not undergoing MFx	MFx patients had Outerbridge IV, and had 8 weeks of protected weight bearing Non-MFx patients had Outerbridge III or less, and had 3 weeks PWB 2 patients (10%) progressed to THA
Byrd and Jones [68] (IV)	Case Series (no)	9	9 MFx = 3	51 (56%) No	24	NR	Weight bearing as tolerated. MFx Patients protected-weight bearing 10 weeks	Mean mHHS pre versus post-op MFX +52.3 -> 88.6 Non-MFx +47 -> 48.8 3 MFx patients returned to high levels of function (martial arts, horse riding, fitness activities) as per the authors	Not adequately powered to detect a difference
Philippon *et al.* [69] (IV)	Case Series (no)	–	9	37 (56%) No	20	163	Physiotherapy, toe-touch weight bearing and CPM for 8 weeks (based on Steadman *et al.*, 2002)	At second look arthroscopy: - Average defect fill was 91% - 1 patient had only 25% fill, however also had diffuse Grade IV chondral defects, and had femoral head resurfacing at the time of the second look arthroscopy. - 3 patients had capsulolabral adhesions	9 patients drawn from a larger case series. Possible subsequent selection bias

aBased on the Oxford Centre for Evidence-based Medicine - Levels of Evidence (see http://www.cebm.net/ocebm-levels-of-evidence/).

bAll papers included associated surgery; most papers had multiple associated surgeries in addition to microfracture. Associated surgeries as part of 'hip arthroscopy' included any of: femoral neck osteoplasty, acetabuloplasty, chondroplasty, labral tear repair or debridement, ligamentum teres debridement, capsule plication or release, fibrin glue use, and/or loose body removal, as indicated.

NR = not recorded; MFx = microfracture; PWB = partial weight bearing; CPM = continuous passive motion; mHHS = Modified Harris Hip; NAHS = Non-arthritic hip Score; HOSs = Hip outcome score – sport specific subscale; THA = Total hip arthroplasty.

Microfracture in knees

Despite the popularity, there is increasing evidence that also questions the value of microfracture in knees. Recent reviews by Goyal *et al.*, and Bert, report that the long-term clinical results of microfracture are no better than those for patients who do not have microfracture [16], and that microfracture is not without risks [17].

Goyal *et al.* [16] reviewed all Level I and Level II studies on PubMed and concluded that in the short-term, for young patients with small lesion sizes and low post-operative demands, microfracture was associated with good clinical outcomes. However '*beyond 5 years post-operatively, treatment failure after microfracture could be expected regardless of lesion size*' [16]. The only Level I study directly comparing microfracture with debridement of unstable edges in this review, concluded no improvement at 10 years for patients undergoing microfracture compared with those having debridement [81].

Bert [17] highlighted the risks associated with microfracture; that disruption of the subchondral plate predisposes the bone to the development of subchondral cysts and fragile or brittle bone [17, 82, 83], subsequently accelerating osteoarthritis.

THE REFLECTION OF BIOLOGICAL PROCESSES ON CLINICAL OUTCOME

Most of our basic science understanding of post-microfracture repair physiology comes from animal models [24–27, 36, 50, 51]. Although similar findings are reported in humans who undergo second look arthroscopy with repair tissue biopsy and histopathology [11, 13], the timing of repair stages is likely to be different as it is for different animals. The animal models suggest that microfractured chondral defects are filled with a fibrocartilage scar of predominantly Type I collagen [36], consisting of limited and poorly organized chondrocytes [25], which poorly integrate with surrounding cartilage [25], and start to degenerate at a variable time period of less than 1 year, depending on the animal model used [25, 38]. Progressive degeneration is then noted over time [25].

Once fractured the subchondral bone plate will attempt auto-repair or reconstitution through endochondral and intramembranous bone formation, however this frequently fails [25, 36, 38, 39, 41, 45, 47–49]. Articular repair tissue located on a compromised, unsupportive base is then prone to failure. This presents with increased fibrocartilage repair tissue [48], and increased degeneration of this repair tissue [25].

In addition, damage to the subchondral plate during microfracture, or any other marrow stimulating technique, exposes the subchondral bone to the joint space and if reconstitution of the subchondral bone fails, can lead to fragility and development of subchondral bone cysts [17, 82, 83]. This bone fragility is proposed to accelerate degenerative changes affecting the joint [17]. Infiltration of cytokines and metalloproteinases through the microfracture holes into the bone deep to the subchondral plate [63, 64], and increased fluid pressure causing osteolysis may be implicated in subchondral bone cyst formation [58–61]. 'Collateral damage' to the subchondral plate from the impact of the microfracture awl may also cause localized osteonecrosis [50, 51].

Finally, elevation of the subchondral plate during repair [36], bone tissue overgrowth into the chondral compartment or joint [4, 13, 36, 45, 49, 52–56] and osteophyte formation [55], are all reported but understudied complications of microfracture and damage to the subchondral plate.

The translation of preclinical findings to the clinical situation remains difficult. However, a recent analysis of five failures following marrow stimulation techniques in early osteoarthritic knees has shown fibrocartilaginous repair tissue and incomplete restoration of the subchondral bone [84]. Interestingly, three out of these five cases had a nearly normal macroscopic appearance based on the International Cartilage Repair Society Visual Assessment, underlining the importance of evaluation of the entire osteochondral unit.

THE CURRENT ISSUES WITH THE CLINICAL EVIDENCE ON MICROFRACTURE IN HIPS

Most studies had small [13, 18, 72, 74, 75, 77] or very small [68–70, 73, 78] sample sizes, with the majority of the data underpowered to detect smaller effect sizes. The largest studies were from Haviv *et al.* [71] (381 patients enrolled, 29 had microfracture), Byrd and Jones [79] (220 patients enrolled, 58 had microfracture), Fontana and de Girolamo [76] (144 patients enrolled, 77 had microfracture) and Philippon *et al.* [80] (122 patients enrolled, 47 had microfracture). In general, these larger studies had high losses to follow up [71, 76, 80], or disparity in loss to follow up, with microfractured patients having twice the loss the follow-up of non-microfractured patients [76, 80]. This increased loss to follow up introduces a reporting bias that may be in favor of patients having microfracture, especially for the studies with disparity in loss to follow up.

Numerous studies gathered data from predominantly young, male and athletic patients, with small cartilage defect sizes, introducing a selection bias and a difficulty in generalizing or extrapolating findings to general patient population who present with cartilage defects. Of the 15 original studies included in this review, the authors

observed mean ages of <50 years for 13 studies [13, 18, 69, 70–76, 78–80], less than 30 years for five studies [70, 72–74, 78], predominantly male participants (>75%) in seven studies [13, 70, 71, 73–75, 78], exclusive inclusion of athletes in five studies [70, 73–75, 78] and mean defect size to undergo microfracture of <200 mm^2 in five studies [13, 18, 69, 74, 75]. The mean cartilage defect size was not recorded for six studies [68, 72, 73, 78–80], which may mask the level of bias introduced.

No long-term data were available for our review of microfracture in the hip, most studies had a short follow up of 2 years or less [13, 18, 68, 69–71, 75, 79]. Only one study achieved medium-term follow up of 5 years [76]. The lack of long-term data is problematic. Microfracture in knees shows improvement in patient function in the short-term, but not long-term efficacy [16]. Basic science suggests a worsening of outcomes long-term as subchondral bone degeneration is accelerated by microfracture through the subchondral plate [17, 82, 83]. We hypothesize that long-term data may show a worsening of outcomes for patients undergoing microfracture, compared with controls not undergoing microfracture. If this is true, the technique is unethical and should be abandoned.

The highest level of clinical evidence identified, for the use of microfracture in hip arthroscopy, was Level III, and this was only achieved by one study [18]. All other studies were of Level IV evidence. Microfracture generally did not improve functional outcomes any more so than what was observed in comparison groups not undergoing microfracture [18, 71, 74, 77, 79, 80]. Patient function improved from baseline in all studies, regardless of whether microfracture occurred or not. This is likely due to confounding factors, such as the other intra-operative procedures undertaken (e.g. femoral neck osteoplasty, acetabuloplasty, chondroplasty, labral tear repair or debridement, ligamentum teres debridement, capsule plication or release, and/or loose body removal, as indicated) as part of the umbrella-treatment term of 'hip arthroscopy'. Confounding intra-operative treatments and variable rehabilitation programs were found in all of the studies reviewed.

There were numerous limitations across the studies, and the effect of bias and confounding on the results of the clinical data should not be underestimated. Only three studies had a control group [18, 74, 75], the rest were case series without a control [13, 68, 69, 70–73, 78–80].

CONCLUSION

Given the developing evidence for subchondral cyst formation and acceleration of degenerative changes following microfracture in animal models, we recommend that surgeons avoid any procedure that involves disruption of the subchondral plate until long-term safety data are available in humans. It is important to appreciate how well patients, who do not have microfracture, do following hip arthroscopy with the other associated surgeries undertaken. It seems the addition of microfracture, although technically easy, is not justified based on the available data. To test the effect of microfracture as a treatment for full thickness cartilage defects in the hip, an adequately powered, long-term, randomized controlled trial (specifically comparing microfracture with a control group of patients not undergoing microfracture) is required. Such a design would also have to adjust for confounding surgeries and rehabilitation programs.

CONFLICT OF INTEREST STATEMENT

None declared.

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