Autogenous Osteochondral Morselised Grafts for Full Thickness Osteochondral Defects in the Knee Joints of Pigs

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ABSTRACT

The aim of this study is to firstly ascertain the survival of autogenously grafted morselised cartilage for full thickness osteochondral defects in knee joints of pigs. Secondly, it is to determine the quality of the grafted cartilage that survives and to score to it based on a recognised and tested system of indices and thirdly, to recognise, if any, the potential for reconstitution of the osteochondral junction. Two groups of five pigs were followed up for six and 12 weeks. Similar osteochondral defects were created in the medial condyles of both knees with the right medial femoral condyle defect filled with graft and the left used as control and filled with gel foam. At the end of the study period, an independent pathologist assessed the defects macroscopically and microscopically with an accepted and comparable histological scoring system. Macroscopically, there was better filling of the defect and restoration of bony contour in the grafted group compared to the control. Microscopically, at six weeks, filling of the defect, nature of predominant tissue, matrix staining and nature of cells all showed significantly better histological score than the control using the Mann-Whitney U test at the level of significance of $p<0.05$. At 12 weeks, in addition to the above, the reconstitution of osteochondral junction also showed a significantly better score. Comparing the test groups at six and 12 weeks, the reconstitution of the osteochondral junction was significantly better at 12 weeks. In conclusion, the autogenous osteochondral morselised graft persisted as mature hyaline cartilage with good histological score at six weeks with significantly better reconstitution of osteochondral junction occurring at 12 weeks. The use of morselised graft allows for the inclusion of bone graft which possibly allows for larger amounts of donor tissue and thus the possibility of treating larger defects. In the human model the donor site would be the non-weight bearing surfaces of the knee such as the intercondylar notch as described by Walgenbach A and Stone KR at the 1997 Annual Meeting of the American Academy of Orthopaedic Surgeons in San Francisco.

Keywords: Autogenous osteochondral grafts, Morselised grafts, Osteochondral defects, Hyaline cartilage, Articular cartilage

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INTRODUCTION

Articular cartilage (hyaline cartilage) consists primarily of a large extracellular matrix (90%) with a sparse population of highly specialised chondrocytes (10%) distributed throughout the tissue[1]. The primary components of extracellular (ECM) are proteoglycans, collagens and water with other proteins in smaller amounts. These combine to provide the tissue with its unique and complex structure and mechanical properties. Articular cartilage is also avascular, aneuric and alymphatic[1,2].

Injury to articular cartilage, partial or full thickness, is a common injury following trauma due to road traffic accidents, sport injuries and fall from heights. Repair of the cartilage refers to the replacement of damaged or lost cells and matrix with new cells and matrix[3]. Unfortunately the repaired tissue often restores neither the original structure nor function of the articular cartilage[4-7]. Factors that limit the response of cartilage to injury include firstly, lack of a blood supply and therefore a poor inflammatory response. Secondly, the lack of undifferentiated cells also contributes to the poor repair potential of articular cartilage. Lastly, the highly specialised nature of chondrocytes also limits its potential for regeneration and repair[7-11].

Significant advancements have been made in the field of artificial prosthetic joint replacement in osteoarthritic joints, but the treatment of articular cartilage defects in younger patients (under 50 years of age) remains problematic because of limited lifespan of the prosthesis. Up to recently, methods available for the repair of osteochondral defects were subchondral abrasion, drilling and microfractures which at best produced the bio-mechanically inferior

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fibrocartilage[12,13].Therefore despite the incomplete understanding of articular cartilage repair, there is extensive efforts in what is now termed biological resurfacing. This involves the healing of the articular cartilage defect in the most biological way in terms of the structure and function of the articular cartilage so as to prevent the onset of degenerative changes and the need for prosthesis in younger patients[6].

The methods used so far for biological resurfacing include perichondrium transfers[14], periosteal transfers[15,16], ostechondral autografts[17,18] and the most recent development of autologous chondrocyte transplant[19,20]. This study concentrates on osteochondral grafts of which morselised autogenous ostechondral graft is a subgroup and the focal subject of this study. The other subgroups of osteochondral grafts are mosaicplasty[21,22], allografts[18] and mesenchymal cell-based repair of articular cartilage as described by Wakitani et al[23].

Walgenbach A and Stone KR (1997) had described a surgical technique and preliminary results in 20 cases of morselised cartilage and bone grafts to traumatic and arthritic defects in the knee joints (in their clinical practice), presented at the 1997 Annual Meeting of the American Academy of Orthopaedic Surgeons in San Francisco, as yet unpublished[24].

This study is based on the technique pioneered by Walgenbach A and Stone KR presented at the 1997 Annual Meeting of the American Academy of Orthopaedic Surgeons in San Francisco which consists of creating full thickness osteocartilagenous defect in the knee joints of pigs and subsequently filling it up with autogenous morselised cartilage and bone graft.

The aims of the study are threefold and are as follows:

1. To ascertain the survival of the grafted cartilage.
2. To determine the quality of the grafted cartilage that survives and to score to it based on a recognised and tested system of indices.
3. To recognise if any the potential for reconstitution of the osteochondral junction.

METHODS

This experiment consisted of 10 adult pigs weighing about 30-35kg. The pigs were selected as the experimental model because the thickness of the cartilage is comparable with that of human articular cartilage and they can easily tolerate operative trauma. They were grouped into two, the first group consisting of five pigs which were followed up for six weeks and the second group of five pigs which were followed up for 12 weeks. Both knees were operated at the same sitting and right medial femoral condyles (RMFC) were used as experimental site and the left femoral condyles (LMFC) as control sites. The specially devised cylindrical metallic instrument (8 mm in diameter) with sharp cutting edge on one end and metallic hammer was used to harvest the graft and to create the defects in the femoral condyles.

A sharp knife and a kidney dish were used to morselise the graft manually. Postoperatively, the pigs were allowed to move freely with fresh access to food and water. They were sacrificed at six weeks and 12 weeks and grouped as discussed below.

Surgical procedure

Under general anaesthesia and with proper aseptic measures, the knee joints were opened through a medial parapatellar incision. Both femoral condyles of both knees were exposed and a circular full thickness defect measuring about 8 mm in diameter and 10 mm in depth was created on a weight-bearing surface of the medial femoral condyles by means of a cylindrical sharp cutting instrument known as a dowel (which is the instrument used for harvesting donor cartilage in mosaicplasty) and mallet. Based on the fact that the thickness of the articular cartilage is about 3 mm, a 10 mm depth was chosen as it would then include articular cartilage, subchondral bone and cancellous bone which after being morselised would increase the tissue available for grafting. The osteochondral grafts harvested from both the knees were morselised with a sharp cutting knife in a kidney tray manually and the grout-like material thus prepared were transplanted in the test site ie the RMFC. The graft is then pressed in to the defect with thumb pressure for two to three minutes until the graft adhered to the bleeding bed of the condyle with a “Velcro”-like quality and no fixation was used. The control site ie the LMFC was packed with absorbable gelatin sponge otherwise known as gel foam. The wounds were cleaned thoroughly with normal saline and closed in layers.

Postoperative care

The pigs were kept in big individual cages and allowed to move freely with free access to food and drinking water. The operated knees were not immobilised. Postoperative antibiotic cover was intramuscular injection of ampicillin 500 mg and cloxacillin 250 mg daily for five days. The pigs were assessed once daily for condition of the wound, standing and walking abilities. The postoperative course was uneventful in all the pigs.

The pigs were labelled Pig 1 to Pig 10 according to the order of surgery such that Pig 1 was operated first and Pig 10 last. Pig 1 to Pig 5 were sacrificed at 12 weeks and Pig 6 to Pig 10 were sacrificed at six weeks. These labels are reflected in the relevant

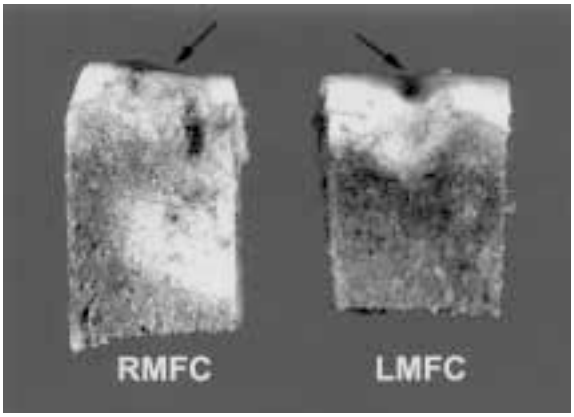

Fig. 1 Paracoronal cuts of the test and control knees at 12 weeks
LMFC: Left Medial Femoral Condyle which is the control knee
RMFC: Right Medial Femoral Condyle which is the test knee
Arrows show the area where the osteochondral defect was.

tables. The pigs were sacrificed with high dose intracardiac pento-barbitone (1500 mg). Anterior posterior and lateral radiographs of both knees were taken just before the pigs were sacrificed.

Both knees were reopened through the same parapatellar approach and the lower end of the femur exposed by denuding the soft tissue attachments. The knee was subsequently disarticulated. Both condyles form both femurs were harvested form the distal femur using a reciprocating electric saw.

Macroscopic observations were done on both the test and control sites. Vertical paracoronal cuts were made and the macroscopic cross-sectional findings were recorded. These were then photographed (Fig. 1).

The specimens were then fixed in 10% buffered formalin and dehydrated using alcohol solutions in increasing concentrations of 70%, 95% and 100% using a tissue processing unit (Leica, Germany). These specimens were then mounted in wax and sliced 4 microns thick with a microtome (Reichertchung, Leica, Germany) and stained with Haematoxylin & Eosin (H & E); Periodic Acid Schiff (PAS)/Alcian Blue and Vangieson/Alcian Blue and Masion Trichrome. H & E was the stain for routine light microscopy. PAS stained glycogen and basement membrane. Alcian Blue was used specifically for acid mucopolysaccharides and Masson Trichrome was used to colour collagen fibres green. Safranin 'O' which was used previously for matrix staining was now being replaced by Vangieson/Alcian Blue[25].The histological slides thus prepared were scored by a histopathologist according to the scoring system as described below.

ANALYSIS

Macroscopic analysis

The macroscopic features used to analyse the test knees were healing of the incision, defect size at the end of test period, the colour of the filled defect, the surface quality of the regenerated tissue. Other parameters used were: stability of the grafted tissue, relation to the margin, level of new tissue and finally restoration of contour. These features were compared to the control knees.

Table I. Histological Parameters used for Histological Aggregate.

Parameter Under Study	Score
Filling of defect	
125% - Above Articular Surface	1
100% - At Articular Surface	0
75% - At Osteochondral Junction	1
50% - At Subchondral Level	2
25% - At Bone	3
0% - None	4
Nature of Predominant Tissue	
Mature Hyaline Cartilage	0
Immature Hyaline Cartilage	1
Undifferentiated Mesenchymal Cells	2
Fibrous tissue	3
Reconstitution of Osteochondral Junction	
Yes	0
Almost	1
Not Close	2
Bonding to Adjacent Cartilage	
Bonded at Both Ends	0
Bonded At One End of Partially at Both	1
Not Bonded	2
Matrix Staining	
Normal	0
Reduced Staining	1
Significantly Reduced	2
Faint Staining	3
No Stain	4
Cells	
Normal	0
Diffuse Hypercellularity	1
Cloning	2
Hypocellularity	3
Structural Integrity	
Intact	0
Partially Disrupted	1
Completely Disrupted	2

Microscopic analysis

The histological grading scale used is adopted with modification from two studies i.e. "The chondrogenic potential of free autogenous periosteal grafts for biological resurfacing of major full-thickness defects in joint surfaces under influence of continuous passive motion" by O'Driscoll[26-30] and "A semiquantitative scale for histologic grading of articular cartilage repair" by S. Pineda[31]. The categories are as shown in the chart (Table I).

The modifications made are:

1. Reconstitution of Osteochondral Junction was

Table II. Macroscopic Observation at 6 weeks.

Pig Number		Surface Regularity	Stability	Relation to Margin	Incision	Defect Size (mm)	Colour
Pig 6	Control	Smooth	Stable	Incorporated	Healed	7x7	Dark Red
	Test	Smooth	Stable	Incorporated	Healed	7x7	Pink
Pig 7	Control	Smooth	Stable	Incorporated	Healed	8x8	Dark Red
	Test	Smooth	Stable	Incorporated	Healed	9x7	Pink
Pig 8	Control	Smooth	Stable	Incorporated	Healed	9x8	Dark Red
	Test	Rough	Stable	Incorporated	Healed	8x6	Pink White
Pig 9	Control	Smooth	Stable	Incorporated	Not Healed	9x6	Dark Red
	Test	Rough	Stable	Incorporated	Healed	8x5	Pink White
Pig 10	Control	Smooth	Stable	Incorporated	Not Healed	9x5	Dark Red
	Test	Rough	Stable	Incorporated	Healed	7x5	Pink White

Table III. Macroscopic Observation at 12 weeks.

Pig Number		Surface Regularity	Stability	Relation to Margin	Incision	Defect Size (mm)	Colour
Pig 1	Control	Smooth	Stable	Incorporated	Healed	8x7	Faint White
	Test	Smooth	Stable	Incorporated except inferiorly	Healed	8x6	Faint White
Pig 2	Control	Smooth	Stable	Incorporated	Healed except lateral crack	7x6	White
	Test	Smooth	Stable	Incorporated except inferiorly	Healed except lateral crack	8x7	Pink White
Pig 3	Control	Smooth	Stable	Incorporated	Healed	7x5	Faint White
	Test	Smooth	Stable	Incorporated	Healed	8x8	Pink White
Pig 4	Control	Smooth	Stable	Incorporated	Healed	9x7	White
	Test	Smooth	Stable	Incorporated	Healed	7x6	Faint White
Pig 5	Control	Smooth	Stable	Incorporated	Healed	9x7	Faint White
	Test	Smooth	Stable	Incorporated	Healed	8x9	Faint White

inferred by the islands of cartilage closest to the osteochondral junction.

2. The Matrix Staining was inferred by the matrix of the predominant tissue.
3. Bonding to Adjacent tissue was inferred by bonding of any island of tissue with the borders of the osteochondral defect.
4. Structural Integrity referred to the absence of vertical cracks in the regenerated tissue.

The modifications were necessary as unlike the previous studies for which it was designed, the tissue within the gap is not homogenous and consists of islands of ostechondral fragments of varying sizes. Some of these concerns are addressed by the scoring system used by Wakitani et al[23]. However, we used the present system with modification as extension of an earlier study done to allow for comparisons.

Statistical analysis

The aggregate of the scores from the histological analysis was tested for the statistical significance using the Mann-Whitney U test at the level of significance of $p<0.05$.

RESULTS

Macroscopic Parameters

The macroscopic features taken into account are as described above. All incisions were well healed. All grafts were also macroscopically well incorporated. However, generally there was slight shrinkage in the diameter of the defects (Table II and Table III).

The most stark difference between the control and test knees was the colour. The test knees were found to be pink to pink white at six weeks (Fig. 2) and generally faint white at 12 weeks (Fig. 1 and Fig. 3). However, all the control knees revealed defects that were dark red in colour.

Filling of the defect was complete in 40% of test knees both at six and 12 weeks. The defects in all control knees remained depressed (Fig. 2 and Fig. 3).

Microscopic Parameters

The histological features that were taken into account are as described above. The scores were then converted into aggregates and subsequently applied to tests for statistical significance.

Keeping in mind that the lower the aggregate the better the quality of the regenerated tissue the

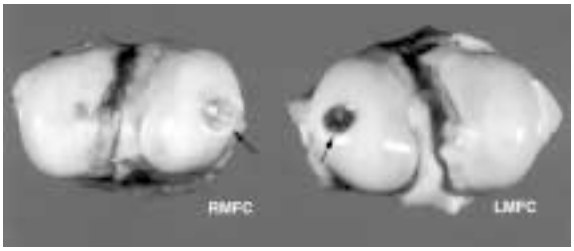

Fig. 2 Macroscopic view of the test and control knees at six weeks
LMFC: Left Medial Femoral Condyle which is the control knee
RMFC: Right Medial Femoral Condyle which is the test knee
Arrows show the area where the osteochondral defect was.

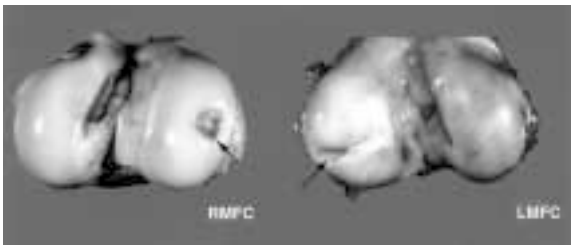

Fig. 3 Macroscopic view of the test and control knees at 12 weeks
LMFC: Left Medial Femoral Condyle which is the control knee
RMFC: Right Medial Femoral Condyle which is the test knee
Arrows show the area where the osteochondral defect was.

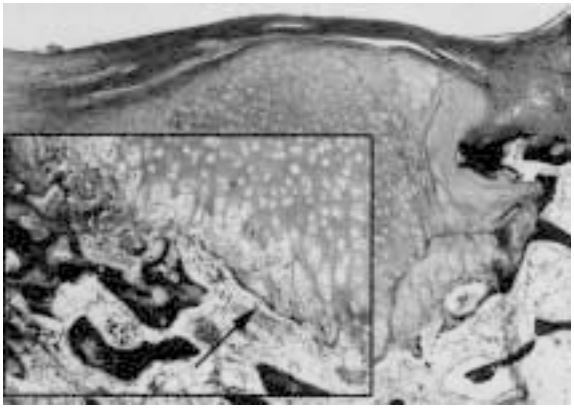

Fig. 4 Histological specimen at high power taken from an osteochondral defect filled with morselised osteochondral graft at 12 weeks using Haematoxylin and Eosin stain. The inset shows the osteochondral junction at a higher magnification. Arrow shows the reconstitution of the osteochondral junction.

Table IV

	Aggregate scores of Test Knees	Aggregate scores of Control Knees
At 6 weeks		
Pig 6	0.43	2.29
Pig 7	0.71	2.29
Pig 8	0.43	1.86
Pig 9	0.86	2.29
Pig 10	0.57	2.14
At 12 weeks		
Pig 1	0.29	1.86
Pig 2	0.29	2.00
Pig 3	0.57	2.00
Pig 4	0.57	2.00
Pig 5	0.29	2.57

Table showing aggregate scores of control and test knees at six and 12 weeks. The closer the aggregate score is to 0, the closer the histological appearance to hyaline articular cartilage. See text for statistical significance.

Table V

Parameter	P value
Filling of defects	0.011
Nature of Predominant tissue	0.003
Matrix Staining	0.005
Cellularity	0.008

Histological parameters found to be better than control knees at six weeks at a confidence level of $p<0.05$

Table VI

Parameter	P value
Nature of Predominant tissue	0.003
Matrix Staining	0.004
Cellularity	0.004
Reconstitution of Osteochondral Junction	0.018

Histological parameters found to be better than control knees at 12 weeks at a confidence level of $p<0.05$.

following table shows the aggregate scores of the test knees compared to the corresponding control knees at six weeks and at 12 weeks (Table IV). Just at a glance, it is apparent that the test knees have better scores both at six weeks and 12 weeks.

When tested for statistical significance the scores were significantly better with p values of 0.008 and 0.007 at six weeks and 12 weeks respectively.

However, when the aggregate for the test knees at six weeks were compared to those at 12 weeks there was no statistical difference.

Analysis of the knees at six weeks, showed that the parameters that scored better than the control were filling of defects, nature of predominant tissue, matrix staining and nature of the cells. The p values for these factors are as shown (Table V).

Similarly the parameters that scored better at 12 weeks were nature of predominant tissue, matrix staining, nature of cells and reconstitution of the osteochondral junction. The p values are as shown (Table VI).

When individual parameters between the test knees at six weeks and those at 12 weeks were compared reconstitution of the osteochondral junction was significantly better at 12 weeks with p value of 0.018 (Fig. 4).

DISCUSSION

Due to the poor regenerative potential of articular cartilage, there has been since the early sixties, attempts of replacing it with ostechondral grafts. However the results of these studies have not been as conclusive at that by Hangody et al.

Hangody et al[21,22] from Hungary (1994-96) successfully treated the full thickness defects of the knees and ankle joints as the result of chondroplasty, traumatic chondral defects and osteochondritis dissecans in human under the age of 50 years with multiple cylindrical osteochondral grafts of varying diameters of 2.7 mm, 3.5 mm, and 4.5 mm, grafted into the recipient site in mosaic-like pattern. The grafts were taken from the non-weight bearing femoral periphery of the patello-femoral joint to eliminate the donor site morbidity. With the combination of multiple grafts, the recipient site was filled with 60% to 80% hyaline cartilage and the fibrocartilage "grouting" growing upwards from the prepared cancellous bed would complete the method of treatment called the mosaicplasty. With this technique done under arthroscope they showed that patients benefited clinically and physically in their daily active lives. The ultrasound, MRI and CT arthropathy revealed good congruity and satisfactory cartilage thickness of the replaced area, with hyaline fibrocartilage transpositions in the transplant and surrounding cartilage.

However, despite the impressive results, the procedure popularised by Hangody remains technically demanding with the added disadvantage of limited donor sites. This lead to research directed towards simpler method of articular cartilage replacement such as that proposed by A Walgenbach and Kevin R Stone in presentation at the 1997 American Academy of Orthopedic Surgeons in San Francisco[24]. In his study 23 full thickness lesions (average size of 283.3 mm diameter) were grafted with articular cartilage and cancellous bone from the intercondylar notch. Patients were non-weight bearing for four weeks and used a CPM each night. Thirteen patients underwent second-look arthroscopy, six with biopsy. Twenty-one of 22 patients were satisfied, with pain scores significantly improved. The cartilage appeared smooth. The histologic appearance was of hyaline cartilage in three of six biopsies, a slight Fibrocartilagenous component in one biopsy, and predominantly fibrocartilage in two biopsies to date. Collagen typing revealed a high percentage of Type II collagen. This study allows for the inclusion of bone graft which possibly allows for larger amounts of donor tissue and thus the possibility of treating larger defects. However, being a clinical study, not all patients were biopsied and more importantly there were no controls. Thus an animal study like ours would allow for all the test knees to be biopsied and comparisons made to suitably matched controls which in our case is the contralateral knee. The reason morselised graft was chosen was to match the human model but with a more objective and scientific approach for comparisons of the test and control knees.

Analysing the macroscopic observation, we found the colour of the defect improved with time. This is attributed to the increasing cartilage content with time. However, we also observed that 60% of the defects remained depressed even after 12 weeks. This we think is due to the varying degree of resorption of bone graft in the defects.

With respect to the histological study, it must be emphasised the grading system was created for periosteal transplant and as modified as described above. Microscopically we found generally better histological scores in the test knees with evidence of osteochondral reconstitution at 12 weeks. However, the bonding and the structural integrity of the grafts were found not to be significantly better. The fact that the cartilage grafts were in the form of islands may have accounted for it.

Based on the above observation and data intepretation a possible postulate would be firstly, the cartilage on the surface remained alive in situ for the first six weeks. Resorption of the osteochondral grafts beneath the surface occur subsequently accounting for the macroscopic depression seen. In the final phase, the surface cartilage remains at 12 weeks and regenerate at the edges sustained by motion and synovial fluid factors[32-34].

CONCLUSION

Based on our aims the conclusions we made were:

1. There was good survival of the grafted morselised cartilage and bone.
2. There was generally statistically significant better histological scores of the test knees compared to the control knees.
3. There was reconstitution of the osteochondral junction seen at 12 weeks and this was statistically significant when compared to the controls.

There were however limitations to this study. There was no collagen typing done. In addition there was also no bio-mechanical testing done. This would add accuracy in ascertaining the quality of regenerated cartilage.

With regards to future directions, a longer period of follow-up may be considered in order to ascertain further survival or otherwise of the grafted tissue. The limitations as described will also be addressed. It would in addition be interesting to compare our findings with other methods of biological resurfacing. The next phase would be a clinical case-controlled prospective study.

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