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SCUOLA DI DOTTORATO DI RICERCA - FACOLTÀ DI MEDICINA E CHIRURGIA
DIPARTIMENTO DI SCIENZE CLINICHE E MOLECOLARI

Osteoarticular damage in the knee: new frontiers in joint regeneration and substitution

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Ciclo XIV – Nuova Serie

Abstract

Acute cartilage injury represents a major clinical problem affetting patients younger and younger since competitive sport activity has become largely widespread. The so-called biological resurfacing has moved its first steps in the early 90's with the aim to restore native cartilage and to avoid or delay the need for joint substitution. Since then, great technical and medical progress has occurred. However the target to reproducibly restore native hyaline (or even hyaline –like) cartilage with good mechanical properties has still been missed. In fact most of the cartilage we are able to regenerate is fibrocartilage, with scarce mechanical properties, which, does not guarantee long-term durability and prevention of osteoarthrosis. Therefore the efforts of the scientific community are still directed to improve the quality of the regenerated cartilage. In the last few years the possible combination of multipotent, autologous mesechimal cells and scaffolds has emerged as viable option to target hyaline cartilage regeneration.

The first part of this thesis focuses on the association of a source of mesechchimal stem cells - the bone marrow concentrate - and two different scaffolds; one made of collagen and the other made of a combination of hyaluronan and polyglycolic acid. The scaffold and the cells are associated in two novel surgical techniques for cartilage repair in the knee. The outcomes of these techniques have been analysed and compared from the functional arthroscopic and histological point of view. We hypothesize that both these techniques have the potential to regenerate hyaline or hyaline-like cartilage and painless motion.

Chronic joint degeneration is a major social problem since the average age of western countries is increasing year after year and so is the need to move and be active even later in life. Osteoarthritis of the knee is one of the first causes of pain and disability among the elderly people. Knee substitution (i.e. total knee replacement) aims to re-establish knee function and painless motion. In the past forty years knee prosthesis have made huge progress in terms of design improvments, material developments and clinical outcome. Even though most of the patients who have undergone a knee substitution have good or excellent results, it remains a percentage of patients scarcely satisfied because of pain, instability, tightness or failure of the implant. Therefore there is still room to improve this highly successful procedure.
Among the different prosthetic designs the conforming, mobile bearing designs are the ones that guarantee low shear stress, wear and debris production and therefore maximum durabiliry of the implant. Fully conforming mobile bearing prosthetic design may be implanted both preserving and resecting the posterior cruciate ligament. The role of the posterior cruciate ligament in mobile bearing prosthesis is unclear since there are prosthetic designs which require its sacrifice and others that allow its preservation.

The second part of this thesis focuses on the clinical and functional outcomes of patients who underwent total knee replacement with a mobile bearing prostetic design either with or without posterior cruciate ligament sacrifice. We hypotesize that patients with posterior cruciate ligament preservation may have better knee motion and feeling due to increased proprioception linked to the ligament retainment.

List of peer-reviewed publications arising from this thesis

1. Single-stage cartilage repair in the knee with microfracture covered with a resorbable polymer-based matrix and autologous bone marrow concentrate.
Enea D, Cecconi S, Calcagno S, Busilacchi A, Manzotti S, Kaps C, Gigante A.
Knee. 2013 Dec;20(6):562-9

2. One-step cartilage repair in the knee: collagen-covered microfracture and autologous bone marrow concentrate. A pilot study.
Enea D, Cecconi S, Calcagno S, Busilacchi A, Manzotti S, Gigante A.
Knee. 2015 Jan;22(1):30-5

3. Retained versus resected posterior cruciate ligament in mobile-bearing total knee replacement: a retrospective, clinical and functional assessment.
Enea D, Cigna V, Sgolacchia C, Tozzi L, Verdenelli A, Gigante A.
Musculoskelet Surg. 2015 Aug;99(2):149-54

Table of contents

PART I
NEW FRONTIERS IN
JOINT REGENERATION

List of Figures

List of Tables

List of abbreviation

AC = Articular cartilage
ACI = Autologous chondrocyte implantation
ACL = Anterior cruciate ligament
AMIC = Autologous matrix induced chondrogenesis
BMC = Bone marrow concentrate
BMP's = Bone morphogenetic proteins
CCI = Characterised chondrocyte implantation
C-CMBCM = collagen-covered microfracture and bone marrow concentrate
COMP = Cartilage oligomeric protein
CPM = Continuous passive motion
CR = Cruciate retaining
CS = Cruciate sacrificing
CMBMC = covered microfracture and bone marrow concentrate
ECM= Extra cellular matrix
FB = Fixed bearing
FDA = Food and drug administration
FGF-2 = Fibroblast growth factor 2
GKS = Global knee system
FSE = Fast Spin-Echo
GRE = Gradient echo
IBPS = Insall-Burstein posterior stabilized
IGF-1 = Insulin-like Growth Factor-1
KSS = Knee society score
IKDC = international knee documentation committee
LCS = Low Contact Stress
OA = osteoarthritis
MACI = Matrix assisted chondrocyte implantation
MB= Mobile bearing
MBK = Medially biased kinematics
MFX = Microfracture
MRI= Magnetic resonance imaging
MSC = Mesenchymal stem cell
OA = Osteoarthritis
OAT = Osteochondral autograft transfer
PCA = Porous-coated anatomical knee
PCL = Posterior cruciate ligament
PDGF = Platelet derived growth factor
PGA-HA-CMBCM = Polyglycolic acid/hyaluronan-covered microfracture and bone marrow concentrate
PRP =Platelet Rich Plasma
PS = Postero-stabilized
ROM = Range of motion
VAS = Visual analogic scale
ST = Standard deviation
TC = Total condylar
TGF-β = Transforming growth factor beta
TKR = Total knee replacement
TRAC = Two Radii Area Contact
VEGF = Vascular Endothelial Growth Factor

Part I

New Frontiers in

Joint Regeneration

1. Cartilage and cartilage repair strategies

1.1 INTRODUCTION

Lesions of the articular cartilage (AC) are a common pathology of joints which can affect people of all ages resulting in a wide range of clinical presentations. Articular cartilage defects at the time of arthroscopy are present in about 60% [1] of knees however, it is unclear how many of these defects are actually symptomatic and require surgical intervention. The population continues to live longer and remains active into later life and as a result the number of cartilage surgeries performed is increasing, (more tha half a million procedures performed yearly in the US).

Hunter observed in 1743 that "cartilage once destroyed never heals". Nowdays this is not entirely true. Although AC has a poor ability to regenerate itself, there is potential for repair. Understanding of AC pathophysiology is improving, yet the mechanism of regeneration of hyaline cartilage continues to elude us. What is clear is the distinction between traumatic and degenerative lesions (i.e. osteoarthritis). Any particular type of lesion may require a specific form of treatment.

1.2 COMPOSITION OF ARTICULAR CARTILAGE

Hyaline cartilage is a highly specialised tissue with a regional organisation. Figure 1.1 shows the zonal architecture of hyaline cartilage. The osteochondral unit is made up of subchondral bone, calcified cartilage and the, radial, transitional and tangential or superficial zones of the articular cartilage itself.

Fig. 1.1. The zonal architecture of articular cartilage

It develops along a path of bone morphogenesis therefore it's production is under similar conditions and signalling factors as bone [2]. The growth plate separates cartilage from bone via a line of proliferating chondrocytes which go on to hypertrophy and form bone. It is at this stage that the cell numbers in AC do not multiply, instead the bulk of the tissue is made up of extracellular matrix (ECM).

AC contains 60-80% water [3]. The predominant cell type is the chondrocyte (5% wet weight) which is responsible for ECM production. They are spherical and surrounded by round small lacunae, but become more flattened as they get closer to the superficial zone, where they are fibroblastic in shape. They often group together in columns forming chondrons (2-4 cells), which are orientated along collagen fibres [4]. The ECM is made up of collagen fibres (25% wet weight) of which Type II predominates (95%), but also includes types VI, IX and XI with type X in the calcified layer. These fibres are anchored to the calcified layer then run perpendicularly to it crossing each other in arcs at the superficial zone. The cells within the superficial zone are thus orientated horizontally and along with the collagen network provide resistance to shear. They also

secrete lubricin (also known as Superficial Zone Protein), a molecule which is responsible for reducing the coefficient of friction and thus providing cartilage with such favourable tribiological properties .

Negatively charged hydrophilic proteoglycan molecules (mostly aggrecan and hyaluronan) protrude from the net of collagen fibers. The dense collagen network is somewhat restrictive to the hydration of these molecules thus they are only hydrated to about 40-60%. As a result, the swelling pressure which is generated provides the compressive stiffness of cartilage [5]. During the early degenerative process, when the collagen fibres are disrupted, the proteoglycans can become more hydrated thus causing the cartilage to become bulcky and soft.

Smaller glycoproteins also exist, fibronectin and cartilage oligomeric protein (COMP) which have a role in cell adhesion, and growth factors such as Bone Morphogenetic Proteins (BMP's). Their role is under intense investigation and in many ways remain least understood [5].

Tissue turnover is mostly governed by a balance between the matrix metalloproteinases (MMP-3, MMP-8, MMP-9, MMP-13 and aggrecanases 4&5 predominating) and the Tissue Inhibitors of Metalloproteinases (TIMPS). Over expression of one or other is a likely contributor of OA [6].

AC is avascular and aneural and receives its nutrition from the synovial fluid, as a result of mechanical movement of the tissue producing a diffusion gradient. AC is immunopriveledged in that it does not contain immune cells. Therefore chondrocytes secrete lysozyme to counteract microorganisms [5].

1.3 TYPES OF CARTILAGE INJURY

Once the cartilage is damaged, a degenerative process begins. The aetiology of cartilage degeneration which leads to osteoarthritis is multifactorial and many different risk factors have been implicated. Mechanical factors such as direct trauma, instability, malalignment and loss of meniscal chondroprotection have a role, as do metabolic factors such as diabetes, alcohol abuse and obesity [7]. It is therefore difficult to target one specific cause.

The depth of the injury will influence the healing potential of cartilage. Cartilage defects which do not extend to the subchondral bone do not spontaneously for the small number of chondrocytes within the ECM, their inability to migrate to the zone of injury and their relative inability to regenerative large amounts of ECM. It means these defects will usually progress. Full thickness defects which penetrate the subchondral bone do have the potential for intrinsic repair due to the communication gained with the marrow cavity and the mesenchymal stem cell (MSC) population which allow repair tissue to be. However, this is not a regenerate tissue as the repair tends to be fibroblastic in origin [8]. Eearly OA behaves very differently. An increase in matrix molecule synthesis is often recognised. However, once loss of matrix eventually exceeds that which is deposited a net loss of ECM results. The chondrocytes are noted to proliferate and form clusters, and cell hypertrophy is often observed. Loss of chondrocytes in the superficial zone occurs followed by fibrillation, fissuring, erosion, subsequent denudation of bone and subchondral alteration [5].

1.4 THE ROLE OF MAGNETIC RESONACE IMAGING

Pain and mechanical symptoms such as locking or catching are characteristic of eraly stage cartilage injury. Loss of movement and reduced function predominate in the latest stages of OA.

Magnetic Resonance Imaging is the gold standard for diagnostic imaging and treatment planning. A 1.5T magnet or stronger must be used with a dedicated extremity coil to be able to use MRI as an assessment tool. The main sequences employed are T2 weighted Fast Spin-Echo (FSE) with or without fat suppression and T1 weighted 3D gradient echo (GRE). The FSE images show cartilage to be dark in contrast to the high signal of synovial fluid and bone marrow. Thus surface and matrix irregularities will be shown with increased signal. GRE sequences produce high signal intensity in the cartilage compared to that low in bone and synovial fluid. The 3D nature of these images allows improved visualisation and volume measurements [9].

1.5 SURGICAL TECHNIQUES FOR CARTILAGE REPAIR

Prior to consider a cartilage repair procedure, the surgeon has to plan the treatment according to biology of the defect and the physical condition and requirements of the patient. The strong will of the patient to take part in an extended rehabilitation programme should be ascertained. The nature of the patient's employment and sporting activities will have a significant impact on what procedure is chosen. Demotivated patients will have to be advised not to performe any cartilage repair procedure.

1.5.1 Lavage and Debridement

This procedure is a palliative and no tissue regeneration may be obtained with this technique. The procedure consists in the removal of unstable flaps of cartilage and loose bodies and should be performed if the patient exhibits mechanical symptoms. Early mobilisation and weight bearing as tolerated is encouraged and this is the only real strength of this procedure. A study which compared arthroscopic lavage to placebo found that neither arthroscopic lavage nor debridement were better than placebo [10]. Debridement should not be offered as a treatment apart from in patients who suffer mechanical symptoms and signs in whom more aggressive treatments are not acceptable.

1.5.2 Microfracture and Perforation

Microfracture or perforation of the subchondral bone represent the so-called "Marrow stimulation techniques". They involve penetrating the subchondral bone plate to allow bone marrow blood in the joint cavity. This allows marrow stromal cells containing mesenchymal stem cells (MSC's), platelets and other chemotactic factors to collect within the defect. The original techniques described such as Pridie drilling have gone out of favour for the more refined microfracture technique described by Steadman [11, 12] (Fig. 1.5.2.1). Following debridement of the perilesional cartilage producing a perpendicular shoulder of cartilage, 3-4 mm deep holes are made in the subchondral bone 2-3mm apart, starting in the periphery, working into the centre of the defect. Unlike Pridie drilling, this maintains greater mechanical stability of the subchondral bone and collapse is not seen as readily as in previous techniques.. The rehabilitation seems to form an

integral part of the procedure and the original authors maintain that the intensive rehab period must be adhered to for the procedure to be successful. The procedure is easy to perform, cheap, minimally invasive and well tolerated by the patient. Recently nanofracture have been introduced.

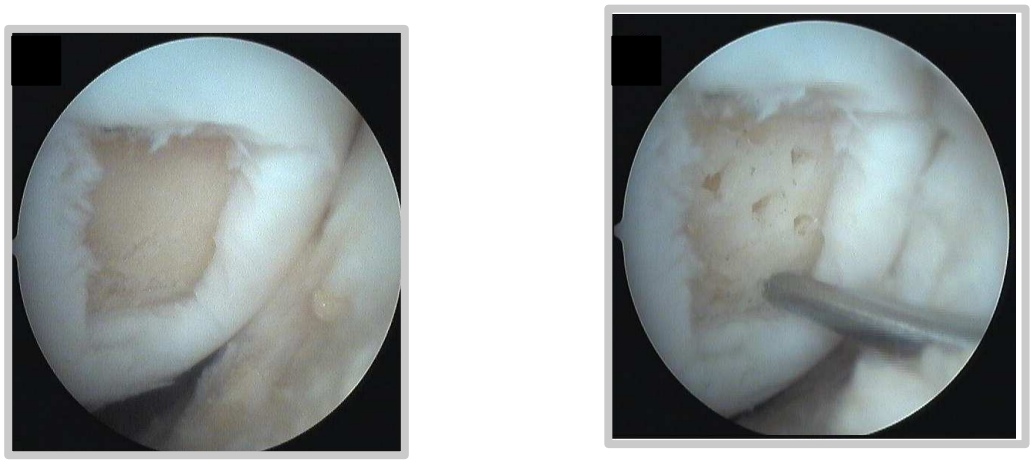

Fig. 1.5.2.1 The microfracture technique

Studies have shown microfracture is able to give a fibrocartilagenous reparative response which mostly provides symptom relief for up to 2 years. Steadman et al have published data on 72 patients with defects less than $4cm^2$ who underwent microfracture with follow-up of 7-17 years [11]. Eighty percent of patients improved with Lysholm scores improving from 59 to 89, and Tegner activity scores improving from 6 pre-operatively to 9 post-operatively. Gobbi reported similar results in a group of athletes but at 2 years noted that 80% of patients had a reduction in Tegner score [13]. This may be as a result of the less durable fibrocartilage which is produced but also the poor fill of the defect, particularly around the margins with poor integration with the native articular cartilage, which may also be related to the size of the defects treated. This was shown histologically by Dorotka et al. in an ovine model, with improved defect fill found when the clot was stabilised with a collagen membrane [14].

1.5.3 Microfracture and scaffold

To overcome the shortcomings of the original thechnique microfracture has been augmented with a collagen I/III matrix (Chondroguide, Geistlich Biomaterials) which soak up the blood clot from the subchondral holes, providing a scaffold for cells and chemotactic factors to reside (Fig. 1.5.3.1). The membrane can be fixed with fibrin glue or 6/0 vicryl sutures. Autologous Matrix Induced Chondrogenesis (AMIC) has shown promising results however we await long term data [15]. This may represent the future of marrow stimulation techniques. The first part of this thesis will focus on a novel surgical technique that represents an evolution of the original AMIC technique.

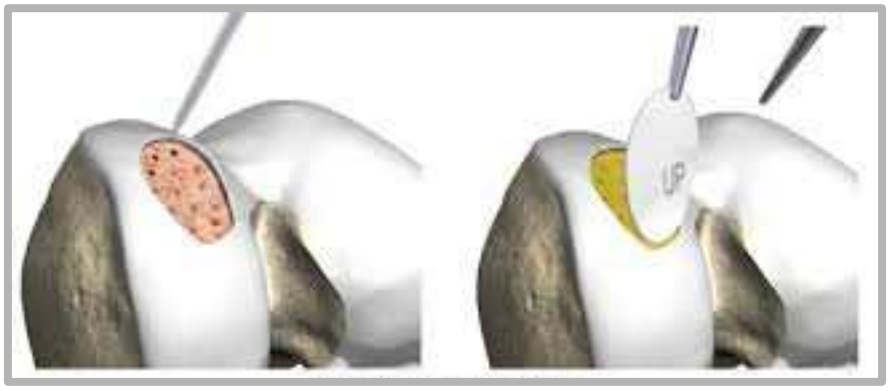

Fig. 1.5.2.2 Autologous matrix induced chondrogenesis (AMIC)

1.5.4 Osteochondral autograft transfer (OAT) - Mosaicplasty

In this technique osteochondral plugs are harvested from a non-weight bearing articular surface (lateral trochlear ridge or notch) and transferred to a pre-prepared cylindrical hole within the defect. It is the only procedure which produces hyaline cartilage within the defect,. For single plug transfer, the size of the defect will be the limiting factor. Problems such as joint congruency and donor site availability are encountered hence mosaicplasty techniques have been developed.

Mosaicplasty involves the transfer of a number of smaller defects, allowing a congruent joint surface (Fig. 1.5.4.1). It is extremely technically demanding and donor site morbidity remains a problem (lateral trochlear ridge not truly non-weight bearing). Both techniques suffer from poor

graft incorporation, with mosaicplasty particularly suffering with poor integration in gaps between the plugs and native cartilage.

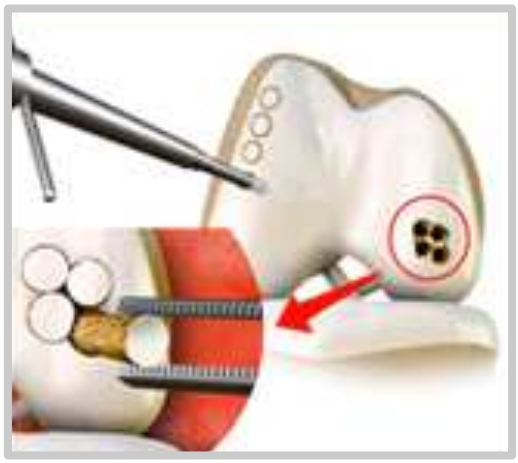

Fig. 1.5.4.1 Mosaicplasty

Mosaicplasty has shown mixed results with a number of studies showing superior outcomes to marrow stimulation techniques. Hangody et al showed that 87% of patients had good to excellent results at 5 years following mosaicplasty compared with 0-34% of patients who were randomised to 1 of 3 marrow stimulation techniques [16]. In a further study looking at a group of competitive athletes, the same group found 100% of patients had a good to excellent result at greater than one year with 63% returning to full sports [17]. Bentley et al have since shown improved outcomes with Autologous Chondrocyte Implantation over mosaicplasty in their RCT with 88% showing good to excellent results compared to 69% at a mean of 19 months [18].

Although good results have been reported the use of mosaicplasty seems to be less widely utilised due to the technical difficulty, problems with congruency and donor site morbidity. The use of a single osteochondral transfer in small isolated defects is more acceptable.

1.5.5 Autologous Chondrocyte Implantation (ACI)

The process of transplanting autologous chondrocytes in suspension to a cartilage defect was first described clinically by Brittberg et al in 1994 [19]. A biopsy of normal cartilage from the non weight bearing aspect of the ipsilateral knee is taken during the initial arthroscopic procedure. Chondrocytes are then isolated and expanded in-vitro. The cell suspension is then returned to the defect during the second stage procedure, and held in place with a periosteal patch, harvested from the proximal tibia, sutured over it to keep the cells in place. This procedure has since evolved to using a collagen membrane instead of periosteum: is called second generation ACI or ACI-C. Large defects (>4cm^2) can be treated as can multiple or even in some cases, kissing lesions [20] (Fig. 1.5.5.1).

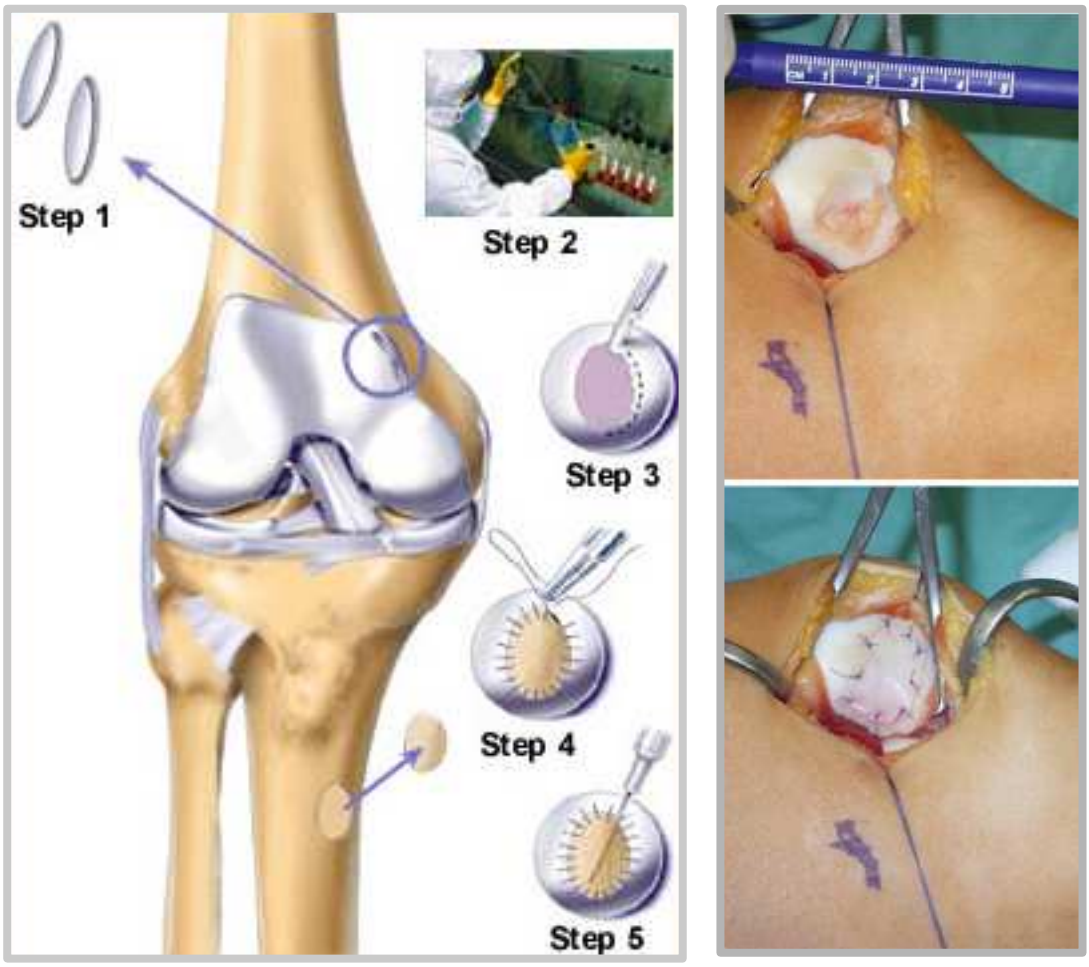

Fig. 1.5.5.1 Autologous chondrocyte implantation (ACI)

Good to excellent results have been reported in 85-92% of patients at 2 years in a number of observational cohort studies [21]. A number of randomised studies have been published comparing ACI to other cartilage repair procedures. Horas et al showed that an improvement in symptoms could be established with both ACI and OATS however the speed of recovery of ACI was slower[22]. Bentley et al compared ACI to mosaicplasty in 100 patients with similar demographics and lesion size. At a mean of 19 months, 89% of patients who had ACI showed good to excellent results compared with 69% in that of mosaicplasty [18]. But Dozin et al found an improvement in 88% of mosaicplasty patients in their study compared to 68% in the ACI group. The numbers in this study are small, and interestingly, 31.4% of patients were excluded due to improvement in symptoms following debridement at the time of the arthroscopic assessment/biopsy.They were not included in the final analysis .

There are randomised controlled trials comparing ACI to microfracture [23, 24]. The study by Knutsen et al. has shown no difference in clinical and radiographic outcome between the groups at 5 years, however, the study is underpowered. No correlation was found between histology grade and clinical outcome however those with the best histology at two years did not exhibit any failures. The more recent study by Saris et al. incorporates a novel chondrocyte characterisation system which supposedly correlates with improved histology and outcome. One year results favour ACI over microfracture in terms of histomorphometry however functional outcome as measured by the KOOS score is similar in both groups at 12-18 months assessment.

1.5.6 Matrix Assisted Chondrocyte Implantation (MACI)

Matrix assisted chondrocyte implantation (MACI) (Genzyme, Cambridge, MA) was among the first variations from ACI original technique and has been in clinical use for a number of years. This technique is also numbere among the so-colled third-generation ACI (Fig. 1.5.4.1). MACI employs a collagen matrix on which chondrocytes are expanded in-vitro and then transferred into the defect. The membrane can be held with fibrin glue or sutures. Benefits of this include the ease of

application of the membrane and also the possibility of performing the procedure totally arthroscopically.

Two further randomised trials, the first by Bartlett et al has shown ACI and MACI to be comparable at 1 year [25], and that done by Gooding et al [26] which has shown similar functional outcome at two years between ACI with periosteum patch compared to a collagen membrane. Of note, 36% of the periosteum group required debridement of the graft due to periosteal hypertrophy.

Other problems with this technique exist. Two operations are required, it is very expensive to culture cells and the repair tissue still is not reproducibly hyaline cartilage. However, in a histological study by Briggs et al examining ACI-C grafts one year following implantation, mRNA for type II collagen was found to be produced by chondrocytes, irrespective of the quality of the repair tissue[27]. Similarly, our group has shown that MACI can lead to the formation of hyaline-like cartilage tissue [28], and that patellar MACI can lead to good results when associated to tibial tuberosity trasposition [29]

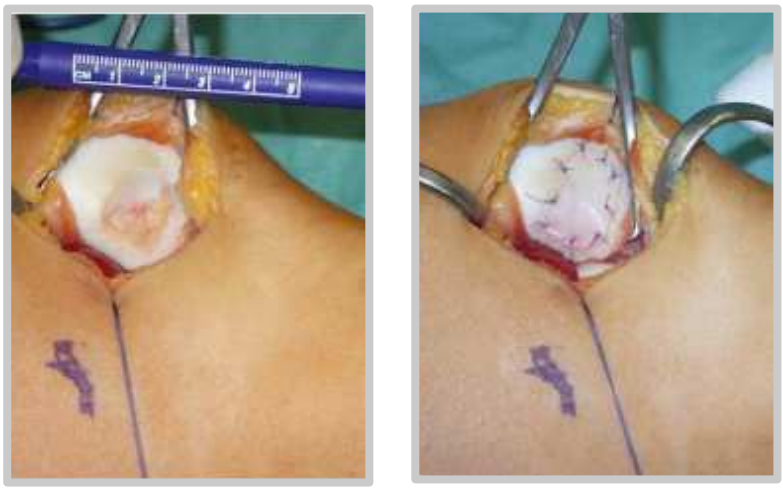

Fig. 1.5.6.1 The matrix assisted chondrocite implantation (MACI) on the patella. From Gigante et al 2009 [29].

Other products currently on the market which are similar to MACI include Hyalograft C (Fidia Farmaceutci, Italy), Bioseed-C (BioTissue Technologies, Freiburg, Germany), CaRes (Arthrokinetics, Macclesfield, UK), Cartipatch (TBF Tissue Engineering, Bron, France) and Novocart (TETEC AG, Reutlingen, Germany). Each utilises in-vitro culture of chondrocytes in the

scaffold matrix followed by implantation. This enables 3D culture of chondrocytes preventing dedifferentiation down a fibroblastic lineage and loss of phenotype. Novel methods of implantation and fixation are developing allowing minimally invasive and arthroscopic techniques to be used. Although many of these products have produced satisfactory clinical outcomes, we wait to see if they provide any benefit over other aforementioned cartilage repair techniques.

1.5.7 Osteotomies and meniscal transplants

Joint environment preservation is essential to successful cartilage repair. If mechanical imbalance malalignment, instability or the lack of meniscus is not corrected the repair will undergo abnormal mechanical loads. Combinations of distal femoral, high tibial or tibial tubercle osteotomy with anterior cruciate ligament reconstruction and meniscal allograft/collagen meniscal implant can be done simultaneously or staged, depending on the degree and amount of correction required.

Varus/Valgus osteotomy*:* In physiological loading of the knee 60% is transmitted through the medial compartment and 40% through the lateral. Although there is no good clinical evidence to support it, more authors suggest performing staged or simultaneous osteotomy to unload a defect/repair if the mechanical axis falls within the affected compartment. Mina et al have demonstrated in a cadaveric model that load is equally distributed in both compartments if a corrective osteotomy is performed to 0-4 degrees valgus. Complete unloading of the medial compartment can be achieved with 6-10 degrees of valgus [30]. The problem with trying to prove this concept is that if procedures are performed simultaneously it is difficult to ascertain which has the biggest impact on the functional outcome. To perform a randomised control trial would take large numbers and likely be very difficult to recruit to achieve statistical power. We are therefore left with published case series such as those by Minas who found an improvement in Cincinnati rating scale and SF-36 scores at two years in a group of 71 salvage cases where multiple defects were treated simultaneously with osteotomy and ACL reconstruction. Ninety percent of these salvage patients were happy with their treatment at last follow-up [31].

***Tibial tubercle osteotomy**:* A similar concept is found within the patellofemoral joint (PFJ). Increased loading of chondral defects associated with maltracking should be corrected following cartilage restoration procedures. Combinations of lateral release, medial patellofemoral ligament (MPFL) reconstruction and tibial tubercle osteotomy can be employed. The Fulkerson tibial tubercle osteotomy employs the anteromedialisation of the tibial tubercle which not only corrects maltracking but also reduced the load transmitted through the PFJ. Farr has shown improved results in complex PFJ defects treated with ACI and osteotomy +/- MPFL reconstruction with improvements seen in Cincinnati rating, Lysholm and VAS at a mean of 1.2 years [32]. Again, no studies have been performed to conclude which procedure has the greatest impact [29].

***Meniscal allograft transplantation/Collagen Meniscal Implant**:* It is well documented how loss of meniscus can lead to progressive degenerative change of the involved knee compatment. The chondroprotective role of the meniscus is recognised and thus transplantation with allograft (Fig. 2.16) or tissue engineered meniscus is an accepted procedure. Although good results have been reported with both allograft transplantation and Collagen Meniscal Implantation [33] alone, a study by Deie et al found an unsatisfactory outcome when allograft transplantation was performed in the presence of a medial femoral condyle articular cartilage defect [34]. We would therefore suggest that the procedures should be performed in combination so as to benefit from the load sharing role of the new meniscus tissue, thereby protecting the cartilage graft.

1.5.8 Hyaluronic Acid

There is objective evidence to show that HA can provide symptom relief in degenerative conditions. Further randomised controlled trial continue to be published looking at specific preparations and delivery to maximise its affect. Evidence pointing toward the role of HA in chondroprotection is less prevalent however a study by Tytherleigh-Strong et al demonstrated its potential positive role in cartilage repair when used in conjunction with osteochondral autograft transfer [35]. Further

evidence will be required before it should be incorporated as standard into cartilage repair procedures.

1.5.9 Postoperative care

Every rehab protocol applied to cartilage repair procedures will have to focus on the perfect balance of implant stimulation via mechanical load and prevention of implant detachment or delamination. It is well established from preclinical studies that chondrocytes require mechanical load to stimulate the production of ECM and remain in a chondrogenic phenotype. The type of surgery performed and the location of the implant will govern how early weight bearing can commence. The benefit of osteochondral grafting is that early weight bearing can be tolerated due to the stability of the graft. This is not the same scenario with ACI/MACI or microfracture as the repair graft has to be given time to embed in the subchondral bone. Mechanisms of fixation therefore also continue to evolve to allow early range of motion, weight bearing and hopefully a quicker return to function or sport.

1.6 CONCLUSION

No one procedure is best for all types of defect and for all the patients. Indeed, the procedure should also be tailored to the patient's expectations and functional requirements. We therefore require a method of differentiating which procedures should be used and for which lesion and patient. The treatment algorithm has to take into account the anatomical location and size of defect and the mechanical environment to which it resides togheter with the specific skill and experience of the surgeon. To date the majority of current treatments are still unable to regenerate reproducibly hyaline cartilage. Biologics and tissue engineering will hopefully give us the opportunity to improve our tissue regeneration capabilities and ultimately patient outcome.

2. Articular cartilage engineering

2.1 TISSUE ENGINEERING CONCEPT

Hunziker describes tissue engineering as "the art of reconstituting mammalian tissues, both structurally and functionally" [8]. Tissue engineering strategies are now being employed with the goal of improving the quality of the repair tissue, its longevity and ultimately patient outcome. The purpose of this chapter is to outline the different aspects of tissue engineering and how they may be utilised to good effect in AC repair.

Tissue engineering involves the delivery of cells and/or bioactive molecules on a scaffold to a defect to achieve tissue regeneration. Different combinations of cells and growth factors can be utilised with and without scaffolds. The pioneers Langer and Vacanti detailed this concept back in 1993 [36]. Since then it has been used in clinical practice for many tissues including dermal and neural regeneration. In AC research there has been extensive studies performed in-vitro however we are now seeing these concepts being brought through into clinical practice.

2.2 SCAFFOLDS

The ideal scaffold should mimic the 3D environment of the extracellular matrix (ECM), provide structural support to the regenerate and surrounding tissues and provide an increased surface area to volume ratio for cellular migration, adhesion and differentiation. At the same time it has to be biodegradable, reabsorbing with the right timing and without toxic by-products [37].

Is should have the right consistency to be fixed to the defect site, facilitate cell attachment and regulate cell expression [38]. Porosity and interconnectivity are important to allow cell migration and the passage of nutrients and waste products and may affected cell adhesion and proliferation in collagen/GAG scaffolds. The optimum pore size has been estimated to be between 100 and 500 μm [39]. Scaffold can be classified into natural and synthetic polymers.

2.2.1 Natural polymers

Natural scaffolds have the theoretical advantage of providing a more effective environment for cell adhesion and proliferation. They can be divided into protein based matrices such as collagen and fibrin, and carbohydrate based matrices such as alginate, agarose, chitosan and hyaluronan.

Collagen has been investigated extensively and is now used in clinical practice in many forms. Collagen possess ligands which facilitate cell adhesion and can influence cell morphology, migration and differentiation. Although autologous chondrocyte implantation (ACI) was originally described using a periosteal patch over the defect, collagen is also now used [21]. An example is Chondro-Gide (Geistlich Biomaterials, Wolhausen) which is a mixture of Type I and Type III porcine collagen produced in a bilayered structure which allows chondrocyte adhesion while maintaining a watertight patch over the chondral defect. This has evolved further to matrix assisted chondrocyte implantation (MACI) where chondrocytes are expanded on the collagen membrane ex-vivo then re-implanted. A study by Bartlet et al has shown that both ACI and MACI produce similar results at two years [25]. Further developments have lead to a simplified procedure: the clinical use of Chondro-Gide as a scaffold augmentation of microfracture, the so called autologous matrix induced chondrogenesis (AMIC) [15]. Type II collagen, which is scarcely adopted on the market (no off-the-shelf product is adopting type II collagen), has shown good biocompatibility and potential for hyaline-like cartilage repair on rabbits [40].

Fibrin is a 3D natural net formed from a reaction between fibrinogen and thrombin which has favourable porosity and degradation characteristics producing non-toxic physiological by-products. It successfully supported chondrocytes in an equine cartilage defect model in-vivo [41].

Alginate is an anionic polysaccharide which is derived from seaweed. Alginate cultures have been shown to aid redifferentiation of dedifferentiated chondrocytes which have lost their phenotype due to monolayer expansion. Alginate has also been used successfully in-vivo. Diduch et al have demonstrated chondrogenesis in MSC's supported within alginate beads in rabbit osteochondral

defects [42] however, there are concerns over biocompatibility of both alginate and agarose, therefore they are not widely employed in clinical practice.

Hyaluronan is a component of the ECM with the ability to stimulate chondrogenesis in MSC's. In order to be enough strong to be implanted and to be manipulated hyaluronan requires crosslinking thereby possibly compromising its biocompatibility [43]. Hyaff is an esterfied hyaluronan scaffold which has been use extensively in clinical AC repair practice. On the market as Hyalograft C (Fidia Farmaceutici, Italy), it has been associated with cultured chondrocytes and has shown good results at three years comparable to standard ACI [43]. Minimal exposure is required as it may be pres-fitted into the defect. Results in patellofemoral lesions have also been found to be satisfactory [44].

Chitosan is a bicopolymer of glucosamine and N-acetylglucosamine. Its degradation products are non-toxic and are involved in the synthesis of AC, including chondroitin sulphate, dermatan sulphate, hyaluronic acid, keratin sulphate and glycosylated type II collagen. An example of its clinical use is BST Cargel (Biosyntech, Canada) which is a chitosan/glycerol copolymer hydrogel which is mixed with blood and injected into a chondral defect following microfracture. Recent results results in clinical practice have shown an improvement over microfracture alone [45].

2.2.2 Synthetic polymers

Synthetic polymers include ***polylactic acid (PLA), poly glycolic acid (PGA)*** and their derivatives ***poly L-Lactide*** and ***poly(lactic-co-glycolic) acids (PLLA, PLGA)***. They have been used extensively in-vitro and in-vivo partly due to their acceptance by the FDA for their use as suture material since early 80's. They are easy to produce and their dissolution and degradation. May be easily controlled. However, they do not possess natural sites for cell adhesion therefore these often need to be added. They are broken down by a hydrolytic reaction thus high concentrations of acidic by-products and particulates can be released causing inflammation, giant cell reactions and chondrocyte death due to a reduction in pH. Verhaegen et al. have recently published a review of the literature in which the use Trufit CB osteochondral plug (Smith & Nephew, San Antonio,

Texas) is not adviced [46]. Trufit is a biphasic synthetic plug made of polylactide co- glycolide (PLG) which is supplemented with calcium sulphate. It has been designed as an 'off the shelf' osteochondral scaffold for the treatment of small, isolated full thickness osteochondral defects.

2.3 CELLS

It is still not clear if the presence of added cells is essential for cartilage regeneration and, which cells are most suitable. If opting for cell application literature has been focused mainly on chondrocytes or stem cells of different derivations (autogenic or allogeneic).

Chondrocytes: Since the first publication of the ACI technique [19], much attention has been focused on the use of autologous chondrocytes in suspension under a watertight periosteum or collagen patch. However the ability to regenerate hyaline cartilage has not been achieved in a reproducible fashion by this method, two surgeries are required, and the procedure is very expensive. With regards to the eventual repair tissue associated with ACI, it is not clear from which cell source this is generated. Breinin et al have shown similar results in a canine model with ACI compared to a periosteum patch alone [47]. It may be the case that the periosteal progenitor population as well as communication with the bone marrow may provide the improved repair tissue. However, Dorotka et al have shown in a goat model that collagen membranes augmented with a homogenous population of chondrocytes added to a microfracture defect create significantly better repair tissue than microfracture and collagen alone (AMIC) in terms of defect tissue fill and histological grade [48]. These results suggest that adding chondrocytes to collagen matrices may be the key due to the availability of integrin binding sites. Bartlett et al have shown comparable results when chondrocytes are used in suspension with a collagen membrane (ACI-C) versus chondrocytes expanded in the collagen membrane ex-vivo (MACI) [25].

Another method of maintaining the chondrogenic phenotype is characterised chondrocyte implantation (CCI, Tigenix, Leuven Belgium). This involves a genetic marker profile predictive of the capacity to form hyaline-like cartilage in-vivo in a constant and reproducible manner. Saris et al

have compared this technique of cell expansion and implantation to microfracture and found superior histological scores [24].

For the purposes of tissue engineered cartilage repair, an 'off the shelf' option would be more appealing to both patient and surgeon. **Allogeneic chondrocytes** may provide this however little research has been published with their use. Encouraging results from a human pilot study and no adverse events have been reported [49].

Stem Cells: Stem cells by definition have the 'capacity for self renewal or unlimited self-renewal under controlled conditions' and 'they retain the potential to differentiate into a variety of more specialised cell types [50]. Thus, these are cells with multipotent differentiation capacity. It is the **adult mesenchymal stem cell** which is of most interest in AC repair. They represent an autologous supply of cells which can be easily harvested from a number of different tissues including bone marrow, adipose tissue, muscle, periosteum and synovium.

A number of different terms have been used referring to different populations of cells which have resulted in some confusion, such as marrow stromal cells, mesenchymal progenitor cells and mesenchymal stem cells (MSC). The International Society for Cellular Therapy have thus stated cells that qualify as **MSC** need to have **p**lastic adherence in cell culture; positivity for surface antigens including CD105, CD73 and CD90, and negative for haemopoetic markers including CD45 and CD34 and the ability to differentiate into at least osteoblasts, adipocytes and chondroblasts in standard in-vitro conditions [51].

By analysing these characteristic it is possible to differentiate which cell type is being used in the literature. However it is important to notice that some haemopoetic cells such as granulocytes and monocytes often show adherence to plastic. Therefore, a sample of bone marrow separated by density centrifugation and plastic adherence remains a heterogeneous cell population. It is frequent that there is not a "pure" stem cell culture, but rather a culture in which a subset of cells are stem cells [52].

In-vitro, MSC's have been shown the abilityto differentiate into chondrocytes under certain conditions. The application of growth factors such as fibroblast growth factor 2 (FGF-2) and transforming growth factor beta (TGF-β) have been particularly useful.

The majority of in-vivo research using MSC's has used rabbits. Encouraging results have been shown with a number of studies, each using different carrier systems, with improvements in histological and biomechanical endpoints [53]. Most of the researchers employed culture expanded MSC's; however, a fibronectin coated hyaluronan based sponge as a carrier for bone marrow into rabbit full thickness defects without the isolation and expansion of MSC's has been used [54]. In this study no statistical difference in histology was seen between control and treatment groups. This may be due to the small number of MSC's present within the constructs due to lack of concentration and/or expansion. In a recent study a specially designed centrifuge (SmartPReP 2, Harvest Technologies, Plymouth MA) which can concentrate the total nucleated cell number in a bone marrow aspirate by way of density centrifugation has been used. Full thickness cartilage lesions were treated in 12 horses. Improved scores were found in treatment over control groups and 8 months, both macroscopic and histological scores were significantly improved in treatment over control groups [55]. This is extremely important because it has been possible to concentrate MSC's in the operating theatre, without the need for cell culture facilities.

A small number of studies using MSC's in the human population have been published. Human patients underwent high tibial osteotomy and cartilage grafting on the medial femoral condyle with culture expand bone marrow derived MSC's embedded in collagen type I gels [56]. Twelve had MSC seeded defects which at 42 weeks were found to have a cartilage like appearance with hyaline-like cartilage at biopsy. However, this was not statistically different to defects without cells. The same group published a case series using the same system treating patellofemoral defects [57]. Although knee outcome scores had improved with time, biopsy revealed fibrocartilage.

Allogeneic MSC's represent an 'off-the shelf' prospect for cartilage repair. Due to their potential immunopriveledged nature it is possible they can be implanted into defects without rejection. They

do not seem to initiate alloreactive lymphocyte proliferative responses. However, it may be that MSC's require specific carrier materials and the addition of growth factors to stimulate chondrogenic differentiation.

2.4 GROWTH FACTORS

Both chondrocytes and MSC's are influenced by signalling molecules within the ECM which include hormones, cytokines and growth factors. It has been shown that an imbalance between the anabolic and catabolic signalling factors has a significant impact on the development of osteoarthritis. This delicate balnace therefore also plays a significant role in the regenerative process. Growth factors work in the locale environment in an autocrine or paracrine fashion, influencing a variety of cell types. They are often secreted in an inactive form requiring activation. A number of different growth factors have been demonstrated to have an action on AC repair. A specific discussion of the single growth factor is not argument of this thesis, however a list of the main growth factors influencing AC repairis provided:

- Transforming Growth Factor Beta (TGF-β)
- Bone morphogenetic proteins (BMP's)
- Insulin-like Growth Factor-1 (IGF-1)
- Fibroblast growth factor (FGF)
- Platelet Derived Growth Factor (PDGF)
- Vascular Endothelial Growth Factor (VEGF)

Platelet Rich Plasma (PRP): The ability to concentrate platelets and apply them to local defects providing a source of autologous growth factor has become of interest in orthopaedic surgery, particularly AC tissue engineering. It is a relatively cheap and easy way to provide PDGF, TGFβ-1, and FGF-2 directly to a defect without the need to use recombinant proteins which need to be passed through regulatory channels before clinical use.

3. One-step cartilage repair with polyglycolic acid/hyaluronan membrane associated with microfracture and bone marrow concentrate

3.1 INTRODUCTION

Cartilage lesions occur frequently and are a common cause of knee symptoms and disability, and may progress to severe osteoarthritis (OA) [58, 59]. Therefore, an ideal cartilage repair procedure should recreate hyaline-like cartilage, ultimately prevent OA [24] and restore the articular surface. Different surgical options are now available to treat cartilage defects, which have to be chosen mainly according to defect size, patient functional needs and expected cost-effectiveness. Among others, the microfracture (MFX) treatment is a commonly used and cost effective first-line treatment option for focal cartilage defects [12, 60]. In addition, autologous chondrocyte implantation (ACI) and matrix and/or scaffold-assisted ACI [25, 61-64] are regarded as second-line treatment for small and a first line option for defects larger than 2 to 4 cm^2 [65].

The limits of the MFX treatment are with respect to lesion size and to long term functional improvements [24, 66]. However, high costs and the need for two interventions in ACI and ACI-related procedures [67] have prompted the search for new and improved single-stage cartilage repair methods. Autologous matrix-induced chondrogenesis (AMIC) has emerged as a new technique utilizing a porcine collagenic scaffold combined with fibrin glue, autologous serum and microfractures [68, 69]. Newer procedures favour synthetic polymer scaffolds like polyglycolic acid/hyaluronan (PGA-HA) scaffolds for covering of microfractured defects have shown the potential to regenerate hyaline-like cartilage [64, 70-72]. All these techniques have in common that the microfractures should allow for the in-growth of mesenchymal progenitor cells from the subchondral bone into the scaffolds, enrich the cells within the defect and guide them towards cartilaginous tissue formation [73].

Since the number of stem or progenitor cells may be reduced with age [74] and subchondral progenitors may show a low potential to form hyaline-like repair tissue in early osteoarthritis [75],

the enrichment of the defect with autologous BMC or bone marrow-derived cells seems to be attractive. In particular BMC from the iliac crest may be of interest, since twice the percentage of cells show mesenchymal stem cell markers compared to cells harvested from blood during the microfracture procedure [76]. Recently, it has been shown that intra-articular application of iliac crest BMC and marrow aspirate in hyaluronan improved the outcome of the microfracture treatment in full thickness cartilage defect, in the horse model [77] and in the goat model [78]. These findings, for instance, have led to modification of the original single-stage technique involving the addition of BMC to treat talar osteochondral lesions [79].

In this study chondral cartilage lesions have been treated with MFX and defects were covered with PGA-HA scaffolds immersed with autologous BMC from the iliac crest. The aim of this chapter is to analyze the clinical and histological outcome of PGA-HA-covered microfractures and bone marrow concentrate (PGA-HA-CMBMC) [80].

3.2 MATERIALS AND METHODS

3.2.1 Study design

From April to October 2010, nine consecutive patients with symptomatic chondral lesions of the knee underwent arthroscopic MFX and implantation of the PGA-HA matrix (Chondrotissue®, BioTissue AG, Zurich, Switzerland) seeded with autologous BMC from the iliac crest (PGA-HA-CMBMC). After ethical committee approval, full informed consent was obtained from each patient. Inclusion criteria were: lesion size $\geq$ 1,5 cm^2, age $\leq$ 60, chondral defect Outerbridge type III or IV, full rehabilitation protocol compliance, full anamnesis available, signed consent, full surgeon report available. Exclusion criteria were tibia-femoral or patella-femoral mal-alignment, knee instability, kissing lesions, advanced OA, rheumatic arthritis, metabolic or neoplastic diseases. Every patient, after informed consent, was asked to undergo a second look arthroscopy with biopsy for assessing the state of the repair at 12 months follow-up. Every patient was also scheduled for a post-operative MRI with a 1.5 Tesla scanner. Failure was defined as the need of a new surgical procedure to treat persisting pain or effusion in the previously operated knee. Patients were retrospectively analyzed with standardized assessment tools such as the IKDC score [81], the Lysholm score [82], the VAS pain score and the Tegner activity scale [83].

3.2.2 Surgical technique

The CMBMC surgical technique has been described in detail by Gigante et al. [80]. Briefly, for bone marrow harvest, a small area over the iliac crest donor site was draped. A 2.5 mm Jamshidi needle was inserted percutaneously into the iliac crest, sixty ml of bone marrow blood were aspirated and processed with the MarrowStim Concentration kit (Biomet, Warsaw, IN) according to the manufacturer's instructions, obtaining 3-4 ml of BMC. The PGA-HA matrix was immersed with the BMC and kept till implantation.

After diagnostic arthroscopy to confirm the indication for the procedure, the chondral lesion was debrided, measured and microfractures were performed using appropriate awls (Fog. 3.1). The measured size of the lesion was used to adjust a rubber template to the exact shape of the defect.

The PGA-HA matrix was cut to match the defect shape and size. The water flow was stopped and water was aspirated from the joint cavity. A 10:1 mixture of 1-2 mL fibrin glue and BMC was applied to the lesion bed using a long needle. The PGA-HA matrix immersed with BMC was inserted through the appropriate portal with a grasper and placed with a probe. Then an additional 2-3 mL of the fibrin glue-BMC mixture were dispersed over the matrix and allowed to solidify for 2-3 min. Finally, exceeding fibrin glue-BMC was removed and the knee repeatedly flexed and extended to check membrane stability.

For rehabilitation, the patients started continuous passive motion (CPM) on day 4-5 and partial weight-bearing at 3 weeks, progressing to full weight-bearing at 6 weeks. Isometric quadriceps and hamstrings training and straight leg raising were advised during the non-weight-bearing period. Light sports activities such as swimming, cycling or jogging on even soft ground were allowed at 6 months. Permission to participate in unrestricted sports activity was given after 12 months.

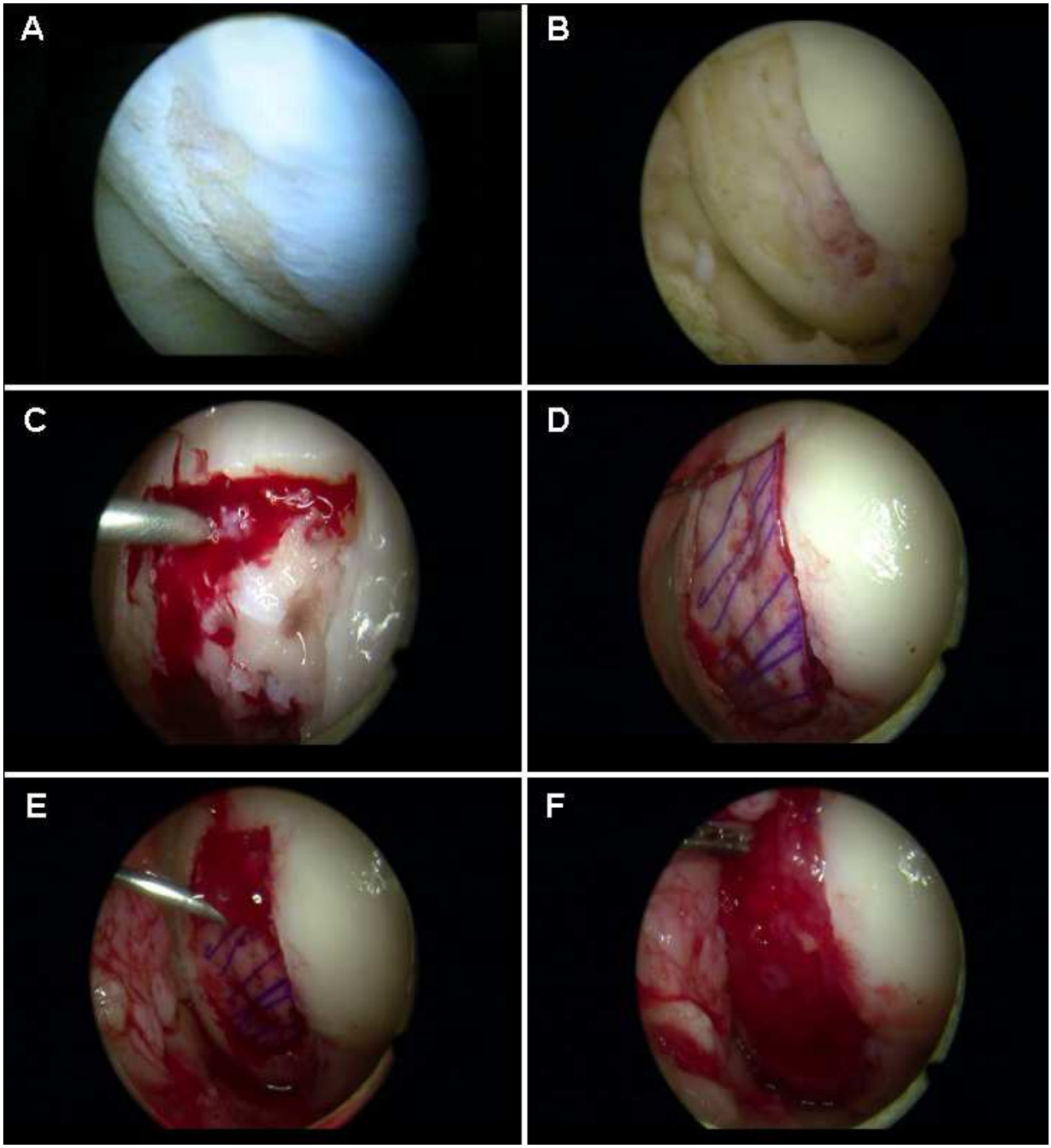

Fig. 3.1 Arthroscopic CMBMC technique. **a** The cartilage defect is identified; **b** debrided and microfracture is performed **c** The water flow is stopped and the mixture of fibrin glue and BMC is deposited on the bed of the defect. **d** The scaffold immersed with BMC is set in place (in this picture a PGA-HA scaffold is represented); **e** and covered with the rest of the fibrin glue-BMC mixture injected through a long needle. **f** Final appearance of the repaired defect. (From Enea et al. 2012 [84])

3.2.3 Second-look arthroscopy

Two patients consented to second-look arthroscopy and biopsy harvest. Three additional patients consented to second-look arthroscopy but did not consent to biopsy. Biopsies were taken with a standard 2.5 mm diameter Jamshidi needle. The specimens were placed in 10% formalin and sent for histology processing.

3.2.4 Histology

Histological characteristics of the repair tissue were evaluated. Specimens were decalcified, paraffin-embedded and stained with Safranin-O to detect the presence of glycosaminoglycans. Polarized microscopy was used to discriminate between hyaline-like cartilage and fibro-cartilage. The International Cartilage Repair Society (ICRS) II Histology Scoring System [85] was used to evaluate the quality of the repair tissue. Histological evaluation was performed blindly by two different investigators and scores were averaged.

3.2.5 Statistical Analysis

The paired t-test was performed for the IKDC score, the Lysholm score and the VAS to compare pre- and postoperative values. Data are expressed as means with standard deviations. The nonparametric Wilcoxon-signed rank test was performed for the Tegner activity scale to compare pre- and postoperative values. Data are expressed as medians and interquartile ranges. For all tests, $p<0.05$ was considered significant. The statistical software SPSS (Version 17.0) was used for biometric analysis.

3.3 RESULTS

3.3.1 Clinical Outcome

Patients' characteristics are shown in Table 3.1. Previous surgeries were: 4 meniscectomies, 3 articular debridement and 1 anterior cruciate ligament (ACL) reconstruction. Concomitant interventions at the time of surgery were 1 ACL calcification removal, 1 osteo-chondral fragment fixation, 1 meniscectomy and 1 trochlear resurfacing. No patient-related or device-related complications were encountered. All patients followed the standardized rehabilitation protocol.

At 22 (+/-2) months follow-up, patients treated with PGA-HA-CMBMC showed significant ($p<0.05$) improvement in IKDC subjective score from 68 pre-operatively to 88 post-operatively, in Lysholm score from 52 to 86 and in VAS pain score from 7.4 pre-operatively to 1.5 post-operatively (3. 2). The Tegner activity scale showed no significant difference from pre-injury (4) to post-operative levels (4) at latest follow-up, but significant improvement in the activity level from post-injury (3) to post-operative activity levels (4).

The procedure failed in one patient, who needed a re-operation due to persisting pain. The patient (latest VAS=8) was subjected to second look arthroscopy that showed the persistence of the defect at the medial femoral condyle. This female patient, with a body mass index (BMI) of 33, is currently losing weight in order to undergo a new surgical intervention.

Table 3.1 Characteristics of patients prior to surgery

Variables	**PGA-HA-CMBMC (n=9)**
Age at surgical intervention [86]	48 (±9)
Gender [Male, n (%)]	5 (55)
Localization [MFC, n (%)]	6(66)
Number of previous surgeries	0.9(±0.3)
Associated pathology [Yes, n (%)]	7 (77)
Correction of pathology [Yes, n (%)]	4 (44)
Lesion size [cm^2]	2.6 (±0.5)
Follow-up [months]	22 (±2)

PGA-HA-CMBMC = polyglycolic acid/hyaluronan-covered microfracture and bone marrow concentrate; MFC = Medial Femoral Condyle

Table 3.2 Outcome data

Score	**PGA-HA-CMBMC (n=9)**
Lysholm Pre-op.	68 (±10) †
Lysholm Post-op.	88 (±18) †
IKDC Pre-op.	52 (±12)†
IKDC Post-op.	86 (±15)†
VAS Pre-op.	7.4 (±2.2) †
VAS Post-op.	1.5 (±2.7) †
Tegner Pre-injury	4 (4-6) α
Tegner Post-Injury	3 (2-3) α, β
Tegner Post-op.	4 (3.5±6) β

PGA-HA-CMBMC = polyglycolic acid/hyaluronan-covered microfracture and bone marrow concentrate; Lysholm, IKDC and VAS are expressed as mean (±SD).Tegner is expressed as median (interquartile range).
† Pre-op. statistically significantly different from Post-op. (t-test); α Pre-injury statistically significantly different from Post-injury; β Post-injury statistically significantly different from Post-op. (Wilcoxon sum rank test). Post-op refers to the latest follow-up.

3.3.2 Arthroscopic and MRI Evaluation

At the time of the second-look arthroscopy all the patients but one were asymptomatic. According to the ICRS CRA evaluation, 1 out of 5 patients treated with PGA-HA-CMBMC was graded normal, 3 nearly normal (Fig. 3.2c, please note the lipid droplet due to biopsy harvest) and 1 abnormal (median 10, range 7-12). The patient scoring 7 was the one that failed.

Four MRI were performed with an average of 10±1.6 months follow-up (range 8-12 months). All patients showed complete defect and volume filling with resurfacing of the articular cartilage to the original cartilage level. Mild bone marrow edema and some subchondral irregularities were observed in all cases. Non-homogeneous cartilage signal was observed in 2 out of 4 cases; fissures were noted in 1 case, surface irregularities in 1 case and a slight hypertrophy of the repair tissue was observed in 1 case.

3.3.3 Histological Evaluation

Biopsies were obtained from two patients. Safranin O staining showed that the repair tissue was rich in proteoglycan and chondrocytic cells. In line with nearly normal MRI findings and improvement in clinical scores, the biopsy proofed hyaline-like repair tissue formation after the implantation of the PGA-HA matrix immersed with autologous BMC. The repair tissue formed in the patient with the failed treatment was rich in chondrocytes but thin and of a fibrocartilagineous appearance. There were no remnants of the PGA-HA matrix and no signs of foreign body reaction or necrosis. According to the ICRS II score they scored respectively an overall of 93 and 41, with a tissue morphology of 100 and 30.

3.4 DISCUSSION

With an average follow-up of 22 months, the PGA-HA-CMBMC technique was safe and effective in improving symptoms of patients affected by focal condylar cartilage lesions, and that the PGA-HA matrix has the potential to induce hyaline-like cartilage repair tissue in microfracture.

In recent years one-step cartilage repair procedures have evolved that target to treat chondral knee defects and to improve the microfracture procedure [71, 72, 86-88]. All these approaches have in common that the microfracture procedure is used to allow progenitor cells to enter the defect. The diverse procedures differ in the type of matrix that is used to cover the defect, the augmentation with autologous blood derivatives and the surgical technique, including collagen matrices or PGA-HA matrices, the addition of platelet-rich plasma (PRP) and the use of all arthroscopic or mini-open procedures [69, 71, 72, 86-89].

Behrens described the original AMIC (autologous matrix-induced chondrogenesis) technique with the use of a porcine collagen type I/III membrane for covering of the microfractured defect and the injection of fibrin mixed with autologous serum underneath the membrane for the treatment of chondral defects [68, 90]. Gille et al. treated large (mean 4cm^2) chondral defects with AMIC and found significant clinical improvement at an average of 37 months follow-up. However, the quality of the regenerated tissue and the level of tissue filling were not ideal with approximately 1/2 of the MRI scans showing incomplete defect filling and subchondral bone abnormalities [69].

In a retrospective cohort study, Kusano and colleagues reported largest clinical improvement in patients treated for osteochondral defects with the AMIC procedure, while defects in the patellofemoral joint and on the femoral condyle showed less improvement. In addition, half of the patients treated for patellar defects required mobilization under anesthesia due to knee stiffness, tissue regeneration was apparently variable and MRI scans revealed some complete filling, some empty defect and some hypertrophic cartilage repair tissue [86]. In a prospective study, Efe et al. used a type I collagen gel for the treatment of small (1 cm^2) cartilage lesions. The technique did not use the microfracture approach and relied on chondrocyte migration from the surrounding healthy

cartilage. The authors reported good clinical results as assessed by IKDC score, Tegner activity scale and the VAS pain score as well as MRI improvements with complete defect filling at up to 2 years follow-up [88]. Siclari et al. treated tibial and femoral cartilage defects in 52 patients with subchondral perforations made by drilling and a PRP-augmented PGA-HA matrix. The authors reported a significant and clinical meaningful improvement at 12 months follow-up as assessed by the Knee injury and Osteoarthritis Outcome Score (KOOS) [72]. Dhollander et al. reported on a pilot study with five patients using microfracture and a PGA-HA matrix enriched with autologous serum. The authors observed noticeable clinical improvement, however, MRI scans revealed different percentages of incomplete filling, subchondral bone irregularities, subchondral cysts and intralesional osteophytes [89]. The same group analyzed another five patients treated with the original AMIC technique combined with a PRP gel. Again, the favorable clinical outcomes were not matched by MRI improvements. At 2 years follow-up, the authors reported persistence of subchondral bone abnormalities, incomplete filling or hypertrophy of the repair tissue and intralesional osteophyte formation [87].

In the present study, the application PGA-HA-CMBMC led to a significant improvement in all the analyzed clinical assessment tools from baseline to the latest follow-up at 22 months. MRI scans revealed the persistence of bone marrow edema and subchondral plate irregularities, but also showed a complete defect fill in all the cases. These good clinical results were obtained in a challenging patient group with advanced age, and multiple previous and concomitant surgical procedures. In particular a higher age is considered to be critical in microfracture. Kreuz and colleagues found better clinical and MRI outcomes at 3 years follow-up in patients younger than 40 years. Patients older than 40 years showed improvement as assessed by the ICRS scoring at follow-up compared to the pre-operative situation, but the scores deteriorated between 1.5 years and 3 years after the surgery [91]. It has to be highlighted that the average lesion size treated in this study, between 2 and 3 cm^2, was small and could have been treated with success with microfracture. However, the good outcome possibly obtained with microfracture has been shown to potentially

decade with time [36]. Therefore it has been hypothesized that adding BMC and a covering membrane could have been helpful in the present group of patients.

Moreover, the results obtained with PGA-HA-CMBMC after 22 months may be promising for a good future outcome, since in ACI the patient status at two years of follow-up is considered as an important indicator [21].

One obese risk patient with a BMI of 33 (1 out of 9 patients, 11%) required a successive surgical intervention for persistence of pain in the knee. This or even a higher percentage of reoperations must be expected when performing cartilage repair procedures [86, 87, 89]. For instance, in ACI, revision surgeries between 0% and 49% [20, 92, 93] have been reported, while graft failures may occur in 5% to 13% of the cases [20, 94].

Only a few studies have investigated the histological outcomes of one-step procedures in the treatment of articular cartilage lesions. Giannini and colleagues reported the use of BMC and PRP gel with a hyaluronic acid-based membrane or a collagen powder to treat talar osteochondral lesions. In this study a functional improvement was observed for all the patients, and 3 biopsies showed different degrees of tissue remodeling towards hyaline-like cartilage [95]. Siclari et al. performed 10 second look arthroscopies and harvested 5 biopsies. The repair tissue was of a tough condition, appeared whiter than the surrounding cartilage and a certain degree of surface irregularity and an asymptomatic hypertrophy was observed. Histological evaluation uniformly showed hyaline-like cartilage repair with good subchondral integration [72]. In the present pilot study, on average, a nearly normal macroscopic appearance of the cartilage repair tissue was found according to ICRS CRA. Histological evaluation of two biopsies revealed one hyaline-like cartilage repair tissue formation and one fibrocartilaginous tissue formation in the risk patient that needed re-operation. Although statistically not relevant, the fact that one out of two patients showed hyaline-like repair tissue formation may be promising if compared to the previously reported results for ACI and ACI-related procedures [28, 96].

This indicates that cells derived from autologous BMC and seeded on a scaffold may differentiate into mature chondrocytes or may stimulate subchondral progenitor cells released by the microfracture procedure to produce a cartilaginous repair tissue when applied in human adult articular cartilage lesions. These clinical observations may confirm recent *in vitro* results that demonstrated that human MSCs from bone marrow aspirate can proliferate on collagen scaffolds and differentiate into chondrocytes without growth factor supplementation [97].

The mean age of the study population was 48±9 years (range 37-60). Therefore it is likely that some degree of degenerative changes occurred at least in some of the patients. Although osteoarthritic defects are in general not or hardly indicated for current cartilage repair techniques, ACI and scaffold-assisted ACI procedure have been shown to have the capability to improve the symptoms in patients with early osteoarthritis and may postpone the need for prosthetic replacement [62, 98, 99]. However, if compared to original ACI, one-step procedures are relatively inexpensive and have been used in older patients with radiologically confirmed degenerative changes (up to 65 years-old) providing pain relief and good histological results [72]. In addition, the PGA-HA matrix can be cut to the size of the defect and can be securely fixated by gluing like shown in this study as well as by cartilage suture, trans-osseous suture or pin/nail fixation [71, 100]. Biomechanical in vitro studies have shown that covering a cartilage defect with the PGA-based matrix restores the joint compression forces towards forces found in normal joints [101]. Therefore, the textile and mechanically stable felt-like structure of the PGA-HA matrix may be favorable for arthroscopic approaches and for the treatment of degenerative defects that lack an intact cartilage rim. However, further clinical studies involving more degenerative and/or osteoarthritic defects are needed, before the use of such approaches can be recommended unrestrictedly to this patient group.

It has to be highlighted that the procedure detailed in this study and the other “one-step” procedures have been introduced just recently in the clinical practice. To date, the potential to maintain high subjective outcomes at long follow up, the potential to avoid or slow down the onset of osteoarthritis and in general the real benefit for the patient has still to be proven against less

expensive procedures such as microfracture. In this regard, randomized controlled trials versus microfracture and/or versus MACI would be highly beneficial.

Limitations of this study are small sample size, short-term follow-up and lack of control group. In addition, the patients were not stratified for presence of early OA with preoperative plain X-ray. The strength of the present study is that isolated condylar lesions of similar size were treated in absence of limb malalignment and major associated concomitant procedures such as ACL reconstruction or unloading osteotomies, in a full arthroscopic approach. This study also provides clinical follow-up using established cartilage repair scoring systems, MRI and biopsies which may represent an objective assessment of the repair capabilities.

In summary clinical and histological data suggest that the arthroscopic implantation of PGA-HA matrices augmented with autologous BMC in microfractured cartilage defects (PGA-HA-CMBMC) provided short-term significant pain relief and functional improvement. A nearly normal arthroscopic appearance of the repair tissue and a good histological quality of the regenerate tissue were obtained. Randomized controlled trials with a larger study population, longer clinical, MRI and histological follow-up are advisable to improve our understanding of this promising one-step procedure.

4. One-step cartilage repair with collagen membrane associated with microfracture and bone marrow concentrate

4.1 INTRODUCTION

Focal cartilage defects may progress to osteoarthritis (OA) [58, 59]. To be effective a cartilage repair procedure should recreate hyaline-like cartilage and ultimately prevent OA [24].

The limits of the microfracture (MFX) treatment with respect to lesion size and to long term functional improvements [24, 66] and the high cost and the need for two operations of the autologous chondrocyte implantation (ACI) and ACI-related procedures [95] have prompted the search for new one-step cartilage repair methods. Autologous matrix-induced chondrogenesis (AMIC) has emerged as a new technique adopting a collagenic scaffold combined with microfractures [69]. Similar procedures have been developed, adopting synthetic polymers like polyglycolic acid (PGA)/hyaluronan in combination with microfracture and have shown the potential to restore hyaline-like cartilage [70-72]. In all these techniques microfracture should permit the migration of mesenchimal stem cells (MSCs) from the subchondral bone, and the scaffold should keep cells *in situ* and serve as support for tissue differentiation.

The intra-articular delivery of bone marrow concentrate (BMC) and marrow aspirate improved the outcomes of microfracture in full thickness cartilage defect in the horse model [77] and in the goat model [78] respectively. This observation may be possibly explained by the fact that the BMC from the iliac crest contains higher concentration of MSCs with respect to tibial or femoral bone marrow blood, and with greater doubling potential [76]. This observation have led to modifications to the original single-stage technique involving the addition of BMC to treat talar osteochondral lesions [95].

In the present study cartilage lesions have been treated with the association of MFX, BMC from the iliac crest and a collagenic coverage scaffold. The aim of this chapter was to analyse

clinical and histological outcomes of collagen-covered microfracture and bone marrow concentrate (C-CMBMC) for the treatment of patients with full-thickness, focal, condylar knee cartilage defect.

4.2 MATERIALS AND METHODS

4.2.1 Study design

From February 2008 to March 2011, nine consecutive patients with symptomatic chondral lesions of the knee underwent all-arthroscopic C-CMBMC. After ethical committee approval, full informed consent was obtained from each patient. Inclusion criteria were: lesion size ≥ 1.5 cm^2, age ≤ 60, chondral defect Outerbridge type III or IV, adherence to the rehabilitation protocol, full anagraphics available, signed consent, full surgeon report available. Exclusion criteria were tibiofemoral or patellofemoral malalignment, knee instability, kissing lesions, advanced OA, rheumatic, metabolic or neoplastic diseases. Every patient, after informed consent, was asked to undergo a second look arthroscopy with biopsy for assessing the state of the repair at 12 months follow-up. Failure was defined as the need of a new surgical procedure to treat persisting pain or effusion in the previously operated knee. Patients were retrospectively analysed with standardized assessment tools such as the International Knee Documentation Committee (IKDC) score, the Lysholm score the VAS and the Tegner activity scale. Patients were also evaluated with MRI scans at variable follow-up.

4.2.2 Surgical technique

The CMBMC surgical technique has been described in detail by Gigante et al.[80] (See figure 4.1). Briefly, a small area over the iliac crest donor site was draped. After diagnostic arthroscopy to confirm the indication for the procedure a 2.5 mm Jamshidi needle was inserted percutaneously into the iliac crest. Sixty mL of bone marrow blood were aspirated and processed with the MarrowStim Concentration kit (Biomet, Warsaw, IN) according to the manufacturer's instructions, obtaining 3-4 mL of BMC.

The chondral lesion was debrided and microfractures were performed using appropriate awls (Fig 4.2). The lesion main dimensions were measured and reported on a rubber template that was then

adjusted to the exact shape of the defect. A Biocollagen MeRG® collagen membrane (Bioteck, Vicenza, Italy) was cut to match the defect shape and immersed in BMC until implantation.

The water flow was stopped and water was aspirated from the joint cavity. A 10:1 mixture of 1-2 mL fibrin glue and BMC was laid on the lesion bed using a long needle. The membrane was inserted through the appropriate portal with a grasper and fitted into place with a probe. An additional 2-3 mL of the fibrin glue-BMC mixture were injected over the membrane and left to solidify for 2-3 minutes. Finally, the excess of the fibrin glue-BMC mixture was removed and the knee repeatedly flexed and extended to check membrane stability.

The patients started continuous passive motion on day 4-5 and partial weight-bearing at 3 weeks, progressing to full weight-bearing at 6 weeks. Isometric quadriceps and hamstrings training and straight leg raising were advised during the non-weight-bearing period. Light sports activities such as swimming, cycling or jogging on even soft ground were allowed at 6 months Permission to participate in unrestricted sports activity was given after 12 months.

Fig. 4.1 Harvest phases: **a** iliac crest is identified; **b** Jamshidi needle is inserted; **c** bone marrow is aspirated; **d** two syringes are filed; **e** syringes contend is injected in the proper cylindrr and centrifuged; **f** final BMC is obtained; **g** membrane is marked ad cut; **h** membrane is soaked in BMC; **i** membrane is delivered

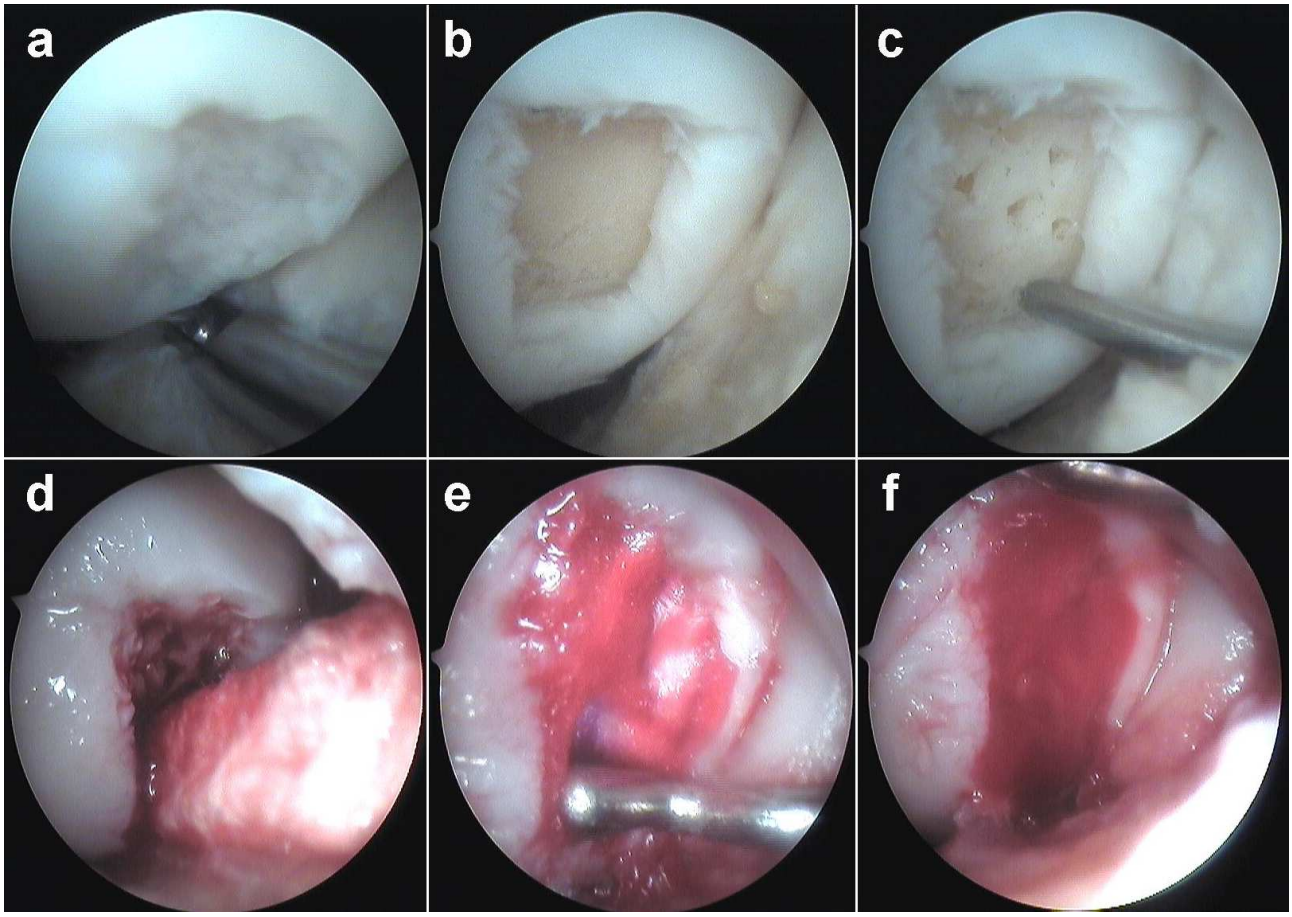

Fig. 4.2 Arthroscopic technique. **a** The cartilage defect is identified; **b** debrided; **c** microfracture is performed with the appropriate awl; **d** The water flow is stopped; **e** and the mixture of fibrin glue and BMC is deposited on the bed of the defect and the collagen matrix immersed with BMC is set in place with a probe; **f** Final appearance of the repaired defect

4.2.3 Second-look arthroscopy

Four patients consented to second-look arthroscopy and biopsy harvest. Biopsies were performed with a standard 2.5 mm diameter Jamshidi needle. The specimens were placed in 10% formalin and sent for histology processing. The quality of the implanted tissue was evaluated by the surgeon using the criteria of the International Cartilage Repair Society [102] Cartilage Repair Assessment (CRA) [102].

4.2.4 Histology

Histological and histochemical characteristics of the repair tissue were evaluated. Specimens were decalcified, paraffin-embedded and stained with Safranin-O to detect the presence of glycosaminoglycans. Polarized microscopy was used to discriminate between hyaline-like cartilage and fibrocartilage. The ICRS II Histology Scoring System [85] was used to evaluate the quality of the repair tissue. Histological evaluation was performed blindly by two different investigators and scores were averaged.

4.2.5 Statistical Analysis

The Student t-test was performed for the IKDC score, the Lysholm score and the VAS to compare pre- and postoperative values. Data are expressed as means with standard deviations. The nonparametric Wilcoxon-signed rank test was performed for the Tegner activity scale to compare pre- and postoperative values. Data are expressed as medians and interquartile ranges. For all tests, $P<0.05$ was considered significant. The statistical software SPSS (Version 17.0) was used for biometric analysis.

4.3 RESULTS

4.3.1 Clinical Outcome

No patient-related complications nor device-related complications were encountered. None of the patients was lost at follow-up. All patients followed the standardised rehabilitation protocol. Patients characteristics and patient-reported outcomes are shown in table 4.1. Associated intervention at the time of surgery were 2 (1 partial meniscectomy and 1 synovectomy) A patient with an unshouldered cartilage defect required a mini-arthrotomy to fix the membrane with polar stitches.

A statistically significant improvement in the mean IKDC subjective score from 49 SD(11) to 82 SD(12), mean Lysholm score from 58 SD(13) to 88 SD(11) and mean VAS from 7.6 SD(1) to 2.3 SD(2.2) from preoperative values to the latest follow-up was obtained ($p<0.05$) (see Table 1 for single values). The median Tegner activity scale showed no significant difference from pre-injury

level of 4 (interquartile range 4-7) to post-operative level of 4 (interquartile range 3.5-6.5) at latest follow-up ($p>0.05$) (see Table 4.1 for single values). On the other hand, a significant increase in the activity level from post-injury 2 (interquartile range 2-3) to post-operative was observed at latest follow-up ($p<0.05$).

One patient (# 9) has met the definition of failure, having undergone a successive surgical procedure for persisting effusion. The patient underwent another cartilage repair procedure in the lateral femoral condyle at another institution; this patient (latest VAS=2, latest Lysholm 82) was not in pain and had a significant improvement from baseline (VAS 7, Lysholm 58), however complained frequent knee effusions after practicing competitive soccer. Another patient (# 7) who did not meet the definition of failure had a worsening of pain and symptoms from baseline (VAS 6, Lysholm 75) to the latest follow-up (VAS 8, Lysholm 68). However his knee function was improved after a cycle of intra-articular platlet rich plasma injections.

4.3.2 MRI evaluation

Three post-operative MRI scans were retrieved with a mean of 7 SD(1.5) months follow-up (range 6-9 months). They have showed in all cases the reconstitution of the original cartilage level. Similarly, bone marrow edema and/or subchondral irregularities were observed in all the cases. Non-homogeneous cartilage signal was observed in 2/3 of the cases; fissurations were noted in 2/3 of the cases, surface irregularities in 1/3 of the cases.

Table 4.1 Patient characteristics and outcome data

Patient	Age	Sex	FU	Side	Size (cm²)	Previous Surgery	Associated Pathology	Associated perocedure	Lysholm pre-op.	Lysholm post-op.	IKDC pre-op.	IKDC post-op.	VAS pre-op.	VAS post-op.	Tegner pre-injury	Tegner pre-surgery	Tegner post-surgery
1	52	f	32	MFC	2.1	2: IM, Sh	chondral lesion II° P/F	-	67	90	51	86	7	3	4	2	4
2	48	f	32	MFC	2.8	1: IM	chondral lesion II° P/F	-	40	96	38	91	7	2	3	2	3
3	36	m	28	MFC	3.0	1: IM	-	-	67	99	57	95	7	3	7	4	7
4	53	m	28	MFC	2.3	3: IM, LCA Cyclop les.	Cyclop lesion, Lat. meniscus rupture, chondral lesion II° F/R	Meniscectomy and shaving	70	78	61	72	9	6	4	2	4
5	41	f	35	MFC	1.8	2: IM, Sh	synovitis	Synovilectomy	40	94	32	84	9	0	4	2	4
6	48	f	28	LFC	2.3	1: IM	chondral lesion II° F/R and LTP	-	51	100	39	98	8	0	6	2	6
7	35	m	14	MFC	3.0	1: IM	-	-	75	68	63	61	6	8	4	2	2
8	48	m	14	MFC	2.8	3: LCA + IM+ MFX, ACI, IM	-	Mini arthrotomy	50	81	54	79	8	3	7	3	6
9	28	m	51	LFC	2.2	1: LM	-	-	59	82	49	78	7	2	9	3	9

FU = follow-up; MFC = medial femoral condyle; IM = internal meniscectomy; Sh = chondral shaving; LCA = anterior cruciate ligament reconstruction; P/F = patello-femoral; MFX = microfracture; ACI = autologous chondrocyte implantation; LTP = lateral tibial plateaux; LFC = lateral femoral condyle; LM = lateral meniscectomy.

4.3.3 Arthroscopic Evaluation

At the time of the second-look arthroscopy all the patients but one were asymptomatic. According to the ICRS CRA evaluation all the 4 C-CMBMC patients were classified as nearly normal (grade 2), the median of the overall assessment being 9.5 (range 9-11).

4.3.4 Histological Evaluation

According to the ICRS II score, the 4 C-CMBMC biopsies scored a mean overall of 64 SD(13), with a mean tissue morphology of 63 SD(19). Hyaline-like matrix was found in only one case (Fig. 4.5d), fibrocartilage was found in two cases (Fig. 4.5a, c) and a mixture of hyaline/fibrocartilage was found in one case (Fig. 4.5b), with hyaline-like cartilage next to the osteochondral junction (Fig. 4.5j) and fibrocartilage next to the articular surface (Fig. 4.5f). Even when hyaline-like cartilage was found, the columnar cell arrangement typical of normal *articular* cartilage was never observed (Fig. 4.5d). The collagen membrane was completely reabsorbed in all the bioptic samples cases.

4.4 DISCUSSION

With a mean of 29 months follow-up, the C-CMBMC technique was shown to be safe and effective in improving symptoms of patients affected by isolated condylar cartilage lesions, and has the potential to induce hyaline-like cartilage repair.

In recent years one-step cartilage repair has become increasingly adopted to treat chondral knee defects [71, 72, 86-89]. The diverse techniques in use mainly differ for the type of scaffold adopted (collagenic [69, 86-88] or PGA/hyaluronan based [72, 89, 101]), for the eventual platlet rich plasma (PRP) augmentation [72, 87] and for the surgical approach (arthroscopic [71, 72, 87] or mini-open [71, 72, 86-89]).

The original AMIC (autologous matrix-induced chondrogenesis) associated MFX, a porcine collagen type I/III membrane and the injection of fibrin mixed with autologous serum underneath the scaffold [68]. Large (mean area 4cm^2) chondral defects have been treated with such technique obtaining a significant clinical improvement at an average of 37 months follow-up. However, the quality of the regenerated tissue and the level of tissue filling were not ideal. Around 1/3 of the MRI scans revealed incomplete defect filling an subchondral bone abnormalities [69].

Kusano et al., in a retrospective study on autologous matrix-induced chondrogenesis (AMIC) did not observed a significant clinical improvement in patients treated for condylar cartilage defects. Moreover, a half of the patients treated for patellar defects required mobilization under anesthesia due to knee stiffness. The authors found inconsistent tissue regeneration. MRI scans revealed some complete filling, some empty defect and some hypertrophic repair [86].

Efe et al. reported on the prospective clinical and MRI follow-up of a three-dimensional collagen gel. The surgical technique did not involve microfracture and relied on chondrocyte migration from the surrounding healthy cartilage. The authors treated 1 cm^2 lesions and reported significant clinical and MRI improvements [88].

Siclari et al. treated 52 patients with the association of subchondral perforations and PRP-augmented PGA/hyaluronan scaffold. The authors reported a statistically significant clinical

improvement at 12 months follow-up [72]. Dhollander et al. reported on a pilot study on the association of microfracture and a PGA/hyaluronan coverage scaffold enriched by autologous serum. The authors observed noticeable clinical improvement, however MRI scans revealed different percentages of incomplete filling, subchondral bone irregularities, subchondral cysts and intralesional osteophytes [89]. The same group analysed patients treated with the original AMIC technique in association with PRP. Again, the favorable clinical outcomes was not matched by MRI improvements. At 2 years follow-up the authors reported persistence of subchondral bone abnormalities, incomplete filling or hypertrophy of the repair and intralesional osteophyte formation [87].

In the present study the C-CMBMC patients obtained a statistically significant improvement in all the analysed assessment tools from baseline to the latest follow-up. MRI scans commonly revealed the persistence of bone marrow edema and subchondral plate irregularities, but also showed a complete defect fill in all the cases. Overall one patient, required a successive surgical intervention to treat persistence of knee effusions the day after practicing competitive soccer. This patient was not in pain having a VAS of 2 at latest follow-up. However this or a higher percentage of reoperations must be expected when performing cartilage repair procedures [20, 86, 87, 89, 94].

More recently peripheral blood progenitors cells or cultured MSCs have been associated with MFX with or without a coverage scaffold to treat knee cartilage defects [103-105]. These procedures have demonstrated to be safe and effective, however they require a first step for the Filgrastim administration and plasma apheresis or for the surgical marrow blood harvest, cell sorting and subsequent culture. Therefore these are not single-stage procedures, require two steps, autologous cells manipulation and are expensive. Moreover the indication for these procedures needs to be confirmed with a previous diagnostic arthroscopy.

Only a few studies have investigated the histological outcomes of one-step procedures in the treatment of articular cartilage lesions [70, 72, 79, 95]. In particular, Giannini et al., associated BMC and PRP gel with a hyaluronic acid membrane or collagen powder to treat talar osteochondral

lesions. In this study a functional improvement was observed for all the patients, and 3 biopsies harvested showed different degrees of tissue remodeling toward hyaline-like cartilage [95]. Siclari et al. performed 10 second look arthroscopies harvesting 5 biopsies. Macroscopic observation showed a whiter appearance of the repairs, a certain degree of hypertrophy and surface irregularity. Histological evaluation uniformly showed hyaline-like cartilage repair with good subchondral integration . In the present study a nearly normal appearance of the repaired tissue was documented according with the ICRS CRA. The histological analysis revealed 1 hyaline-like repairs, 1 mixture of fibrocartilage and hyaline-like cartilage and 2 fibrocartilaginous repairs. The percentage of hyaline-like repair in this study is in line with that previously reported for ACI and ACI-related procedures [28, 96]. The mean overall ICRS II score of both treatment groups of 64 SD(13) is in line with the one recently reported for ACI-related procedures and higher than that reported for microfracture [24, 28]. These histological results indicate that cells derived from autologous BMC and seeded on a scaffold may differentiate into mature chondrocytes and produce a fibrocartilaginous and/or hyaline extracellular matrix when applied in human adult articular cartilage lesions. In particular the presence of hyaline-like cartilage next to the osteochondral junction in the mixed hyaline/fibrocartilage repair could indicate progressive bottom-to-top cartilage remodeling and maturation [106, 107]. These *in vivo* observations confirmed some *in vitro* results that demonstrated that human MSCs from bone marrow aspirate can proliferate on collagen scaffolds and differentiate into chondrocytes without growth factor supplementation [97]. Even though both MFX procedures and one-step procedures adopting scaffolds have been associated with bone osteophytes formation on the bed of the lesion, this was not observed in our patient group neither arthroscopically nor histologically. Since the addition of BMC to the mentioned procedures could theoretically increase this possibility, a longer follow-up is mandatory to explore the potential onset of such bone hypertrophy.

The mean age of the overall population was 43 SD(9) years (range 28-53). Therefore it may be hypotesised that some degree of degenerative changes occurred at least in some of the patients.

However, cartilage repair techniques have been adopted to treat patients with early OA, demonstrating the capability to improve the symptoms and delay the need for prosthetic replacement [108]. Moreover, if compared to original ACI, one-step procedures are relatively inexpensive and have been used in older patients (up to 65 years-old) providing pain relief and good histological results [72].

Limitations of this study are small sample size, lack of control group, and short-term follow up. Moreover the patients were not stratified for presence of early OA with preoperative plain X-ray. The strength of the present study is that isolated condylar lesions of similar size were treated in absence of limb malalignment and major associated confounding procedures such as ACL reconstruction or unloading osteotomies. This study also provides biopsies which represent an objective assessment of the C-CMBMC cartilage repair capabilities.

In summary clinical and histological data suggest that the arthroscopically performed C-CMBMC procedure was safe and provided short-term significant pain relief and functional improvement. A nearly normal arthroscopic appearance of the repair and the potential to regenerate hyaline-like cartilage were documented. A complete fill of the defect was shown by MRI imaging and second-look arthroscopies.

5. Collagen-covered versus Polyglycolic acid/hyaluronan-covered microfracture and bone marrow concentrate.

5.1 RESULTS

5.1.1 Clinical Outcome

No patient-related complications nor device-related complications were encountered. All patients followed the standardised rehabilitation protocol. Patients characteristics according to treatment are shown in Table 5.1. The two treatment groups were homogeneous for all the considered parameters but the number of previous surgical procedures, in that the C-CMBMC group has had a significantly higher number of previous procedures than P/H-CMBMC group ($p=0.03$). Previous surgeries in the C-CMBMC were: 9 meniscectomies, 2 LCA reconstructions, 2 articular debridements, 1 ACI and 1 cyclops lesion removal. Previous surgeries in the P/H-CMBMC were: 4 meniscectomies, 3 articular debridement and 1 LCA reconstruction. Associated intervention at the time of surgery were 2 for the C-CMBMC group (1 partial meniscectomy and 1 synovectomy) and 4 for the P/H-CMBMC group (1 LCA calcification removal, 1 osteochondral fragment fixation, 1 meniscectomy and 1 trochlear resurfacing). In the C-CMBMC group, a patient with an unshouldered cartilage defect required a mini-arthrotomy to fix the membrane with polar stitches. Five patients of the C-CMBMC group and 4 patients of the P/H-CMBMC group were diagnosed of having a cartilage defect by previous explorative arthroscopies or arthroscopies done to treat pre-existing pathologies, the rest of the patients were diagnosed solely by MRI imaging.

Both the treatment groups achieved a statistically significant improvement in the IKDC subjective score, Lysholm score and VAS from preoperative values to the latest follow-up ($p<0.05$) (Table 5.2). For both groups the median Tegner activity scale showed no significant difference from pre-injury to post-operative levels at latest follow-up ($p>0.05$) (Table 5.2). On the other hand, a significant improvement in the activity level from post-injury to post-operative activity levels was observed at latest follow-up ($p<0.05$). In the overall CMBMC population (mean follow-up 26±9

months) the mean Lysholm, IKDC and VAS scores significantly improved from baseline (63±12; 50±12; 7.5±1.6 respectively) to latest follow-up (88±14; 84±13; 1.9±2.5 respectively). Similarly, the median Tegner activity scale significantly improved form post-surgery (2, interquartile range 2-3) to the latest follow-up (4, interquartile range 3.75-6).

One patient of each group have met the definition of failure, having undergone a successive surgical procedure for persisting pain or effusion. The C-CMBMC patient underwent another cartilage repair procedure in the LFC at another institution; this patient (latest VAS=2) was not in pain but complained frequent knee effusion after practicing competitive soccer. The P/H-CMBMC patient (latest VAS=8) underwent a subsequent arthroscopy which have shown the persistence of the MFC defect; this female patient, with a BMI of 33 is currently achieving appropriate body loss in order to undergo a new surgical intervention. Another C-CMBMC patient who did not meet the definition of failure had a worsening of pain and symptoms from baseline (VAS 6, Lysholm 75) to the latest follow-up (VAS 8, Lysholm 68).

Seven post-operative MRI scans (3 C- and 4 P/H-CMBMC) were retrieved with an average of 9±2 months follow-up (range 6-12 months). They have showed in all cases the reconstitution of the original cartilage level. Similarly, bone marrow edema and/or subchondral irregularities were observed in all the cases. Non-homogeneous cartilage signal was observed in 4/7 of the cases.; fissurations were noted in 3/7 of the cases, surface irregularities in 2/7 of the cases and a slight hypertrophy of the implant was observed in 1/7 of the cases. There was consistency of the reported observations among the two treatment groups.

5.1.2 Arthroscopic Evaluation

At the time of the second-look arthroscopy all the patients but one were asymptomatic. According to the ICRS CRA evaluation all the 4 C-CMBMC patients were classified as nearly normal (grade 2), the median of the overall assessment being 9.5 (range 9-11). Out of 5 P/H-CMBMC patients 1

was graded normal, 3 nearly normal and 1 abnormal (median 10, range 7-12). The patient scoring 7 was the one that failed, another patent scoring 8 (low quality repair) was asymptomatic.

Table 5.1 Baseline characteristics of patients according to treatment

Variables	**Collagen CMBMC (n=9)**	**PGA-Hyal. CMBMC (n=9)**	**P**
Age at surgical intervention [years]	43 (±9)	48 (±9)	n.s.§
Gender [Male, n (%)]	5 (55)	6 (66)	n.s.*
Localization [MFC, n (%)]	7(77)	6(66)	n.s. *
Number of previous surgeries	1.7 (±0.9)	0.9(±0.3)	0.03§
Associated pathology[Yes, n (%)]	5 (55)	7 (77)	n.s. *
Correction [Yes, n (%)]	2 (22)	4 (44)	n.s. *
Size [cm^2]	2.5 (±0.4)	2.6 (±0.5)	n.s. §
Follow-up [months]	29 (±11)	22 (±2)	n.s. §

§t-test; *Fisher's Exact Test; MFC=Medial Femoral Condyle

5.1.3 Histological Evaluation

According to the ICRS II score, the 4 C-CMBMC biopsies scored a mean overall of 64±13, with a mean tissue morphology of 63±19. Hyaline-like matrix was found in only one case, fibrocartilage was found in two cases and a mixture of hyaline/fibrocartilage was found in one case, with hyaline-like cartilage next to the osteochondral junction and fibrocartilage next to the articular surface. The 2 P/H-CMBMC biopsies scored respectively an overall of 93 and 41 (mean 67±37), with a tissue morphology of 100 and 30 (mean 65±45). The low-scoring biopsy was of the failed patient.

Even when hyaline-like cartilage was found, the columnar cell arrangement typical of normal *articular* cartilage was never observed. The collagen membrane was completely reabsorbed in all the bioptic samples cases (Fig 5.1).

Table 5.2 Patient-reported outcome data

Score	Collagen CMBMC (n=9)	PGA-Hyal. CMBMC (n=9)	Overall CMBMC (n=18)
Lysholm Pre-op.	58 (±13)§	68 (±10) †	63 (±12) *
Lysholm Post-op.	88 (±11) §	88 (±18) †	88 (±14)*
IKDC Pre-op.	49 (±11)§	52 (±12)†	50 (±12)*
IKDC Post-op.	82 (±12)§	86 (±15)†	84 (±13)*
VAS Pre-op.	7.6 (±1.0) §	7.4 (±2.2) †	7.5 (±1.6) *
VAS Post-op.	2.3 (±2.2) §	1.5 (±2.7) †	1.9 (±2.5) *
Tegner Pre-injury	4 (4-7) α	4 (4-6) α	4 (4-6.5) α
Tegner Post-Injury	2 (2-3) α, β	3 (2-3) α, β	2 (2-3) α, β
Tegner Post-op.	4 (3.5-6.5) β	4 (3.5±6) β	4 (3.75-6) β

Lysholm, IKDC and VAS are expressed as mean (±SD).Tegner is expressed as median (interquartile range).§,†,* Pre-op. statistically significantly different from Post-op. (t-test); α Pre-injury statistically significantly different from Post-injury; β Post-injury statistically significantly different from Post-op. (Wilcoxon sum rank test). Post-op refers to the latest follow-up.

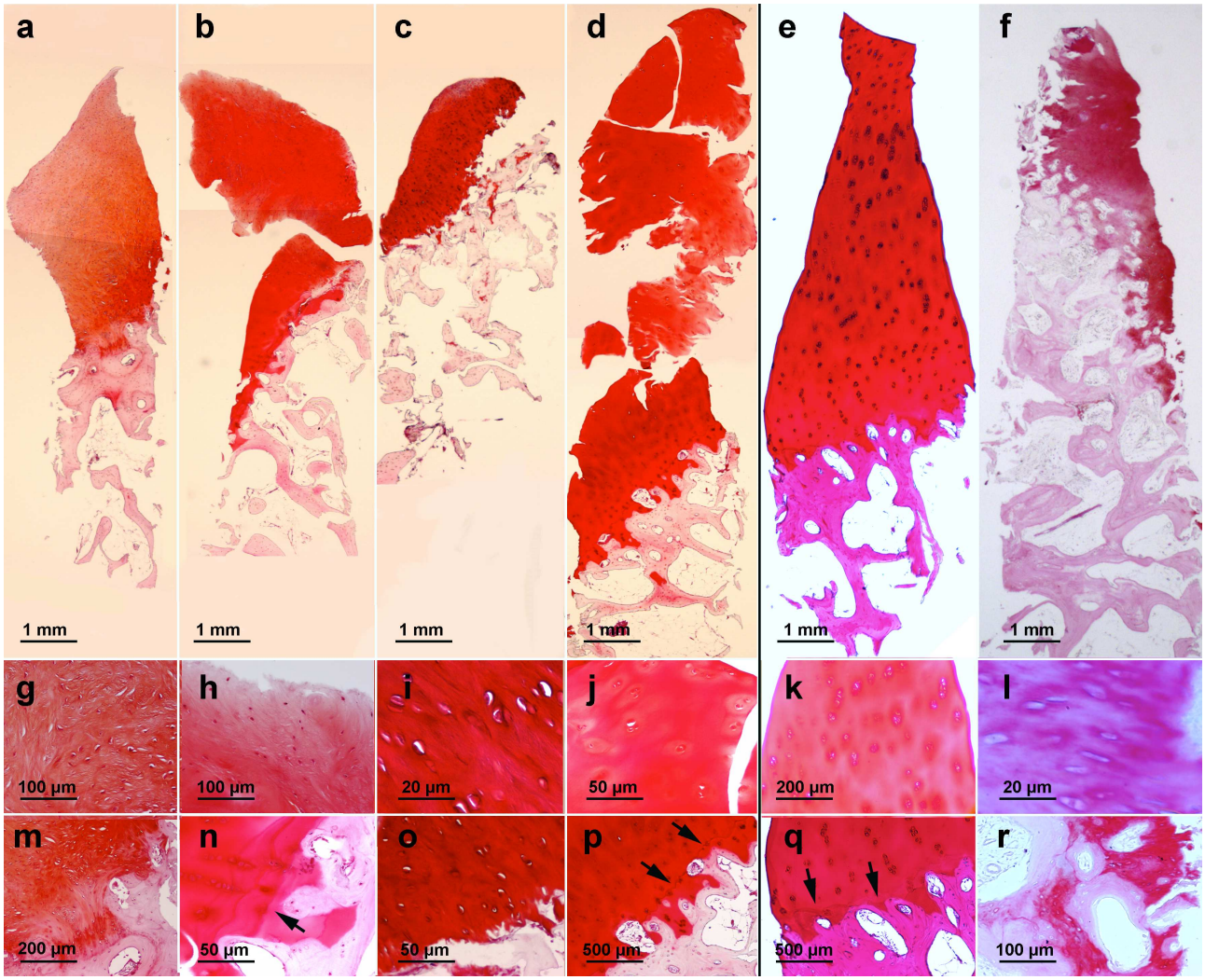

Fig. 5.1 : Biopsies stained with safranin-O. Each column represents a single biopsy (**a-d** are C-CMBMC; **e** and **f** are PGA-HA-CMBMC); Line **a-f** represents the entire bioptic cylinder; line **g-l** represents the chondral matrix; line **m-r** represents the osteochondral junction. Biopsies **a**, **c** and **f** represent a fibrocartilagineous repair. Cells are in fact clearly chondrocytes, but collagen fibres can be seen running within the matrix in different directions (**e, g** and **l**). It has to be noted that the thickness of biopsies **c** and **f** is reduced. Biopsies **d** and **e** represent hyaline-like cartilage repair. They show chondrocytes in large, round lacunae and a glassy matrix with a metachromatic staining for safranin-O (**j** and **k**) and tide mark reconstitution (**p** and **q**, arrows). Biopsy **b** represents a mixed hyaline-like/fibrocartilagineous repair where fibrocartilage may be observed towards the articular surface (**h**) and a glassy matrix with the tide mark reconstitution may be observed close to the osteochondral junction (**n**, arrows). Pictures **d** shows large clefts in the chondral substance which may be artefacts from biopsy harvesting or sample cutting.

5.2 DISCUSSION

The CMBMC surgical thecnique either collagen-covered or PGA/hyaluronan-covered was safe and effective in improving symptoms of patients affected by isolated condylar cartilage lesions, and has the potential to induce hyaline-like cartilage repair. No differences were observed between the two treatment methods.

In recent years one-step cartilage repair has become increasingly adopted to treat chondral knee defects [49, 71, 72, 86, 88, 89] [71, 72, 86-89]. The diverse techniques in use mainly differ for the type of scaffold adopted (collagenic [69, 86-88] or PGA-hyaluronan based [71, 72, 89]), for the eventual platlet rich plasma (PRP) augmentation [72, 87] and for the surgical approach (arthroscopic [71, 72, 87] or mini-open [71, 72, 86-89]).

Gille et al. described the original AMIC technique. The authors treated large (mean area 4cm^2) chondral defects obtaining a significant clinical improvement at an average of 37 months follow-up. However, the quality of the regenerated tissue and the level of tissue filling were not ideal. Around 1/3 of the MRI scans revealed incomplete defect filling an subchondral bone abnormalities [69].

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Siclari et al. treated 52 patients with the association of subchondral perforations and PRP-augmented PGA/hyaluronan scaffold. The authors reported a statistically significant clinical improvement at 12 months follow-up [72]. Dhollander et al. reported on a pilot study on the

association of microfracture and a PGA/hyaluronan coverage scaffold enriched by autologous serum. The authors observed noticeable clinical improvement, however MRI scans revealed different percentages of incomplete filling, subchondral bone irregularities, subchondral cysts and intralesional osteophytes [89]. The same group analysed patients treated with the original AMIC technique in association with PRP. Again, the favorable clinical outcomes was not matched by MRI improvements. At 2 years follow-up the authors reported persistence of subchondral bone abnormalities, incomplete filling or hypertrophy of the repair and intralesional osteophyte formation [87].

In the present study both the C-CMBMC group and the P/H-CMBMC group obtained a statistically significant improvement in all the analysed assessment tools from baseline to the latest follow-up. MRI scans commonly revealed the persistence of bone marrow edema and subchondral plate irregularities, but also showed a complete defect fill in all the cases. Overall 2 patients (11%), one for each group, required a successive surgical intervention for persistence of pain or effusion in the knee. However this or a higher percentage of reoperations must be expected when performing such procedures [86, 87, 89].

More recently peripheral blood progenitors cells or cultured MSCs have been associated with MFX with or without a coverage scaffold to treat knee cartilage defects [103-105]. These procedures have demonstrated to be safe and effective, however they require a first step for the Filgrastim administration and plasma apheresis or for the surgical marrow blood harvest, cell sorting and subsequent culture. Therefore these are not single-stage procedures, require two steps, autologous cells manipulation and are expensive. Moreover the indication for these procedures needs to be confirmed with a previous diagnostic arthroscopy. On the contrary in the present study nine out of 18 patients were diagnosed solely by preoperative MRI scans demonstrating that the CMBMC technique can be a real one-step procedure.

Only a few studies have investigated the histological outcomes of one-step procedures in the treatment of articular cartilage lesions [70, 72, 79, 95]. In particular, Giannini et al., associated

BMC and PRP gel with a hyaluronic acid membrane or collagen powder to treat talar osteochondral lesions. In this study a functional improvement was observed for all the patients, and 3 biopsies harvested showed different degrees of tissue remodeling toward hyaline-like cartilage [95]. Siclari et al. performed 10 second look arthroscopies harvesting 5 biopsies. Macroscopic observation showed a whiter appearance of the repairs, a certain degree of surface irregularity and an hypertrophy. Histological evaluation uniformly showed hyaline-like cartilage repair with good subchondral integration [72]. In the present study both treatment groups showed on average a nearly normal appearance of the repaired tissue according with the ICRS CRA. Similarly the histological analysis revealed a comparable ICRS II score among the two treatment groups. Overall the CMBMC leaded to 2 hyaline-like repairs (33%), 1 mixture of fibrocartilage and hyaline like cartilage (11%) and 3 fibrocartilaginous repairs (66%). The percentage of hyaline like repair in this study is somewhat higher than that previously reported for ACI and ACI-related procedures [28, 96]. The mean overall ICRS II score of both treatment groups (65±19) is in line with the one recently reported for ACI-related procedures and higher than that reported for microfractures [24, 28]. These histological results indicate that cells derived from autologous BMC and seeded on a scaffold may differentiate into mature chondrocytes and produce a fibrocartilaginous and/or hyaline extracellular matrix when applied in human adult articular cartilage lesions. In particular the presence of hyaline-like cartilage next to the osteochondral junction in the mixed hyaline/fibrocartilage repair could indicate progressive bottom-to-top cartilage remodelling and maturation [106, 107]. These *in vivo* observations confirmed some *in vitro* results that demonstrated that human MSCs from bone marrow aspirate can proliferate on collagen scaffolds and differentiate into chondrocytes without growth factor supplementation [97].

The mean age of the overall population was 48±9 years (range 28-60). Therefore it may be hypotesised that some degree of degenerative changes occurred at least in some of the patients. However, cartilage repair techniques have been adopted to treat patients with early OA, demonstrating the capability to improve the symptoms and delay the need for prosthetic

replacement [98]. Moreover, if compared to original ACI, one-step procedures are quite inexpensive and have been used in older patients (up to 65 years-old) providing pain relief and good histological results [72].

Limitations of this study are small sample size, lack of control group, and short-term follow up. Moreover the patients were not stratified for presence of early OA with preoperative plain X-ray. A further weakness is that the number of previous procedures was not homogeneous between the two examined groups. The strength of the present study is that isolated condylar lesions of similar size were treated in absence of limb malalignment and major associated confounding procedures such as LCA reconstruction or unloading osteotomies. This study also provides biopsies which represent an objective assessment of the repair capabilities [109].

5.3 CONCLUSIONS

In summary our clinical and histological data suggest that the arthroscopically performed CMBMC procedure provided short-term significant pain relief and functional improvement. A nearly normal arthroscopic appearance of the repair and a good histological quality of the regenerate tissue were obtained. As hypotesised, no significant differences were observed when a collagenic or a PGA/hyaluronan scaffold were adopted. Randomized controlled trials with a larger population, longer clinical, MRI and histological follow-up are advisable to improve our understanding of this promising one-step procedure.

Part II

New Frontiers in

Joint Substitution

6. Brief history of condylar knee replacement

6.1 INTRODUCTION

The first attempt of treating patients affected by knee osteoarthritis with arthroplasty go back up to the mid-nineteenth century with the use of either a soft tissue interposed within the joint surface or resection of a different amount of bone of both distal femur and proximal tibia.

However the concept on which total joint replacement is based can be traced only after the 1880 in Berlin with Thermestocles Gluck who gave a series of lectures describing a system of joint replacement by unit made of ivory (Fig 6.1.1). The surgeon believed that these unit could be stabilized in bone with cement made of colophony, pumice and plaster of Paris.

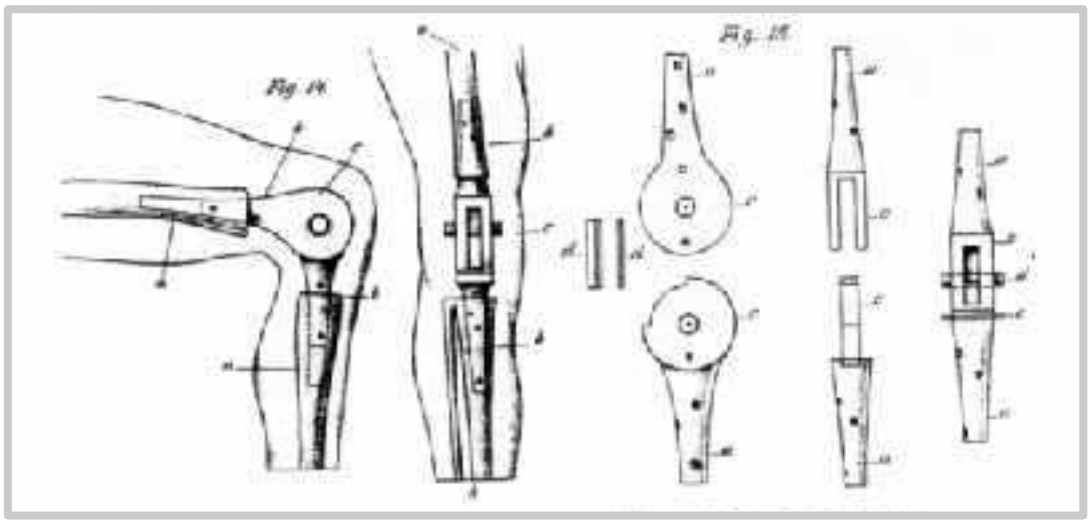

Fig 6.1.1 Gluck's ivory knee

The early twentieth saw the return of interposition arthroplasty with the use of autologous tissue or metallic surface (Campbell and Smith-Petersen, 1940, Fig. 6.1.2) and in the 1950s was developed the first surface replacement of the tibia by McKeever (McKeever, 1960, Fig. 6.1.3) [110]. Only during the 1950s and 1960s at last the knee arthroplasty concept diverged into two theories of total joint replacement: the designer focused their effort toward constrained (or hinged) prosthesis or toward condylar replacement. Moreover in the 1960 methyl-methacrylate was introduced as a

fixation material (definitely FDA approved for general use in US in 1971) and in 1963 high density polyethylene plastic was introduced as a bearing surface.

Fig. 6.1.2 Campbell's interposition device

Fig 6.1.3 McKeever tibial replacement

Condylar replacement knee prosthesis is defined as one where the femoral and tibial load bearing surface are replaced with non connected artificial components. Work on the design of an implant that resurfaced the distal femur and proximal tibia without any direct mechanical link between the components began at the end of sixties at the Imperial College in London. The original design known as Freeman-Swanson (1971) prosthesis consisted of a metal "roller" placed on the distal femur that articulated with a polyethylene tibial tray and requires resection of both cruciate ligaments (Fig. 6.4). It was the first cemented functional design condylar knee. It had equal flexion and extension cuts. It was FDA approved with the name of ICLH knee.

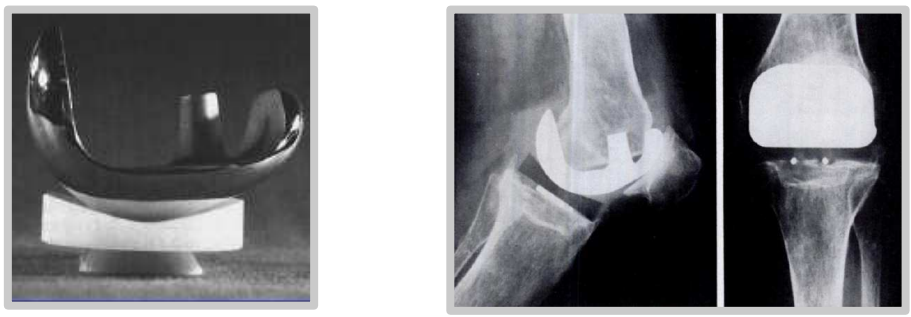

Fig. 6.1.4 Freeman-Swanson knee and a postoperative ICLH radiograph (from Gibbs A. N. et al. 1979 JBJS)

In other part of the world were developed different experiences which carried out to Polycentric knee by Gunston in 1970 (Fig. 6.1.5), Geomedic knee by Averill in 1971 which was the first cemented criciate sparing system (Fig. 6.1.6) and Duocondylar knee (Fig. 6.1.7) system.

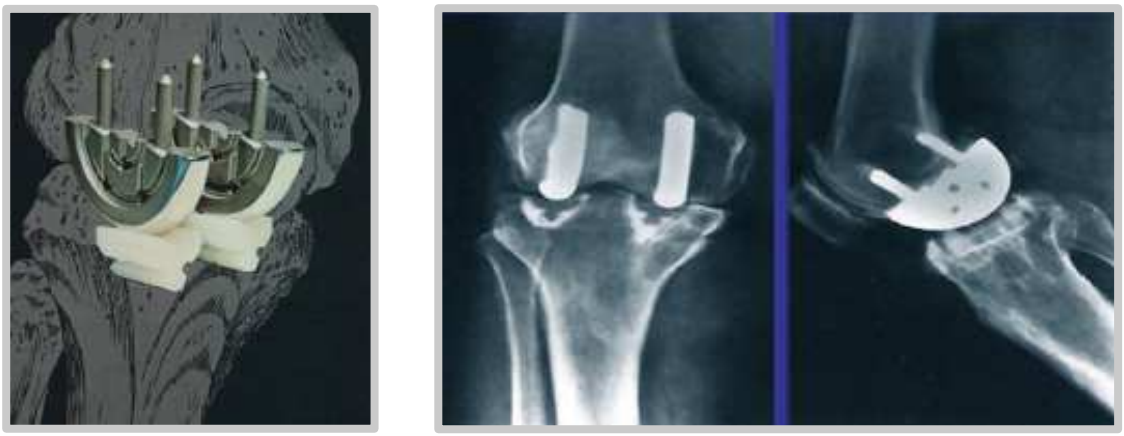

Fig. 6.1.5 Polycentric knee

Fig 6.1.6 Geomedic knee

Fig. 6.1.7 Duocondilar knee

Even if all of these implants were considered unsatisfactory because of a high percentage components mobilizations, break of the components and infection the acquired experience permitted the resurfacing prosthesis planning [111] to occur its successive design phase followed two different ways : the anatomical approach and the functional approach [112].

6.2 ANATOMICAL APPROACH

Anatomical approach based on preserving both cruciate ligaments. The prosthetic geometries were difficult to design and manifacture, the surgery was considered too complex for most surgeons also because of cruciate sparing. However Yamamoto, from the Okayama University Medical School in Japan, was the first to report on implanting an anatomical femoral component with a minimally constrained single-piece polyethylene tibial component in 1970 [113]. The design called the Kodama-Yamamoto knee, consisted of an anatomical femoral mold component, including an anterior femoral flange, made of COP alloy (Co, Cr, Ni, Mo, C, and P). There was a single piece, mildly dished polyethylene tibial component that had a central cutout for preservation of both cruciate ligaments (Fig. 6.2.1).

Fig. 6.2.1 Kodama-Yamamoto knee

Others Authors who followed the same approach were Waugh and Smith who developed in 1971 the UCI knee [114] at the University of California. It had a flat metal backed polyethylene which allowed almost unrestricted rotational freedom and cruciate sparing. In fact it was the first real minimally constrained design. It had not an anterior femoral flange, but a blade to allow for femoral stabilization (Fig 6.2.2).

Fig. 6.2.2 The UCI knee

Townley in 1971 developed the cemented Anatomical knee which had anatomically shaped asymmetrical femoral condyles and asymmetrical patellar flange, largely nonconforming articular surfaces and a tibial gap for cruciate sparing. It was the first prostesis to have a patellar button (Fig. 6.2.3)

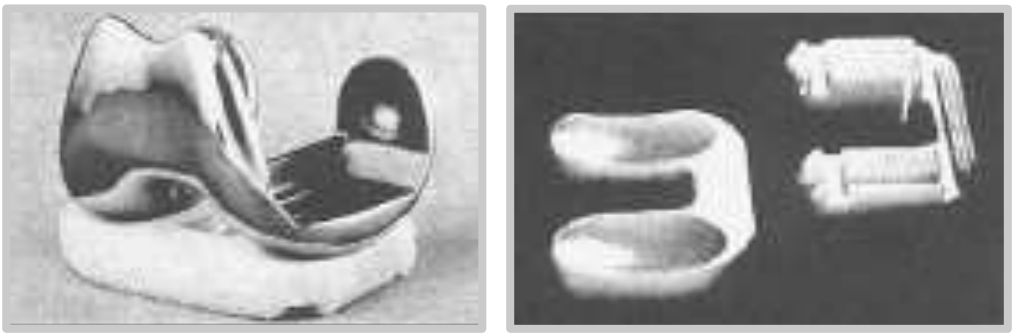

Fig. 6.2.3 The Anatomical Knee

Sheedom developed in 1972 the Leeds knee. It had an anterior anatomical femoral flange and a geometry which allowed for substantial anterior-posterior and rotational laxity in flexion. Polyethylene had to small stems and allowed for cruciate retaining (Fig. 6.2.4).

Fig 6.2.4 The Leeds Knee

At the Hospital for Special Surgery, during the early seventhies (1974), the Duocondylar knee was completely redesign in an anatomical and symmetrical design by Ranawat: the Duopatella (Fig.6.2.5). It had an anterior femoral flange coupled with a patellar button, and a more dished tibial surface were added. The tibial component had a fixation peg (identical to the Total Condylar knee, the archetype of the functional approach) and a small posterior rectangular cutout specifically designed for the preserved posterior cruciate ligament: it was the first prosthesis to sacrifice only the ACL.

Fig. 6.2.5 Duopatella knee

Although the results of Duopatella were extremely good at the HSS the posterior cruciate–preserving approach would be developed in Boston at the Robert Breck Brigham Hospital [114-116]. In Boston the medial tip of the femoral trochlear flangewas removed, creating right and left designs based on the asymmetry of the proximalfemoral flange. This was done to reduce the medial overhang seen in small female rheumatoid patients. The posterior cruciate–sparing version of the Robert Brigham Hospital would later evolved in the PFC knee (Cintor Division of Codman; later, Depuy, Johnson & Johnson) (Fig 6.2.6).

Fig. 6.2.6 PFC Knee

At the same time Peter Walker, Clement Sledge and Fred Ewald, continued the Duopatella concept in the posterior cruciate–retaining version of the Kinematic knee (Howmedica) (fig 6.2.7), which was implanted by Ewald in June 1978. This would evolve into the posteriorcruciate–sparing version of the Kinematic II, Kinemax, and Kinemax Plus systems (Howmedica).

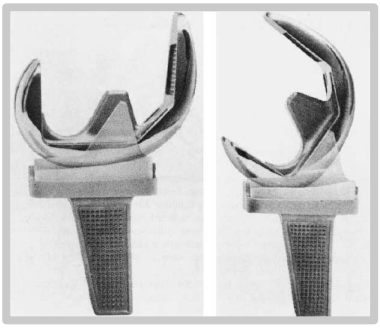

Fig 6.2.7 The Kinematik Stabilizer knee (here the PS versioni s shown)

The 80's saw the significant advances in the knee arthroplasty, particularly in the area of surgical technique and instrumentation. Kenna, Hungerford, and Krackow participated in the design of the instruments that were later called the Universal Instruments. Their tools were based on the anatomical concept of measured resection technique rather than the more functional approach of creating equal and parallel flexion and extension gaps which where used until then. The principal aspect of this new conception was that the bone and cartilage removed were to equal the thickness of the prosthetic material replacing them. Up until this time, fixation of the condylar total knee was primarily achieved with cement.

In January 1980 the first Porous-Coated Anatomical Knee (PCA) was inplanted by Hungerford at Johns Hopkins [117]. The implant was anatomical with asymmetric medial and lateral femoral condyles similar to the Leeds and the original Townley designs. However, for the first time, it introduced porous coating in a total condylar knee for a cementless fixation. Moreover it featured heat pressed polyethylene for weight bearing. Each of the 3 components was backed with metal and a 1.5-mm-thick sintered porous coating of cobalt chrome beads (Fig. 6.2.8).

Fig. 6.2.8 The PCA knee

The Miller-Galante total knee, one of the first knee replacement designed for use with cement or cementless fixation, was first implanted in 1986. The principal innovation of this implant was the choice of a titanium fiber composite for the bony ingrowth surface, because of its well-recognized biocompatibility, and the use of a Titanium Aluminums and Vanadium alloy (Ti6Al4V). The implant is fixed to the tibia with titanium screws and pegs.

The uncemented version for patellar resurfacing consists of a metal-backed patella which is fixed with fiber-mesh pegs. Modularity of tibial polyethylene inserts was incorporate in order to allow better ligamentous tension and possibility of future isolated polyethylene replacement (Fig. 6.2.9).

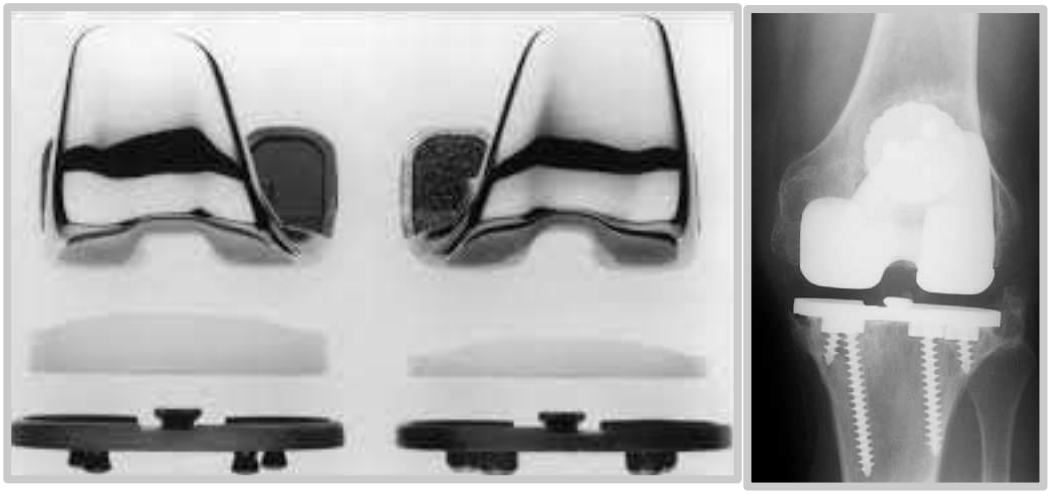

Fig. 6.2.9 The Miller-Galante knee

"Cruciate retaining" prosthesis developed from the anatomical concept were different: some consisted of a relatively flat surface on the sagittal and transversal plane (Kinemax e PCA) while others maintained a more congruent surface on the sagittal plane. Genesis II (Smith&Nephew), Duracon (Howmedica), Nexgen CR (Zimmer), PFC CR (Depuy) represent some actual examples of this conception.

6.3. FUNCTIONAL APPROACH

Designers of the functional approach tried to simplify the knee biomechanics by removing both cruciate ligaments. The ancestor of this concept is considered the Freeman-Swanson knee (ICLH) developed in the early seventies. The first widely used system derived from the functional concept is represented by the Total Condylar prosthesis (TC; Fig. 6.3.1) developed in 1973 at the Hospital for Special Surgery of New York [118].

Fig. 6.3.1 Total Condylar knee

TC prosthesis consisted of two symmetric condylar surfaces with a posterior decreasing radius of curvature and an articular surface made of polyethylene, perfectly congruent in extension and partially congruent in flexion. The TC knee would prove to be highly successful, widely used, and would later demonstrate long survival [119]. Two concerns, however, pointed out the early fases of its clinical use. The femoral component would shift forward, particularly in flexion. In rare cases, this would even result in tibial loosening or anterior dislocation. The second concern was the limited flexion achieved. Average knee flexion with the TC knee was in fact 90° degrees [112].

In 1978 prosthesis Insall-Burstein was designed to correct these problems by replacing the posterior cruciate ligament with a mechanical lock to reduce posterior translation of the femoral component by using a mechanism of a cam articulated with a post on the tibial component.

Fig. 6.3.2 IBPS metal backed (IBPS-II) and allpoly (IPBS-I)

The cam of the femoral component connected with the tibial central spine at about 70 degrees of flexion and then the femur could roll-back so to increase flexion.The first IBPS knee was implanted in 1978 by Insall at the HSS (Fig 6.3.2). The IBPS knee become one of the most successful total condylar knee design [120]. Anterior femoral subluxation was eliminated and average flexion would be 115°. A metal-backed monoblock IBPS tibial component with direct-molded polyethylene was introduced in November 1980: the Insall-Burstein Modular (IBPS II) knee Zimmer [121] (Fig. 6.3.2). The HSS posterior-stabilized knee design would evolve into the Optetrak Posterior-Stabilized knee in 1994, and the Advance Posterior- Stabilized knee (Wright Medical) in 1994.

In the 1980s and 1990s, many variations of these functional designs were introduced by different manufacturers. All of them had the characteristic to produce their motion through a so called **guided motion**, which mean that some characteristics of the motion, such as rollback, are produced by mechanical interaction between the femoral and tibial components. In the Kyocera Bi-Surface knee (Kyocera Corp, Kyoto, Japan; Fig.6.3.3) , for the major part of the flexion range, the knee behaves as a standard condylar replacement with moderately conforming bearing surfaces. Beyond that, the load is transferred to a spherical surface protruding behind from the femoral intercondylar region, contacting within a spherical depression at the posterior of the plastic tibial component.

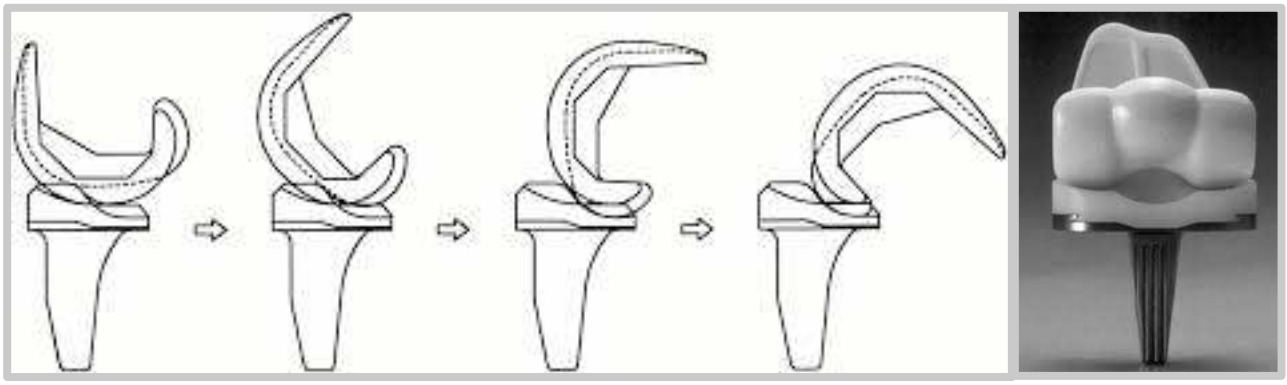

Fig. 6.3.3 The Bisurface knee prosthesis

Another example of guided motion knee is represented by The Medial Pivot knee (Wright Mfg Co, Memphis, TN; Fig. 6.3.4). In that prosthesis the femoral component owns a single radius of femoral curvature and a high level of conformity in the medial compartment where a ball and socket configuration is present. In reason of that configuration the medial side remains in the same position during flexion, but the lateral femoral condyle can displace behind with flexion. The purpose of the medial pivot design is to reproduce a more physiological kinematics with a spherical condylar surface contacting within a spherical depression at the posterior of the polyethylene.

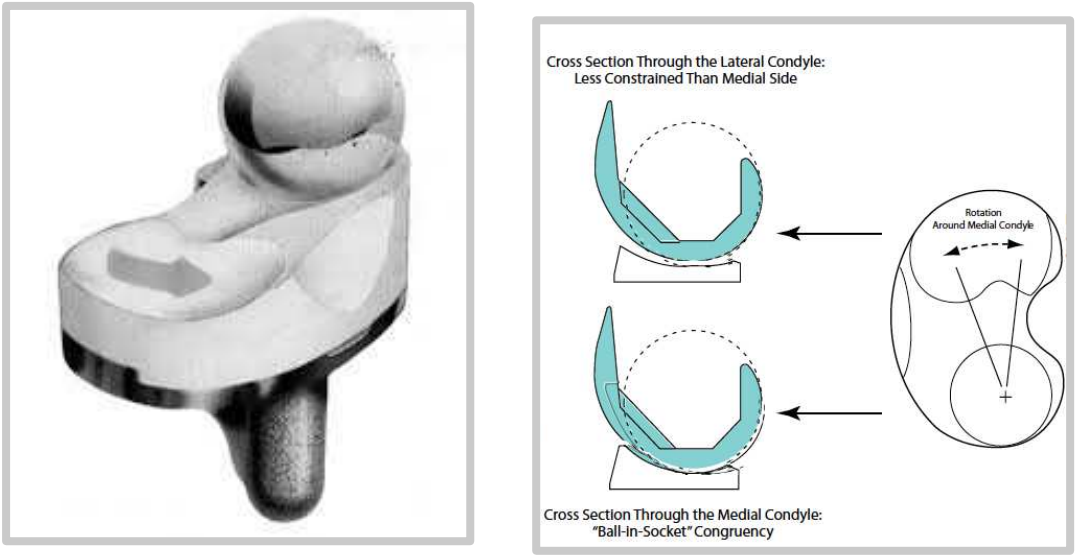

Fig. 6.3.4 The Medial Pivot Knee

One of the most innovative functional approaches to condylar total knee design evolved from a collaboration between an orthopedic Surgeon at the New Jersey Medical School Frederic Buechel and a professor of mechanical engineering Michael Pappas. Their project to achieve a low polyethylene contact stresses while maintaining knee flexion and avoiding overload of the implant bone interfaces started in 1977 [122] with the introduction of the Low Contact Stress (LCS) knee system (Fig. 6.3.5). It was the first complete systems approach to total knee replacement using also meniscal bearing surfaces.

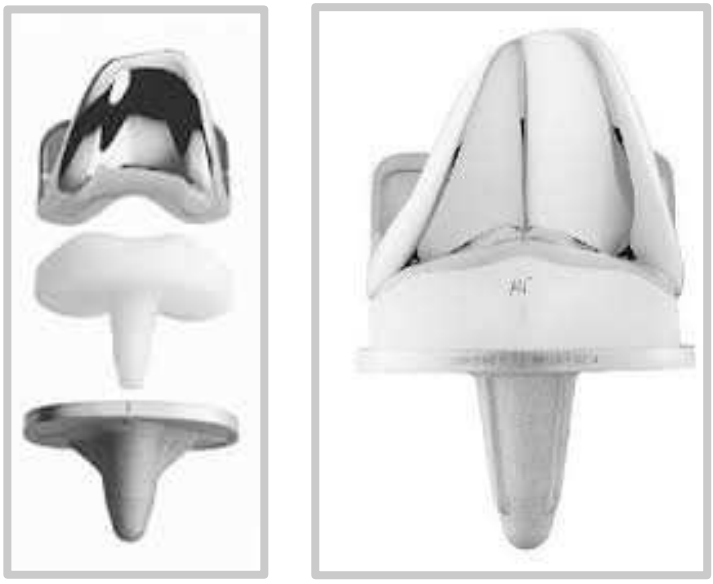

Fig. 6.3.5 LCS rotating platform (low contact stress) knee

6.4 MOBILE BEARING (MB) KNEE

The principal characteristic of the LCS femoral component was based on the same spherical surface on the mediolateral plane while a decreasing radius of curvature from extension to flexion was present on the lateral side. This shape maintained full area contact on the upper meniscal bearing from the 0 to 45° at which walking loads are encountered, and maintaining at least spherical line at deeper flexion angles. In its origin, the LCS, was proposed as a system inclusive of both cruciate-sparing meniscal bearing (Fig. 6.4.1) and PCL-sacrificing rotating platform variant (Fig. 6.3.5), with the latter gaining the majority of popular usage over the time. Afterward the introduction of the

LCS system, several types of mobile bearing knees were produced. They are categorized in according of their conformity: either partially or fully conforming, then a third group is represented by the posterior stabilized MB.

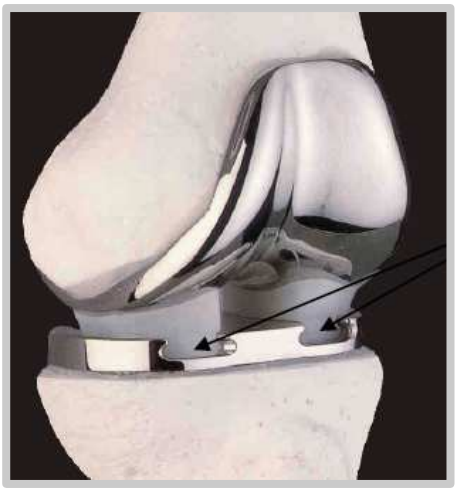

Fig. 6.4.1 The LCS meniscal bearing knee

6.4.1 PARTIALLY CONFORMING MB

The LCS rotating platform other to be the ancestor of all the MB prostheses is also the prototype of the partially conforming one. Belongs to partially conforming knees the Self Aligning MB (Sulzer) designed by Bourne and Rorabeck in 1987 (Fig. 6.4.1.1). This prosthesis is characterized by an oval recess in posterior aspect of the polyethylene which allows unlimited rotation and limited AP translation about a tibial tray peg.

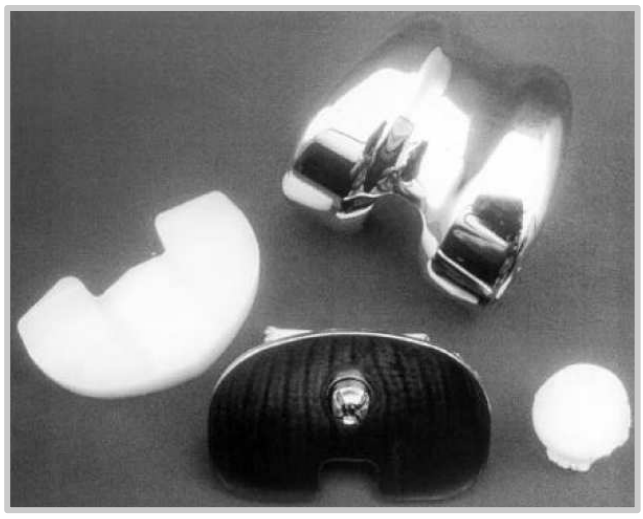

Fig. 6.4.1.1 The Self Alining MB knee

The mobile bearing knee produced by the Waldemar Link in Hamburg in 1990, called TACK, is characterized by the presence in the tibial tray of two semicircular guide that engage circular tracks on both sides of the polyethylene platform, permitting wide rotational movement (Fig 6.4.1.2).

Fig. 6.4.1.2 The TACK knee

The Interax Integrated Secure Asymmetric (Howmedica) prosthesis has nearly fully conformity between femoral condyle and tibial surface in extension and whereas the conformity gradually decrease in flexion. The tibial baseplate has two central posts that engages a curved, t-shaped guide track whitin the meniscal bearing (Fig. 6.4.1.3).

Fig. 6.4.1.3 A radiograph of the Interax Integrated Secure Asymmetric knee

The Total Rotating Knee (Cremascoli) developed by Ghisellini characterized by a central tibia post projecting from the center of the tibial tray. Two type of plastic bearing were available the R type to allow freedom of rotation was intend to be use in case of PCL excision, whereas the RS allowing 10 mm of AP sliding and freedom of rotation, was indicated when the PCL was retained.

6.4.2 FULLY CONFORMING MOBILE BEARING

The progenitor of fully conforming MB knees is certainly the Rotaglide Total knee System (Corin, Cirencester, UK) designed in 1986 by Polyzoides and Tsakonas: the rotaglide femoral component has a constant flexion radius of curvature in the femoro-meniscal articulation, each condyle being part of a sphere of 24 mm radius. This design ensures that congruency is retained throughout the range of flexion. The mobile meniscal bearing has two undercuts which permit up to 5mm of antero-posterior translation and 25° of rotation, 12,5° for each side. The tibial plateau has an anterior bollard that prevents anterior dislocation while restricting the rotation of the platform and another bollard in the middle of the tray that resists posterior dislocation (Fig. 6.4.2.1).

Fig. 6.4.2.1 The Rotaglide total knee system

The Medially Biased Kinematics Knee (MBK) was developed by J Insall, P Aglietti e P Walker in 1992 (Fig. 6.4.2.2). The design concept of this prosthesis is complete conformity between the femoral component and the polyethylene insert at any degree of flexion and during rotation and AP

translation of the tibial insert on the tibial tray. The prosthesis design allow a medially biased kinematics guided by the natural knee's stronger medial structures and greater lateral mobility. The polyethylene has approximately 20 degrees of both internal and external rotation on the tibial baseplate about a D-shaped "mushroom" post. The tibial baseplate translates 4,5 mm in an AP direction. An anterior stop prevents the plastic bearing from sliding off the tibial tray.

Fig. 6.4.2.2 The Medially Biased Kinematics Knee (MBK)

6.4.3 POSTERIOR STABILIZED MB

These design are based on the "cam and post" mechanism on a rotating polyethylene platform. The common feature is the presence of a cam situated between the posterior femoral condyles that engages a post projecting from the mobile polyethylene platform. The "cam and post" mechanism acts as a third weight-bearing condyle to help improve, load transfer and minimize polyethylene stress. Belongs to this category the Two Radii Area Contact (TRAC, Biomet) which was introduced in 1997. More recent designs are the P.F.C. Sigma RPF (DePuy) (Fig. 6.4.3.1) and the LPS mobile Flex (Zimmer) (Fig. 6.4.3.2).

Fig. 6.4.3.1 The PFC sigma RPF knee

Fig. 6.4.3.2 The LPS mobile flex knee

6.5 FUTURE PERSPECTIVE

Technological improvments in the field of knee substitution continues to enlarge the range of solutions for the recovery of joint mobility of the OA knee. Particularly, research focuses on designing more "natural" prosthesis, allowing physiological motion and feeling, which may last longer, and may be implanted with less invasive approach. Some prosthetic design such as some MB prostesis allows for both sacificing or preserving the PCL. The next chapter of this thesis will expolre the functional status of patients who implanted a MB prostietic design with or without PCL sacrifice, to clarify its importance in MB knee substitution.

7. The role of posterior cruciate ligament in mobile-bearing total knee replacement

7.1 AIM OF THE STUDY

Fully conforming, mobile-bearing total knee replacement (TKR) was initially designed using a posterior cruciate-sacrificing (CS) technique. Rotating-platform TKR that could also be performed retaining the posterior cruciate developed afterwards. The purpose of this study was to compare the clinical and functional outcome of patients who had either cruciate retaining (CR) or cruciate sacrificing (CS) TKR at a minimum follow-up of 2 years with the same prosthetic design.

7.2 INTRODUCTION

The role of the posterior cruciate ligament (PCL) in total knee replacement (TKR) is unclear. The published studies have not given a solid base for the decision either to retain or sacrifice the PCL during primary fixed-bearing TKR due to the lack of a significant difference in outcome between the two groups [123]. However it has generally been shown that the posterior-stabilized TKR design with post and cam allows for more reproducible outcomes with respect to cruciate retaining (CR) design, in that it avoids excessive PCL laxity or tightness [123, 124].

The debate over the fate of PCL in TKR has primarily regarded fixed-bearing, primary TKR. Mobile-bearing, fully conforming TKR were initially designed for PCL-sacrificing (CS) such as the LCS rotating-platform [125] (DePuy, Warsaw, IN). Later on this design was adapted for PCL-retaining (CR), but this implied a change into a "meniscal bearing" tibial insert design (LCS Meniscal Bearing, DePuy, Warsaw, IN) [126]. Successively another rotating-platform design was made available both with a CS, CR or with a PCL-substituting, posterior-stabilized (PS) [127] design with a femoral cam and a tibial post (PFC Sigma, DePuy, Warsaw, IN) [128]. More recently other products were released on the market (see Table 7.1).

Table 7.1 Incomplete list of mobile-bearing prosthetic designs

Design	Fate of PCL	Reference
GKS Prime (Permedica, Merate, Italy)	Retained or sacrificed	Present study
PFC Sigma RP (DePuy, Warsaw, IN, USA)	Retained or sacrificed	[128-131]
PFC Sigma PS (DePuy, Warsaw, IN, USA)	Substituted	[128, 130]
LCS RP (DePuy, Warsaw, IN, USA)	Sacrificed	[132-134]
LCS Meniscal bearing (DePuy, Warsaw, IN, USA)	Retained	[132-134]
Innex (Zimmer, Warsaw, IN, USA)	Retained	[135]
E-motion (Braun Aesculap, Tuttlingen, Germany)	Retained or Sacrificed	[124]
Advance (Wright Medical, Arlington, TN, USA)	Retained or Sacrrificed	[136]

PCL= posterior cruciate ligament; GKS=global knee system; PFC =press fit condylar; RP= rotating platform; PS=posterior stabilized; LCS=low contact sterss

Mobile-bearing prosthesis have shown comparable results against the same fixed-bearing, CR design, and against fixed-bearing PS design [137-139]. The high-conformity polyethylene of the tibial insert determines the anterior-posterior stability and allows for some degree of femoral roll-back making the PCL not essential for joint stability. However it has been hypothesized that retaining the PCL may have an important role in preserving an adequate proprioception and in increasing the articular range of motion by preserving the physiological femoral rollback, thus easing stair-climbing performance [140].

Very few studies in literature explored the possibility to retain or resect the PCL adopting the same knee prosthesis without varying the design of the polyethylene insert and metal components [124, 128, 131]. It is therefore still unclear if preserving the PCL may provide an improvement in the clinical and functional outcome.

The aim of this chapter was to compare the clinical and functional outcomes of the same fully conforming, mobile-bearing prosthetic design either retaining or sacrificing the PCL. It was hypothesized that preserving PCL may improve clinical and functional outcomes.

7.3 MATERIAL AND METHODS

All patients who had TKR with the GKS Prime® Permedica, (Merate, Italy) (Fig. 7.1) between March 2002 and April 2010 were reviewed (106 patients, 131 TKR). Of these patients, 5 were died, 4 were unable to come to a clinical appointment because physically or mentally infirm, and 2 refused our request for a clinical appointment. Patients with a valgus deformity (n=4), patient with a diagnosis of rheumatoid arthritis (n=3) were excluded from the study. One-hundred and two arthroplasties in 88 patients were left for examination. All TKR were performed by two orthopaedic surgeons. One of them sacrificed and the other retained the PCL. The same technique (apart from PCL resection or retention) was adopted for all the surgeries. Midline skin incision and a medial parapatellar arthrotomy were performed. An extramedullary tibial guide was used and 3 to 5 degrees of sloope were given as a standard. An intramedullary femoral guide was adopted and the femur was cut with a standard of 5 to 7 degrees of valgus and 3 degrees of external rotation. Soft tissue balancing was never performed as a routine procedure. The patella was not resurfaced during any of these TKR procedures. Tibial component was always cemented. Femoral component was cemented only when bone was considered osteoporotic. A suction drain was positioned and the wound was closed in layers applying a slightly compressive dressing.

The two groups underwent the same rehabilitation protocol. On the second post-operative day the drain was removed and the patients started passive movements with the continuous passive motion (CPM) machine. On the third day patients were allowed to walk as tolerated with the assistance of a therapist. Skin clips were removed 2 weeks post-operatively.

Postoperative assessment included the KSS Score (Knee and Function), visual analogic score (VAS) and a subjective six-point assessment relating to patient status before intervention (6=very satisfied, 5=satisfied, 4=acceptable, 3=scarcely satisfied, 2=unvaried,

1=unsatisfied/worsened). Preoperative clinical evaluation was recovered from patients records. Postoperative clinical evaluation was performed by two residents blinded to treatment.

Continuous variables are presented as means with ranges and standard deviation (SD). The differences between groups were analysed with the Student *t* test for continuous variables. Chi-square test and Fisher's exact test were adopted for categorical variables. The level of significance was set at alpha = 0.05. Data were analysed with the SPSS 17.0 statistical software (SPSS inc., Chicago, US).

Fig. 7.1 The GKS Prime (Permedica, Merate, Italy) fully conforming, rotating-platform design

7.4 RESULTS

Patient demographics are shown in table 7.2. The two groups were comparable for all the variables analysed such as age at surgery, gender, BMI, length of follow-up, preoperative range of motion and KSS scoring.

Table 7.2 Preoperative demographics

	PCL-Retaining (n=46)	PCL-Sacrificing (n=56)	*p* value
Age (years)	70.2 ± 7.6	68.6±6.7	n.s.$^{\alpha}$
Gender (M/F)	18/28	17/39	n.s.$^{\beta}$
BMI (kg/m^2)	30.7±4.8	28.8±4.2	n.s.$^{\alpha}$
Mean follow-up (months)	63.9±20	64.1±28.5	n.s.$^{\alpha}$
Side (R/L)	27/19	30/26	n.s.$^{\gamma}$
Femoral cementing (%)	9/46 (19.5%)	12/56 (21.4%)	n.s.$^{\gamma}$
Flexion contracture (°)	6.3± 9.4(0-25)	8.1±11 (0-25)	n.s.$^{\alpha}$
Maximum flexion (°)	125.6±9.8 (85-145)	129.1± 11.2 (80-150)	n.s.$^{\alpha}$
Total range of motion (°)	118± 12.3 (83-146)	115± 13.6 (71-143)	n.s.$^{\alpha}$
KSS Score Knee	45.2±14.7 (17-84)	46.1±15.1 (18-84)	n.s.$^{\alpha}$
KSS Score Function	39.4±15.3 (0-80)	39.1±17.1 (0-80)	n.s.$^{\alpha}$
VAS	7.7±1.5 (6-10)	8.1±1.9 (5-10)	n.s.$^{\alpha}$

BMI= body mass index; KSS= knee society score; VAS= visual analogic score
$^{\alpha}$= Student's *t* test, $^{\beta}$= Fisher's exact test, $^{\gamma}$= Chi-square test

Post-operative outcomes are shown in table 7.3. PCL retaining group obtained an average maxiumum flexion of 109.8° ± 11.6° (range 85°-145°), an average KSS score knee and function of 78.9 ± 15.4 and 70.6 ± 30.9 respectively, a postoperative average VAS of 2.9 ± 3.1 and a median satisfaction level of 6 (very satisfied).

PCL resection group obtained an average maxiumum flexion of 112.6° ± 13.6° (range 85°-145°), an average KSS score knee and function of 77.5 ± 16.4 and 68.4 ± 27.7 respectively, a postoperative average VAS of 2.8 ± 2.9 and a median satisfaction level of 5 (satisfied).

There were no statistically significant differences among the two groups for KSS score, range of motion, patient's satisfaction, maximum postoperative flexion and revision rate. In both groups the increase in KSS score categories averaged around 30 points.

Table 7.3 Postoperative outcome

	PCL-Retaining (n=46)	PCL-Sacrificing (n=56)	*p* value
Flexion contracture (°)	0.8±1.6 (0-10)	0.9±1.9 (0-10)	n.s. $^{\alpha}$
Maximum flexion (°)	109.8± 11.6 (85-145)	112.6± 13.6 (85-145)	n.s. $^{\alpha}$
Total range of motion (°)	107.9± 12 (80-135)	108.2± 13.1 (80-145)	n.s. $^{\alpha}$
KSS Score Knee	78.9 ±15.4	77.5±16.4	n.s. $^{\alpha}$
KSS Score Function	70.6±30.9	68.4±27.7	n.s. $^{\alpha}$
VAS	2.9±3.1	2.8±2.9	n.s. $^{\alpha}$
Revised	3/46	2/56	n.s. $^{\gamma}$
Satisfaction*	6 (4-6)	5 (4-6)	n.s. $^{\beta}$
Δ KSS Score Knee	33.6±16.1	31.3±17.2	n.s. $^{\alpha}$
Δ KSS Score Function	31.1± 28.6	29.3±26.4	n.s. $^{\alpha}$

KSS= knee society score; VAS= visual analogic score
$^{\alpha}$= Student's *t* test, $^{\beta}$= Fisher's exact test, $^{\gamma}$= Chi-square test
*= satisfaction is expressed as median and interquartile range
Δ= delta

Three cases of revision were documented in the PCL-preserving group (2 infections and 1 aseptic loosening) and two cases in the PCL-sacrificing group (1 infection and 1 aseptic loosening).

7.5 DISCUSSION

Posterior cruciate ligament (PCL) plays a key role in posterior knee stability and in control of the femoral translations. Theoretical advantages of PCL retention in TKR include an improved knee function, range of motion (due to increased femoral rollback) stability and strength, a more efficient gait pattern and a reduced interface stress [141]. Although some reports focus on the inconsistency of the results [124] and in a possible increase in knee laxity after PCL-retaining TKR [142], other studies document that PCL do not stretch and remains stable in the postoperative period [135].

The present study analysed clinical and functional outcome after TKR with a fully conforming, mobile-bearing knee prosthesis either with retention or sacrifice of the PCL. Results were collected at a minimum follow-up of 2 years and at an average follow-up of 4 years.

Very few studies in literature have looked at the clinical and functional outcome of patients who underwent TKR with a rotating-platform, fully conforming implant either sacrificing or preserving the PCL [124, 128, 131, 136] on the same prosthetic design.

Roh et al. have shown no differences among CR and CS mobile-bearing TKR in terms of clinical outcome and final ROM at 2 years follow-up. However, the authors have highlighted that unpredictable complications all occurred in the CR group, and may have been related to PCL laxity or tightness. They have also shown a not physiological kinematic in CR knees, with a paradoxical femoral anterior translation [124].

Hirsch et al. have compared clinical and functional outcome after TKR with a CR, CS or a posterior-stabilized prosthetic design. The authors did not find statistically significant differences in terms of clinical outcome. However they have documented a statistically significant improvement in maximum flexion and ROM for the PS group [128].

Ishii et al. have shown comparable final ROM with no statistical difference among rotating-platform CS and meniscal bearing CR prosthetic design (in this study the authors adopted two similar prosthetic designs, but not the very same design). Interestingly the authors have also

shown a more variable recovery time for the CR design, with more time needed to achieve the final degrees of flexion [126].

Again, Misra et al. have shown no differences in the five-year result of patients who underwent TKR with the same mobile-bearing prosthetic design either with retention or sacrifice of the PCL. The authors highlighted the trend for a higher percentage of patients with a detectable femoral rollback in the PCL-resected group. The authors postulate that the results may be partially explained by the fact that PCL is histologically abnormal in arthritic knees [131].

The findings in the over mentioned studies all suggested that retaining PCL may not play a significant functional role when adopting a fully conforming, rotating-platform knee implant. However the argument is still debated. The aim of this study was to compare the clinical and functional outcome of the same fully conforming, mobile-bearing prosthetic design either retaining or sacrificing the PCL. It was hypothesized that preserving PCL could improve clinical and functional outcome following TKR with a novel knee implant (G.K.S. Prime®, Permedica, Merate, Italy). The hypothesis was rejected in that no significant difference was shown either in the clinical and functional outcome or in the revision rate among CR and CS groups. Although mobile-bearing implants may reach average flection as high as 120-130° [124, 126, 136, 143], the finding of the present study of an average knee flexion of about 110° is not an uncommon [127, 128, 133]. Moreover the maximum knee flexion depends on the preoperative flexion, type of adopted prosthesis design, surgical technique, way of measurement, so that a direct comparison among different studies is almost impossible [126].

The postoperative KSS knee and function score varies widely in literature. The findings of our study were average values of 78 for the knee score and 69 for the function score (considering CR and CS groups together). Although not elevated, these values are comparable with those of

similar studies in literature [130]. Moreover, although KSS scores increased to limited values, the delta (Δ) KSS knee and function increased of about 30 points (table 7.3) as in comparable studies [136].

General revision rate value for primary TKR varies widely in literature. More optimistic reports document a revision rate of 3.4% at 10 years postoperatively [144]. However, almost the same rate of revision rate (3.8%) has been reported within 2 years from the implantation [145]. Similarly, according to the Danish register the revision rate after TKR is between 1.3-2.3% after the first post-operative year, between 2.3 and 4.7% after the second year, and between 4.8 and 6.6% after the fifth year [146]. There were 5 revisions in the present study (5%), which is a value in line with the current literature. It has to be underlined that the setting in which patients underwent surgery was a large referral center, which may have increased the number of revision surgeries due to infection [147]. In similar studies focused on mobile-bearing designs, revision rate of about 5% was reported: Misra and cooworkers reported that out of the 105 knees analysed at 5 years 5 suffered an aseptic loosening and 1 had a deep infection requiring revision (5.7%) [131]. Similarly, out of 90 knees admitted to follow-up, Roh and colleagues reported on 1 case of deep infection and 2 cases of knee instability (lax PCL) and 1 case of polyethylene subluxation (tight PCL) requiring reoperation (4.4%) [124].

This study has some limitations. Firstly it is retrospective in nature, and patients lost at follow-up may have influenced the final result. Secondly, in some of the cases the femoral component was cemented and in some others it was press fitted. However some studies prove that there is no difference among cemented and non-cemented implants in terms of clinical and functional outcome at medium term follow-up [148]. Additionally, radiographic evaluation was not included in the follow-up visit and therefore updated imaging was not

available to couple with clinical data. Lastly, the fact that surgeries were carried on by two different operators adds an element of variability that could not be avoided.

This study has also some peculiar strength. All the procedures were performed by the same group of surgeons and scrub nurses in the same hospital with the same surgical technique. Patella was never resurfaced. This is an important point as it has been demonstrated that patellar resurfacing may have an impact even on the anterior knee pain, on the overall clinical outcome and most of all reoperation rate [149].

7.6 CONCLUSIONS

No statistically significant difference in the clinical and functional outcome was detected when the examined fully conforming, mobile-bearing knee prosthesis was implanted either preserving or sacrificing the posterior cruciate ligament, with a minimum follow-up of two years and an average follow-up of 4 years. In light of these results surgeons may choose indifferentely to resect or preserve the posterior cruciate ligamnet according to their preferences. Posterior cruciate ligament resection may be preferred in that it facilitates the surgical procedure expanding the flexion gap and making the posterior debridement quicker and easier.

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