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### Knee Health Promotion Option for Osteoarthritic Knee: Cartilage Regeneration is Possible

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#### 1. Introduction

Although articular hyaline cartilage was typically considered having no or low potential for regeneration (Zhang L et al., 2009), some still thought that it does have the capacity to grow and remodel extensively during pre- and post-natal development and after trauma (Onyekwelu I et al., 2009). Both direct and indirect evidence of articular cartilage regeneration have been observed by some authors after correction of varus deformity for osteoarthritis of the knee (Kanamiya T et al., 2002; Koshino T et al., 2003). Moreover, unlike the first impression of a more or less static tissue, articular cartilage shows a slow turnover. Anabolic and catabolic pathways were thought to be very much intermingled in articular cartilage (Aigner T et al., 2006). Thus, one of the most important questions in osteoarthritis research is to understand the balance of catabolic and anabolic factors in articular cartilage as this is the key to understand the biology of cartilage maintenance and degeneration.

Osteoarthritis (OA) of the knee is the major cause of chronic musculoskeletal pain and is ranked as a main cause of mobility disability in elderly population. It is a disease process of uncertain multifactorial etiology, which eventually affects the entire joint. Various etiologic risk factors have been proposed, but the exact pathogenesis for OA knee is still unknown. Many literatures mentioned medial compartment is more commonly involved than the lateral one and the pathogenesis may be different (Neame R et al., 2004; Nunez M et al., 2008).

In 2006, we reported that in patients with medial compartment osteoarthritic knees, the prevalence of medial plica was significantly higher than that of others and that two distinct foci of cartilaginous lesion were found on the facing medial femoral condyle in almost all of the patients who had the structure of medial plica (Lyu SR and Hsu CC, 2006). Our further study disclosed the kinematic relationship of the medial plica with the medial femoral condyle during knee motion in vivo (Lyu SR, 2007). In that study, it was revealed that all medial plicae, regardless of their size, would move reciprocally and would keep in touch with the medial femoral condyle during knee motion. Another histomorphological study of the medial plica also implied the close interplay between this structure and the medial femoral condyle (Lyu SR et al., 2009). Moreover, our recent study (Wang HS et al., 2011)

found that the repeated injuries elicited by this abrasion phenomenon might trigger interleukin-1 $\beta$  (IL-1 $\beta$ ) production in medial plica, thus enhance the expression of matrix metalloproteinase-3 (MMP-3). Based on these findings, we developed a concept of arthroscopic medial release (AMR) for the treatment of osteoarthritis of the medial compartment of the knee joint (Lyu SR, 2008). The clinical outcome of this procedure lured us to believe that, by eradication of the abrasion phenomenon between the tight, fibrotic and hypertrophied medial structure and the adjacent medial femoral condyle, the pain of most patients could be reduced and the degenerative process in the medial compartment of some patients might be decelerated or arrested. Recently, we proposed a concept of arthroscopic cartilage regeneration facilitating procedure (ACRFP) that combines arthroscopic medial release (AMR) with conventional arthroscopic procedures including synovectomy, chondroplasty, partial meniscectomy and percutaneous lateral release (PLR) as a rationale for the deliberate arthroscopic management of OA knee. We've found that the elimination of the existing detrimental factors will provide a preferable environment for regeneration of the damaged cartilage.

The main scheme of this chapter will be a step-by-step presentation of the development of a global approach which we call "knee health promotion option (KHPO)" for OA knee. In section 2, a new entity "medial abrasion syndrome (MAS)" and the related hidden lesions will be defined. Its role in the pathogenesis of medial compartmental OA knee will be discussed based on our series of studies. The techniques and clinical outcomes of two novel arthroscopic procedures: arthroscopic medial release (AMR) and arthroscopic cartilage regeneration facilitating procedure (ACRFP) which have been developed according to the rationale conceptualized from the results of our basic research will be described in section 3 and 4. In section 5, a concept of total management of OA knee (KHPO) will be proposed. Finally, conclusions and discussions for the future prospect are presented in section 6.

#### 2. Medial abrasion syndrome (MAS) and the hidden lesions

Medial abrasion syndrome is an unrecognized but common clinical entity caused by the repeated impingement between mediopatellar plica (medial shelf) and the opposite medial femoral condyle during knee motion. This syndrome could explain most of the symptoms and signs of the medial compartment OA knee. In this section, the definition, clinical manifestations and relavant studies to investigate the role of MAS and the correlated hidden lesions in the pathogenesis of OA knee will be presented.

#### 2.1 Medial plica and MAS

The mediopatellar plica is a fold in the synovium representing an embryologic remnant in the development of the synovial cavity of the knee. It is found along the medial wall of the joint originating superiorly, extending obliquely and inferiorly, and inserting on the synovial lining of the infrapatellar fat pad (Dandy DJ, 1990). It is generally agreed that this structure can produce knee symptoms and could be successfully treated by arthroscopic resection when it becomes inflamed, thickened, and less elastic (Dorchak JD et al., 1991; Flanagan JP et al.).

During arthroscopic examination, different degrees of cartilaginous degeneration on the surface of the medial femoral condyle facing the medial plica has been noticed by many authors (Tasker T et al., 1982; Broom MJ et al., 1986; Dupont JY, 1997). According to a study

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conducted in 2006 (Lyu SR and Hsu CC, 2006), the incidence of the medial plica was significantly higher in subjects with osteoarthritis of their knees. Degenerative cartilaginous lesions on the facing medial femoral condyle were found in almost all of the patients who had the structure of medial plica. This study also found that the severity of these lesions has obvious correlation with patient's age and the severity of their plical lesions. In daily clinical practice, we likewise get an impression that the severity of the plical lesions present positive correlation with the severity of the osteoarthritis of the medial compartment as shown in figure 1.



Fig. 1. Arthroscopic findings of the effect of medial abrasion syndrome, the severity of the osteoarthritis of the medial compartment seems to have positive correlation with the severity of gross appearance of the medial plica.

#### 2.2 Clinical manifestations of MAS

In 2004, we conducted an unpublished investigation in order to find out the predisposing factors and presenting symptoms and signs of MAS in a series of 163 patients older then 40 years with 232 knees proven to have medial plica related MAS by arthroscopy. The sensitivity and specificity of each parameter about predisposing factors, symptoms and signs for the diagnosis of the medial plica related medial abrasion syndrome were analyzed. This study conceptualized the following clinical manifestations of MAS.

#### 2.2.1 Predisposing factors

#### Injuries

The presentation of a single episode of injury, such as a falling down with sudden bending of the knee, direct blunt injury over the anterior-medial aspect of the knee, unexpected twisting of the knee or change of position when kneeling.

#### Activities need bending knee

History of repeated or prolonged bending of the involved knee, such as squatting, kneeling, climbing stairs, hiking along slopes, climbing mountains or bicycling, either due to occupational or recreational needs. Prolonged driving or riding any transportation vehicle.

Female

Females tend to bend their knee more than males do in their daily activities.

#### Religion

Some religious worship needs repeated squatting or kneeling.

#### 2.2.2 Symptoms

#### Pain

It is always described as deep-seated, throbbing or cutting ache and would get worse when climbing stairs, sitting with the knees flexed for a long time, rising from a sitting position, or extending the knee against resistance. Night pain or soreness and difficult to find a suitable position when sleeping are also common complaints. Some patients might point out the location of pain over the anterior-medial aspect of the knee.

#### Crepitus

The presentation of the feeling or hearing of a click or crepitus when the involved knee is flexed or extended after prolonged sitting. It may or may not be accompanied by pain.

#### Snapping or locking

Patients might incidentally experience the feeling of giving way, a sense of insecurity or pseudolocking in some particular position. Mostly it occurs when the knee is partially bended during weight-bearing. Sometimes, locking will occur when patients try to walk after sitting or lying for a long time. It will get unlocked after standing for a few minutes.

#### 2.2.3 Signs

#### Localized tenderness

Precise tender area could be identified over the region between the inferior-medial margin of the lower pole of the patella and the ridge of the medial femoral condyle.

#### Palpable band

A palpable band with snapping or crepitation might be found over the above-mentioned tender area.

#### *Provocative test*

A provocative test to reproduce the characteristic pain and snapping of the band might be conducted by compressing the tender point with the thumb of one hand and repeatedly bend the knee with the other hand.

#### 2.2.4 Radiographic findings

Various degrees of rentgenographic manifestation of medial abrasion syndrome could be evaluated by axial view (Merchant's view) of the patello-femoral joint. In the early stage, it is always difficult to be diagnosed due to the concurrent lateral deviation or subluxation of the patella. Sometimes, narrowing of the medial patello-femoral joint space that represents as the clue of abrasion phenomenon might be found by careful evaluation. In more advanced cases, eburnation and bone attrition of the medial femoral condyle and/or medial facet of patella with obvious narrowing of the medial patello-femoral joint space could also be visualized as shown in figure 2.

Progressive narrowing of the medial patello-femoral joint space accompanied by osteophytes formation over the medial margin of patella and medial femoral condyle is the typical findings of severe cases. Subchondral cysts and hypersclerosis sometimes could be noticed over the medial femoral condyle (figure 3).



Fig. 2. A, narrowing of the medial patello-femoral joint is obvious; B, thicken medial plica with synovitis causing medial abrasion syndrome of left knee; C, after arthroscopic medial release, fibrillation of the cartilage surfaces are obvious over medial patello-femoral joint compared to that of the lateral one as was shown in D.



Fig. 3. Rentgenographic and gross appearance of the late effect of medial abrasion syndrome, A, marked narrowing of the medial patello-femoral joint with osteophytes, hypersclerosis and subchondral cysts; B, severe cartilage destruction over medial facet (MF) of patella and medial femoral condyle (MC) compared to lateral ones (LF and LC) could be visualized in this patient received arthroplasty.

#### 2.3 The hidden lesions

Medial abrasion syndrome could give rise to different degrees of cartilagenous degeneration on the surface of medial femoral condyle facing the medial plica. We call it "hidden lesion" because that in most occasions, either due to synovitis or tightness of the joint space in osteoarthritic knees, these lesions are difficult to be found in routine arthroscopic examination. Only after adequate synovectomy could they be clearly visualized by special view as shown in figure 4.



Fig. 4. The unveiling of the hidden lesion, A, the space between medial patellar facet and medial femoral condyle is obliterated by focal synovial tissue; B, during arthroscopic medial release, the hypertrophied medial plica and related tissue were debrided and removed; C, after this procedure, the "hidden lesion" could be visualized.

After proper synovectomy and release of the infero-medial area of patella and the medial gutter, two distinct foci (A and B in figure 5A) of cartilaginous lesions which we call the "hidden lesions" could be found on the edge and anterior part of the medial femoral condyle. The appearance of these focal cartilaginous lesions was unique and different from what has been described by the classical arthroscopic classification of cartilaginous lesions. We classify these lesions into five stages according to the gross appearance of their severity (figure 5). In a retrospective reviewing of the arthroscopic findings of 1587 knees, we found that the severity of the hidden lesions was positively correlated with the severity of the pathologic medial plica, total degeneration score of the knee and patient's age (Lyu SR and Hsu CC, 2006).

#### 2.4 MAS as a cause of medial compartment osteoarthritis of the knee

The aforementioned clinical findings strongly suggest that the medial abrasion syndrome might play a role in the pathogenesis of medial compartment osteoarthritis of the knee. In 2002, we collaborated a research team and began to conduct a series of investigations focusing on the following subjects: establishment of a finite element model of the medial abrasion phenomenon for biomechanical analysis of the possible mechanical effect elicited by this abrasion phenomenon; histopathological study of the gross and histological presentation of the pathological medial plica itself; biochemical analysis of the medial plica and the related pannus-like tissue, and compartment specified joint fluid analysis. In this section, we will describe and summarize the results of these studies and make a conclusive assumption for the role of the medial abrasion phenomenon as an important etiologic factor of medial compartment osteoarthritis of the knee.

#### 2.4.1 Mechanical factor – The finite element model

In order to establish a finite element model for the study of the relationship of medial plica with the facing medial femoral condyle, two pilot experiments were conducted.

First, an experimental study on the tensile strength of mediopatellar plica was undertaken using high precision micro-force tensile tests (Lyu SR et al, 2006). These tests were conducted with plica specimens taken from 61 knees of patients of different ages. The forcedeflection curves resulting from these tests were recorded and transferred to stress-stain curves to get the Young's moduli of these specimens. In addition, pathological tissue dye tests were used to assess the fiber content ratio (FCR) of each specimen. The value of the Young's modulus was plotted versus FCR, and the relation between them was fitted properly using a quadratic regression model. The test results indicated that the value of Young's modulus sharply increased when FCR exceeded 80%. This may lead to higher contact pressure between the medial plica and the adjacent articular cartilage. This study also found that the Young's modulus of the medial plica was positively correlated with the severity of the plica lesion and the patient's age.

In the second study (Lyu SR, 2007), the inner margins of the medial plicae of 30 knees were located by inserting needles percutaneously under direct vision during arthroscopic examination. The topographic changes of the margins of these plicae during knee motion were recorded by fluoroscopy and analyzed. In all types of the medial plicae, regardless of their sizes, shifting (rubbing, sliding) medially was found when the knee was moved from extension to flexion. They remained in contact with the medial femoral condyles during the whole range of motion. This observation disclosed the kinematic relationship of the medial plica with the medial femoral condyle during knee motion may generate some shearing force acting on the cartilage of the medial femoral condyle.



Fig. 5. The hidden lesions, A, gross appearance of the typical hidden lesions (foci A and B); arthroscopic findings of different stage of focus A lesion: A-1, in the stage I cartilaginous lesion, neovascularization and pannus formation are found over the margin of the lesion. Softening of the cartilage could be confirmed by palpation with a probe; A-2, the stage II lesion has all the findings of the stage I lesion. Moreover, flattening and indentation of the cartilage could be identified; A-3, the stage III lesion is a partial thickness cartilaginous damage. The cartilage becomes fissured and fibrillated; A-4, in a stage IV lesion, some areas of subchondral bone are exposed. A shallow gutter representing the imprint of abrasion caused by the medial plica can be identified; A-5, in a stage V lesion, the subchondral bone is completely exposed to form a deep gutter; B, the arthroscopic picture of focus B cartilaginous lesion related to medial abrasion syndrome.

Based on the findings of these pilot studies, a three-dimension dynamic finite element model composed of femur, tibia, cartilage layers and medial plica was recently developed (Lyu SR and Liu DS, unpublished). This validated model was used to investigate and compare the level of cyclic pressures acting on the cartilage of the medial femoral condyles by three different types of medial plicae with various Young's moduli. We found that all types of medial plicae remained in contact with the medial femoral condyles and shift medially when the knee moved from extension to flexion.



Fig. 6. The distribution of contact pressure on the medial femoral condyle elicited by different types of medial plica with Young's modulus set at 110 MPa and the knee model is flexed to 90 degrees. The high-pressure zones (red areas) are well correlated with our clinical findings.

This 3D model (figure 6) demonstrated that the contact pressures were positively correlated with the Young's moduli of the medial plicae. When the Young's moduli of the medial plicae were set greater than 40 MPa, all types of medial plicae would elicit contact pressures higher than 10 MPa on medial femoral condyles, and that is enough to cause apoptosis of chondrocytes in the cartilage tissue according to previous study using a bovine cartilage explant system to evaluate the effects of injurious compression on chondrocyte apoptosis (Loening et al., 2000).

In conclusion, according to the findings of this 3D dynamic finite element model, the close relationship and possible high contact pressure between fibrotic medial plica and medial femoral condyle during knee motion may be an crucial cause of the degenerative change of the cartilage on the medial femoral condyle.

#### 2.4.2 MAS and abnormal gait

Successively, we have conducted an histomorphological study focusing on the gross appearance and histological features of the medial plicae removed from 48 consecutive patients who had received total knee replacement for severe medial compartment

osteoarthritis of their knees (Lyu SR et al., 2010). Histologically, the majority of advanced pathologic presentation was found at the middle and distal portion of the medial plica that might abrade on the articular cartilage of the medial femoral condyle and noticeable cartilaginous lesion was found on the facing medial femoral condyle in all knees. In addition, a small branch of skeletal muscle originating from articularis genu inserting into the proximal synovial stroma of the medial plica was found in all knees (figure 7 A, B). The synovial fold of the distal part of the medial plica was disclosed to have a close relationship with the gracilis tendon sheath (figure 7 C, D).





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Fig. 7. A. A branch of skeletal muscle (SMB) originating from articularis genus was noticed inserting into the proximal part (P) of this medial plica. (A: abrasion portion) B. Microscopically, skeletal muscular fibers (arrows) could be found in the alveolar fibroadipose tissue of this medial plica (×40; H & E stain). C. The synovial fold of the distal part (D) of the medial plica was disclosed originating from the tendon sheath of the gracilis tendon (G). D. After the medial plica was removed, the gracilis tendon (G) could be visualized clearly. (P: proximal and A: abrasion parts of the medial plica)

It has been suggested that abnormal gait pattern may lead to the development of knee OA (Lynn SK et al., 2007). Several studies (Baliunas AJ et al., 2002; Gok H et al., 2002; Landry SC et al., 2007) have noticed that an increased knee adduction and internal rotation moment during the stance phase of gait is associated with knee OA. It was also detected that among individuals with mild radiographic knee OA, those who are symptomatic have significantly higher medial compartment loads than those who are asymptomatic (Thorp LE et al., 2007). The linkage of medial plica with the medial muscle group of the thigh found in this study might give answer to these literature findings which suggested the relationship of gaits with

medial compartment OA knee. During the walking cycle, the irritation of the inflamed medial plicae by the abrasion phenomenon with the medial femoral condyle might evoke reflex contracture of the medial muscle group including vastus intermedialis and gracilis and therefore increase the adduction and internal rotation moment and the medial compartment load of the knee. This correlation could further be proven by subjective improvement of gait pattern claimed by many of our OA knee patients who have received arthroscopic resection of the inflamed medial plica.

The histomorphological findings of this study imply the close interplay between the medial plica and the medial femoral condyle that might play a role in the pathogenesis of medial compartment osteoarthritis of the knee.

#### 2.4.3 Biochemical analysis of medial plica and pannus tissue

The most significant pathological change in OA of the knee is the progressive loss of hyaline cartilage of the articular surface. The expression of IL-1 $\beta$  and matrix metalloproteinase-3 (MMP-3) by pannus-like tissue in the knees of patients with advanced OA suggests that MMP-3 contributes to cartilage degradation (Shibakawa A et al., 2003; Yuan GH et al., 2004). MMP-3 is produced by both chondrocytes and synoviocytes, especially when stimulated by IL-1 $\beta$  (Tetlow LC et al., 2001). Synovial tissue inflammation has been predicted as a pathogenesis factor in early OA (Haywood L et al., 2003; Ayral C et al., 2005; Benito MJ et al., 2005; Ikeuchi M et al., 2005). Joint injury-induced IL-1 $\beta$  expression has been found to enhance MMP-3 release (Techetverikov I et al., 2005; Daheshia M and Yao JQ, 2008; Eder C, 2009), resulting in matrix degradation (van den Berg WB 2001). IL-1 $\beta$  levels in the knee joint were found to be associated with the severity of chondral damage (Marks PH and Konaldson ML, 2005).

In our previous study, pannus-like tissue (figures 5 and 8C) was also observed on the cartilage of the medial femoral condyle opposite the inflamed medial plica in early stage medial compartment OA of the knee (Lyu SR and Hsu CC, 2006). Further observation found that pathologic medial plica could be discovered in every patient suffering from medial compartment OA knee. This study also declared that various degrees of inflammation could be observed in the medial plicae of patients with medial compartment OA of the knee and removal of this structure by arthroscopic medial release could relieve their symptoms or even modify their disease process (Lyu SR, 2008).

In order to determine the role of medial plica and pannus-like tissue (figure 8C) in the pathogenesis of OA knee, expression of MMP-3 in the control synovial membrane, pannus-like tissue and medial plica obtained from early stage OA knee patients were investigated by immunohistochemical staining (Wang HS et al 2011). We found that MMP-3 was highly expressed in the pannus-like tissue (p in figure 8B-b) and medial plica (figure 8B-c), but not in the cartilage (ca in figure 8B-b) or control synovial membrane (figure 8B-a). Immunofluorescent staining also showed that MMP-3 was intensively expressed in medial plica tissue (figure 8C). In this study, the effect of IL-1 $\beta$  on cells isolated from pannus-like tissue and medial plica from early stage OA knees was also determined. Our results demonstrated that these cells expressed significant amount of MMP-3 mRNA and MMP-3 was found being released into the culture medium consequently. Moreover, similar to what were found in both medial plica and pannus-like tissue of late stage OA knees. All of these findings suggest that IL1- $\beta$  might be the triggering factor in MMP-3 expression by these tissues. Since MMP-3 plays a significant role in

the progression of OA, our investigation bring to light that medial plica might be involved in the pathogenesis of medial compartment OA of the knee.



Fig. 8. A, immunohistochemical staining for MMP-3 in pannus-like tissue, cartilage and medial plica. (a) control synovial membrane, (b) pannus-like tissue ("p") or cartilage ("ca") or (c) medial plica. The bar is 20  $\mu$ m in (a) and (b) and 10  $\mu$ m in (c). B, Immunofluorescent staining for MMP-3 in medial plica. (a) Nuclei stained with DAPI (blue), (b) cells stained for MMP-3 (red) and (c) merged image. The bar represents 10  $\mu$ m. The results are typical of those from 16 knees. C, Anatomical location of tissue biopsy in a typical right knee with stage II OA. MP is medial plica, P pannus and C cartilage. (Reproduced and adapted with permission and copyright © of the John Wiley and Sons [Wang HS et al 2011])

We propose that the abrasion between medial plica and the opposite medial femoral condyle may be the cause of inflammation in patients with medial compartment OA of the knee. This repeated abrasion injuries might trigger IL-1 $\beta$  production in medial plica, thus enhance the expression of MMP-3. Our finding of highly expressed MMP-3 mRNA in medial plica than in the control synovial membrane by real-time PCR analysis further supports this hypothesis. Recently, we found that inflammation in patients with medial compartment OA of the knee may also induce the production of other MMPs involved in the pathogenesis of OA knees (Wang HS et al., unpublished data). These findings agree with the observation that removal of pathologic medial plica and its related inflammatory structure by arthroscopy can be effective in symptom relief or even can modify the disease process of medial compartment OA knee (Ikeuchi M et al., 2005; Lyu SR 2008).

#### 2.4.4 Analysis of joint fluid

There are a variety of proteins in the synovial fluid of osteoarthritic knee. These proteins include glycoprotein debris and collagen fragments derived from destructed cartilaginous tissue and enzymes such as metalloproteinase, collagenase and proinflammatory cytokines (interleukin-1 $\alpha$ , interleukin-1 $\beta$ , tumour necrosis factor  $\alpha$ , etc) (Yoshihara Y et al., 2000; Hedbom E and Hauselmann HJ, 2002; Tchetverikov I et al., 2005). All of these proteins in synovial fluid might reflect the pathological status of the knees.

Since the aforementioned abrasion phenomenon between fibrotic medial plica and the opposite medial femoral condyle may continuously produce cartilage debris and give rise to various degree of synovitis, it is interesting to see whether the concentrations of total protein, IL-1 $\beta$  and MMP-3 are different in medial and lateral compartments of these knees.

Recently, we have conducted a study (Lyu SR and Chau LC, unpublished) to analyze total protein, interleukin (IL)-1 $\beta$  and Matrix Metalloproteinase-3 concentrations in synovial fluid of medial and lateral compartments from 14 knees with medial compartment OA received unicompartmental arthroplasty due to medial compartment osteoarthritis. All of these knees were found to have fibrotic medial plica demonstrating abrasion phenomenon with the opposite medial femoral condyle. Figure 9 shows the total protein, IL-1 $\beta$ , and MMP-3 concentrations in the synovial fluid obtained from the medial and lateral compartments of these knees. All sets of sample analyzed revealed significant higher concentration of total protein, IL-1 $\beta$ , and MMP-3 in the medial compartment.



Fig. 9. (a) The total protein concentration and (b) the concentrations of IL-1 $\beta$  and MMP-3 measured by enzyme-linked immunosorbent assay (ELISA) in samples of synovial fluid in medial and lateral compartments of osteoarthritic knees. \*The difference between medial (n = 14) and lateral (n = 14) was statistically significant at P < 0.01 in the Mann Whitney U test.

In contrast to the common point of view that molecules should be evenly distributed within joint cavity, the above findings revealed the existence of big differences of total protein concentration, IL-1 $\beta$  concentration, and MMP-3 concentration between medial and lateral compartments of osteoarthritic knees. The discrepancy in the total protein distribution in synovial fluids may be attributed to the size of the protein molecules. Owing to the gravity and the contour of the tibial plateau, the debris or tissue fragments generated from the medial compartment may not pass freely between medial and lateral compartments of the

knee joint and accumulate in the particular compartment. On the other hand, the local higher concentrations of IL-1 $\beta$  and MMP-3 are likely due to the medial abrasion phenomenon related ongoing pathologic progress in the medial compartment of these knees. Furthermore, the self-abrasion of the rough degenerated cartilaginous surfaces might also be the source of debris generation during daily activities. These findings might be important in the unveiling of pathogenesis or progression of medial compartment OA knee.

#### 2.4.5 MAS as an important etiologic factor for medial compartment OA knee

In summary, as shown in figure 10, our series of studies have discovered the possible mechanism by which the medial abrasion syndrome cause progressive degradation of the cartilage over the medial compartment of the knee.



Fig. 10. Medial abrasion syndrome as an etiologic factor for medial compartment OA knee, the repeated abrasion (millions times per year) between medial plica (represented by yellow curved line) and the medial femoral condyle will cause: A, chondrocyte and matrix damage due to direct mechanical shearing force; B, synovitis around medial plica due to trauma will produce cytokines (such as IL-1 $\beta$ ) and cartilage degradating enzymes (such as MMP-3); C, the debris and particles shedding down from the damaged cartilage accumulate in the medial compartment, further elicit third party abrasion over the weight bearing area.

Depending on the size and the severity of fibrosis of the medial plica, the abrasion itself will produce abnormal shearing force on the opposite cartilage of the medial femoral condyle and cause various degree of cartilaginous damage. On the other side, this abrasion phenomenon elicits repeated injury to the medial plica itself and results in focal synovitis that will trigger the production of cytokines such as IL-1 $\beta$  and then upgrades the production of cartilage degradating enzymes such as MMP-3. The continuous shedding of cartilaginous debris and production of cartilage drgradating enzymes make the whole medial compartment in a

consistently detrimental condition for the maintainance of normal cartilage metabolism and thus progressive "degeneration" results. Moreover, the painful sensation of inflammation of medial plica might evoke a reflex contracture of the pes anserinus muscle group and increase the loading of the medial compartment thus further jeopadize the cartilage.

According to our theory, medial abrasion syndrome, if present, might produce life long harmful effects on the general environment of medial compartment of the involved knee and disturb normal cartilage metabolism thus bring about the process of "degeneration".

#### 3. Surgical treatment of MAS

In order to remove the detrimental medial abrasion syndrome, we have developed a novel arthroscopic procedure that we called arthroscopic medial release (AMR) for capsular release (Lyu SR, 2008). The target of the capsular release was the layer III, so called "true capsule" of the 3-layers medial supporting structure (Warren LF and Marshall JL, 1979). As shown in figure 11, the capsulectomy extends superiorly to the midline of suprapatellar pouch. Inferiorly, it extends to the upper margin of medial meniscus. Anteriorly, it extends to the medial margin of patella. Posteriorly, it is undertaken to remove portion of the conjoined part of layer II and III till the gracilis tendon is visualized. Only the deep medial ligament was severed by this procedure and the medial stability should not be disturbed much.



Fig. 11. A: The extent of the medial capsulectomy is shown in the hatched area of the line drawing of the lateral view of the knee joint. The line marked by \* is the level of cross section above the meniscus as shown in B. B: The crossed-hatched area indicates the extent of the capsulectomy above the medial meniscus. Note that only the deep medial ligament is severed. The tendon of gracilis could be visualized after the procedure. (Reproduced and adapted with permission and copyright © of the British Editorial Society of Bone and Joint Surgery [Lyu SR, 2008])

The adequacy of the medial release could be checked by passing the scope under the patella and verified if the previously tightly closed medial patellofemoral joint space could be easily opened and the medial retinaculum visualized when the knee was put in full extension position.



Fig. 12. For a complete arthroscopic medial release (MAS), A, proximally, the genu articularis muscle attachment (arrow) should be released; B, the anterior synoviomeniscal junction (arrow) should be release; C, the medial gutter should be cleared to its posterior corner (arrow); D, the synoviomeniscal junction of the medial meniscus (arrow) should be clearly seen; E, in some case, release of the fascia of pes anserinus (arrow) should be performed; F, before medial release; G, after medial release.

According to our experience of performing this procedure (Lyu SR, 2008), the outcome of 255 knees in 173 patients for varying stages of osteoarthritis involving the medial compartment supports our contention that AMR is a good modality for the treatment of osteoarthritis of the medial knee joint in the aspect of symptom relief. It can reduce the pain in the majority of OA patients over a period of at least 4 years. In some cases, we also found the evidence that AMR could modify the disease process and satisfied the patients.

#### 4. Arthroscopic cartilage regeneration facilitating procedure (ACRFP)

The clinical outcome of the AMR lured us to believe that, by eradication of the abrasion phenomenon between the tight, fibrotic and hypertrophied medial plica related structure and the opposite medial femoral condyle, the pain of most patients could be reduced and the degenerative process in the medial compartment of some patients might be decelerated or arrested. Therefore, we propose a concept of arthroscopic cartilage regeneration facilitating procedure (ACRFP) that combines arthroscopic medial release (AMR) with synovectomy, abrasional chondroplasthy, partial meniscectomy or percutaneous lateral release (PLR) as a rationale for the deliberate arthroscopic management of OA knee. We believed that the elimination of the detrimental factors including medial abrasion phenomenon, focal or generalized synovitis, chondral flaps, meniscus flaps or lateral compression phenomenon will provide a preferable environment for the regeneration of the damaged cartilage.

In the year of 2005, 571 knees of 367 patients having medial compartment osteoarthritis with or without patellofemoral compartment involvement received this procedure. There were 95 (26%) male and 272 (74%) female and the mean age was 60 years (range, 29 to 82). The Knee Society score and the knee injury and osteoarthritis outcome score were used for subjective outcome study. The roentgenographic changes of femoral-tibial angle and joint space width were evaluated for objective outcome. The mean follow-up period was 38 months (range, 36 to 49). There were 505 knees in 326 patients (88.8%) available with more than 3 years follow-up. The subjective satisfactory rate for the whole series was 85.5%. For 134 knees with complete follow-up evaluation, the Knee Society score and all subscales of the knee injury and osteoarthritis outcome score improved statistically. The femoral-tibial angle improved from 1.52 degrees (95% confidence interval, 0.84~2.19) to 1.93 degrees (1.21~2.64) (p=0.03). The joint space width increased from 2.03 millimeters (1.81~2.24) to 2.18 millimeters (1.97~2.38) (p=0.01). The degeneration process of the medial compartment was found being reversed in 82.1% of these knees according to the radiographic evaluation. Examples of cartilage regeneration are shown in figures 13~16.



Fig. 13. Cartilage regeneration demonstrated in the medial compartment of the left knee of a 56 years old lady having stage II OA; A, cartilage erosion was found over the medial femoral condyle opposite the removed pathologic medial plica; B, the defect was found regenerated during the second-look arthroscopy 3 years later when the same knee suffered from hemoarthrosis after a falling down accident.



Fig. 14. A self-control example showing the benefit of ACRFP: A, pre-operative AP standing view of a 61 years old male with grade III OA over medial compartment of right knee and grade II OA over medial compartment of left knee, ACRFP was performed for his right knee; B, 46 months later, he came back due to marked disability over his left knee, the condition of his right knee was excellent and the degenerative process ceased compared to the progressively degenerated left knee; C, unicompartmental arthroplasty was necessary for his left knee that hadn't received ACRFP.



Fig. 15. An example of reversal of natural degenerative course by ACRFP in a 70 years old male patient having grade IV OA over his right knee: A, pre-operative standing AP view showing grade IV OA over medial compartment of his right knee; B, three years after ACRFP, the joint space reopened and the FTA improved from 7 degrees varus to 3 degrees varus.

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Fig. 16. Another example of reversal of natural course by ACRFP: A, AP standing view of a 58 years old female patient having bilateral grade IV OA with subluxation of medial femoral condyle; B, three years after ACRFP, obvious improvement of the radiographic manifestation could be observed.

Based on this constitutional study, we proposed a concept that by a purposeful eradication of all prejudicial factors in the degenerative knee, the jeopardized cartilage will have the chance to regenerate by its natural character. In comparison with the uncertain beneficial mechanism and the diversity of outcomes of current popular arthroscopic techniques for osteoarthritis of the knee, this concept of ACRFP has more precise rationale of treatment. The main theme of ACRFP is to remove any abnormal abrasion or impingement phenomenon and reestablish soft tissue balance in medial compartment and patellofemoral joint. For knees demonstrating medial abrasion phenomenon, medial release (Lyu SR, 2008) was performed to relieve the tension and abrasion between the tight, fibrotic and hypertrophied medial plica and the adjacent medial femoral condyle that have been described in previous studies (Lyu SR and Hsu CC, 2006; Lyu et al., 2006; Lyu SR, 2007; Lyu et al., 2010). On the other hand, in knees demonstrating lateral compression syndrome over patellofemoral joint, percutaneous lateral capsular release that has the benefits of tension release and denervation (Calpur OU et al., 2005; Paulos LE et al., 2008) was added.

The immediate effect of ACRFP is to release the strain caused by chronically inflamed soft tissue and to eradicate the hypertrophied synovium that may cause pain in the degenerative knees over the medial compartment and patellofemoral joint. Furthermore, this procedure might also bring forth to long-term favorable effects as a consequence of the global improvement of the environment of the knee joint for cartilaginous regeneration.

According to the experience of performing this procedure, the radiographic evaluations and clinical outcome studies have demonstrated that, by removal of all existed catabolic factors, the anabolic pathway of the damaged cartilage might become dominant and regeneration unveiled. The data support our contention that arthroscopic cartilage regeneration facilitating procedure is a good modality for the treatment of medial compartment osteoarthritis of the knee joint with/without patellofemoral joint involvement. It could modify the disease process of this common disease.

#### 5. The future: Knee health promotion option (KHPO) for OA knee

Based on the findings of our research regarding MAS and the clinical outcome of ACRFP, an integrated protocol shown in figure 17 for the treatment of OA knee that we call "knee health promotion option (KHPO)" has been developed and put into practice in our center since 2007. The details of this protocol for global management of OA knee will be presented in this section.



Knee Health Promotion Protocol for OA Knee

ACRFP: arthroscopic cartilage regeneration facilitating procedure

PCRFM: post-operative cartilage regeneration facilitating modalities

Fig. 17. Protocol of KHPO, the key determinant of success is to obtain complete consensus from the patient about this novel concept before enrolling him/her into this protocol. In our practice, the patients will be put under strict surveillance from case manager and nursing specialist during the whole process.

#### 5.1 Clinical staging

The first step of knee health promotion option for the treatment of OA knee is thorough evaluation of the patient's general condition and establishing the clinical staging for each compartment of the knee by standard rentgenographic examination including standing anteroposterior, lateral, and Merchant's views. The degree of joint space narrowing, presentation of osteophytes and alignment measured by femorotibial angle were the main parameters evaluated. The staging of OA of the whole knee is given as the most advanced stage of the three compartments. We have been using this staging system since 2000 and noticed its high correlation with the corresponding arthroscopic findings (as the example of medial compartment shown in table 1).

Stage	Joint Space Narrowing	Osteophyte	FT angle	Arthroscopic findings
Ι	Doubtful	No	Normal	Smooth surface, loss of normal elasticity
II	Definite, no more than 1/2	Doubtful	> 0	Uneven surface, superficial to moderate cartilage damage (bubbling, fibrillation)
III	Marked, more than 1/2	Definite	Around 0	Deep cartilage damage (chondral flap, subchondral bone exposed < ½ area)
IV	Complete obliterated	Marked	< 0	Full thickness cartilage damage (subchondral bone exposed > ½ area)

Table 1. Clinical staging for medial compartment based on the rentgenographic findings and possible correlated arthroscopic findings.

#### 5.2 Decision making for treatment option

Once the clinical staging of each compartment has been made, the decision of treatment option for idividual patient could be made according to the guideline listed in table 2. For stage I ~ III patients, KHPO is the best choice compared to osteotomy and arthroplasty. In stage IV patients, although arthroplasty is usually recommended, KHPO sometimes still has its value considering patients' preference and biopsychosocial condition.

Stage	КНРО	Osteotomy	Arthroplasty
Ι	++++	-	-
II	++++	-	-
III	+++	++	+
IV		++	++++

Table 2. Recommendation of treatment option for different stage of OA knee.

#### 5.3 Conservative treatment before ACRFP

All of the stage I and II patients and some of the stage III patients should be recommended to encounter into this supervised conservative treatment for at least 3 months. The sine qua non for a successful conservative treatment is to make patients and the family completely understand the concept of treatment. The medial abrasion phenomenon as an important etiologic factor should be emphasized. Daily activities, job and exercise modification could then be tailored for individual patient focusing on the avoidance of the medial abrasion phenomenon. In general, activities and exercises need repeated knee bending are regarded as harmful. The following recommendation shown in table 3 for activities and exercises is an example according to this principle.

Suitable	Harmful	
Walking	Stairs or mountains climbing	
Jogging	Squatting (e.g. gardening)	
Golf	Bicycling	
Swimming using freestyle or butterfly	Swimming using breaststroke	
stroke		

Table 3. Recommendation for suitable or harmful activities and exercises for OA knee

Home-based rehabilitation exercises including muscle strengthening and soft tissue stretching around the knee should be instructed and followed up under close surveillance from special personnels such as case managers or nursing specialists.

#### 5.4 Post-operative cartilage regeneration facilitating modalities (PCRFM)

After the detrimental factors including medial abrasion syndrome, lateral compression syndrome, synovitis, chondral debris and meniscus flaps that have been proven as the main causes of cartilage damage are eliminated by ACRFP, the purpose of the post-operative care is to unveil and facilitate the natural repairing ability of the degenerated cartilage.

During the first 3 months after ACRFP, the aim of rehabilitation is to prevent scar contracture and consequent recurrent medial abrasion phenomenon. Gentle deep bending stretching exercise is encouraged after each session of quadriceps strengthening exercise.

To facilitate cartilage regeneration, strict rules about engaging into appropriate daily activites and exercises as listed in table 3 should be followed during the first post-operative year. The rationale of this precaution is to avoid repeated bending of the knee that might produce shearing force harmful for cartilage regeneration. Muscle strengthening and soft tissue stretching exercises around the knee should be conducted as long as possible.

#### 6. Conclusion

The concept of knee health promotion option (KHPO) for the treatment of OA knee could be summarized in figure 18. From our series of studies and long-term clinical observation, we have defined a new entity - medial abrasion syndrome (MAS) and realized that it might be the main etiologic factor for the idiopathic medial compartment osteoarthritis of the knee joint. This syndrome could clarify most of the recognized symptoms, signs and risk factors of this common disease. Combined with other detrimental factors such as lateral compression syndrome, focal synovitis, chondral debris and meniscus flaps, the normal metabolism balance of articular cartilage is jeopadized and the knee "degenerates". If these detrimental factors could be eliminated by ACRFP in time and KHPO undertaken, the natural repairing power of the articular cartilage could be revived and the "degenerated" knee might "regenerate". In our clinical outcome study, the radiographic evaluations have demonstrated that, by removal of all existing catabolic factors, the anabolic pathway of the damaged cartilage might become dominant and regeneration unveiled.

In conclusion, we have conceptualized a novel theory for the global management of OA knee. We propose that, by a purposeful eradication of all prejudicial factors in the degenerative knee, the jeopardized cartilage will have the potential to regenerate. In comparison with the uncertain beneficial mechanism and the diversity of outcomes of current popular arthroscopic techniques for osteoarthritis of the knee, our concepts of AMR,

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ACRFP and KHPO have more precise rationale for the treatment and could bring hope to the majority of patients.



MAS: medial abrasion syndrome; LCS: lateral compression syndrom;

KHPO: knee health promotion option

Fig. 18. A, multiple detrimental factors cause imbalance of cartilage metabolism and the knee continue "degeneration"; A-1, different life span of normal (yellowish green line) and degenerated knee (purple line); B, KHPO could revive the natural repairing capacity of cartilage and "regeneration" could be anticipated, B-1, KHPO could reverse the "degeneration" process and change the direction of purple line.

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Osteoarthritis is one of the most debilitating diseases affecting millions of people worldwide. However, there is no FDA approved disease modifying drug specifically for OA. Surgery remains an effective last resort to restore the function of the joints. As the aging populations increase worldwide, the number of OA patients increases dramatically in recent years and is expected to increase in many years to come. This is a book that summarizes recent advance in OA diagnosis, treatment, and surgery. It includes wide ranging topics from the cutting edge gene therapy to alternative medicine. Such multifaceted approaches are necessary to develop novel and effective therapy to cure OA in the future. In this book, different surgical methods are described to restore the function of the joints. In addition, various treatment options are presented, mainly to reduce the pain and enhance the life quality of the OA patients.

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