Role of High Tibial Osteotomy in Cartilage Regeneration – Is Correction of Malalignment Mandatory for Success?

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Abstract

Malalignment of the knee can cause debilitating symptoms such as pain, resulting in a decline in function and mobility. Surgical options that exist to address this problem include realignment osteotomies and joint replacements. Realignment osteotomies are the more appropriate options in certain patient populations, especially with regard to age and level of activity. Since a high tibial osteotomy (HTO) was first used to manage malalignment of the knee and osteoarthritis, different techniques involving the use of specialized implants have been developed and further refined to good effect. There has also since been much research into the field of cartilage restoration techniques, both as a standalone treatment option and as an adjunct to a realignment osteotomy. This review attempts to detail the origin and the evolution of HTO, particularly in regard to combining this tried and tested procedure with adjunct cartilage restoration techniques, and the overall patient outcomes. A literature search on PubMed was performed, and articles pertaining to the outcomes of the use of an HTO and cartilage restoration techniques were reviewed. The literature in this field indicates good outcomes in terms of objective measurements of cartilage regeneration (such as arthroscopic visualization and magnetic resonance imaging evaluation) and subjective patient outcome scoring systems (such as the International Knee Documentation Committee and Lysholm scores) with a realignment osteotomy alone, and studies have shown that patient outcomes can be further improved with the use of a cartilage restoration procedure as an adjunct.

Keywords: *Cartilage regeneration, high tibial osteotomy, knee osteoarthritis, malalignment, outcome surgery*

MeSH terms: *Osteotomy, cartilage, articular, knee joint*

Introduction

Malalignment of the knee is well associated with the development of medial unicompartmental osteoarthritis,[1,2] due to altered biomechanics passing through the knee joint leading to different loading of pressures in different compartments of the knee. This is a cause for concern for a surgeon when deciding between a knee replacement and/or a high tibial osteotomy (HTO), especially with regard to patient factors such as age and level of activity.[3-6] HTO is a valuable treatment modality in correcting malalignment and thereby relieving the symptoms associated with medial unicompartmental osteoarthritis.[3]

In recent times, there has been a trend toward combining an HTO with cartilage restoration techniques, such as microfracture (MFX), abrasion arthroplasty, subchondral drilling, autologous chondrocyte implantation (ACI), osteochondral autograft transfer system (OATS), mosaicplasty, and the use of stem cell therapy, in an effort to promote cartilage healing and afford patients a better functional outcome.[7] This field of interest, although relatively new, can potentially offer surgeons new possibilities into providing their patients with the best possible surgical outcome.

Brief History of High Tibial Osteotomy

HTO was first introduced to correct primary knee deformities and was then used to treat osteoarthritis of the knee in 1958.[8-10] It was subsequently popularized as a treatment modality for medial unicompartmental osteoarthritis in 1965 after Coventry *et al*.[11] published long term results. Surgical techniques have since been refined, and several forms have been described depending on the type and degree of knee malalignment.[12] These include lateral closing wedge osteotomy, medial opening wedge high tibial osteotomy (MOWHTO),

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dome osteotomy, Chevron osteotomy, and use of external fixators with gradual correction of knee malalignment.

Types of High Tibial Osteotomies

The HTO technique used to treat medial unicompartmental osteoarthritis described by Jackson and Waugh[13] in 1961 involved division and removal of the head of the fibula, with a subsequent dome osteotomy below the level of the tuberosity, and immobilization in a full-length plaster cast.

Subsequently, in 1969, Coventry[14] presented on a new stepped staple [Figure 1], to overcome the previous issues with conventional staples being unable to fully engage the distal end of the osteotomy site. Jackson and Waugh[15] later went on to further discuss different techniques of the HTO involving curved osteotomies, transposition of the tibial tuberosity, and conventional wedge osteotomies. Fixation used involved Charnley clamps and Steinmann pins and later staples and a cast.

Different techniques later developed include the development of a special blade plate,[16] leaving the anterior cortex of the distal fragment and the posterior cortex of the proximal fragment intact to create an interlocking effect at the osteotomy site,[17] elevation of the tibial tuberosity,[18] and oblique osteotomies for oblique plain corrections.[19] Leaving a hinge of bone intact increases stability of the osteotomy site but can also have effects on the tibial slope after bony union.[20] In the 1980s, Insall *et al*.[21] published a paper on the outcomes of the use of HTO to treat osteoarthritis and highlighted the importance of ensuring the proximal tibial segment was not too thin, to minimize the risk of avascular necrosis of this proximal fragment, reminding the surgeon to take extra caution during preoperative planning and the surgery itself.

Several other implants have been used to provide the surgeon with different options. In addition to the above mentioned implants, these include tubular plates,[22] L-plates,[23] lag screws,[24] cannulated blade plates,[25] and buttress plates[26] [Figures 1 and 2].

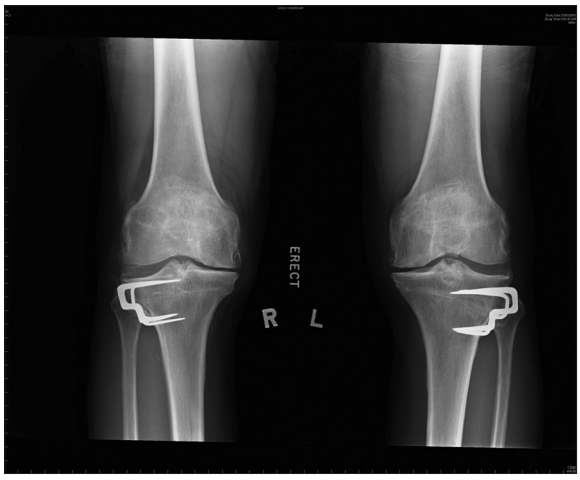

Figure 1: X-rays of both knee joints anteroposterior views showing coventry stepped staple

In recent times, the lateral closing wedge osteotomy has gradually given way to the MOWHTO technique [Figure 2]. This technique has been claimed as being technically easier, with reproducible and predictable correction of malalignment, good maintenance of bone stock, and lower risk of injury to the peroneal nerve.[27-30] Similarly, there are different techniques for performing MOWHTO, as well as different implants for use in acute correction of malalignment, such as Puddu plate, TomoFix (Synthes) plate, and the Aesculap plate. Hernigou *et al*.[31] described an osteotomy proximal to the tibial tuberosity and the use of three autografts of differing heights, or a cement block, to correct malalignment without causing a new flexion deformity. In addition to this, there have been developments of existing implants, such as rigid precontoured plates for stabilization of MOWHTO in obese patients.[32]

Improvements to MOWHTO wedges have also been developed, such as coating wedges in hydroxyapatite to aid osteointegration. The use of autografts or allografts to fill the bone gap in the MOWHTO is also an important factor. An allograft is typically cadaveric and is commonly fresh-frozen or freeze-dried. It eliminates the need for harvesting a graft, reducing the surgical duration and blood loss. Synthetic allografts can be used and are made of osteoconductive materials for bone regrowth through the structural scaffold. Materials include coralline hydroxyapatite, calcium sulfate, ceramics, and calcium phosphate cements. Autografts are usually harvested from

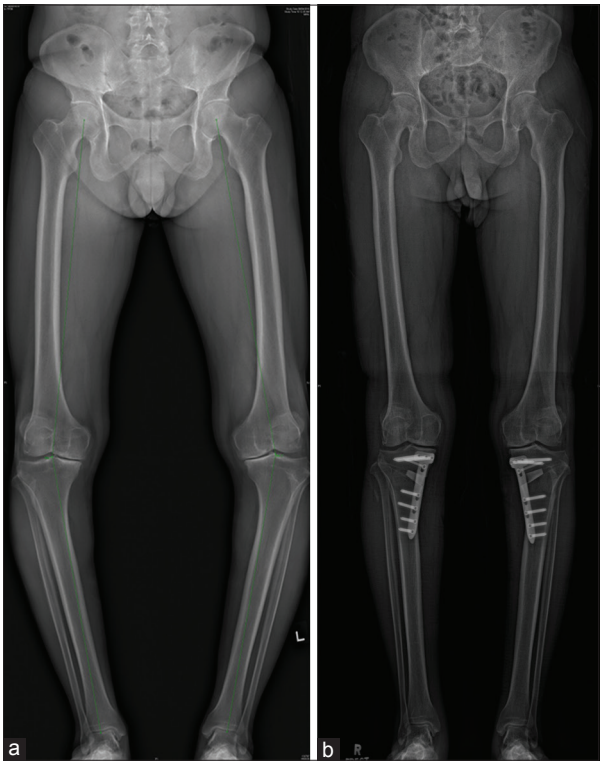

Figure 2: (a) Preoperative and (b) postoperative scanogram of both lower limbs showing a varus deformity of the knee using medial opening wedge osteotomy with TomoFix (Synthes) medial high tibial plate

the iliac crest and are beneficial as they minimize exposure to communicable diseases and provide an osteoinductive, osteoconductive, and osteoproductive material, aiding bony union. Kuremsky *et al*. have demonstrated a higher success rate with the use of autografts compared to allografts.[33]

In patients with a varus deformity, correction of the malalignment with an HTO can offload the medial compartment of the knee and has been shown to promote healing of the damaged articular cartilage.[34-37] the use of an HTO without additional cartilage restoration procedures has been extensively reviewed, and patient outcomes vary according to patient factors such as severity of articular cartilage injury, age, condition of the patellofemoral joint, functional preoperative range of motion, presence of previous surgery, stability of the knee joint, and presence of ligamentous laxity.[3] in their review of the literature, Amendola and Bonasia found that an HTO was most appropriate in a young patient with isolated medial unicompartmental osteoarthritis, with a good range of motion and without ligamentous laxity. they also found that the use of plates with spacers was associated with a better outcome.[3] recent trends in studies analyzing the outcomes of HTO indicate that an MOWHTO is currently the preferred procedure, given that it is less technically demanding and has a lower rate of complications,[27-30] and provides greater ease if the need for conversion to a total knee arthroplasty arises later on in the patient's life.[38]

The HTO was the first surgical treatment modality developed to address knee malalignment and resultant osteoarthritis but has been performed less often with the development of joint replacement techniques. The combination of cartilage restoration techniques with HTO has surfaced in the recent years, with interesting results thus far. This review is therefore aimed at examining the current literature on whether the correction of malalignment of the knee through HTO is necessary for cartilage restoration procedures to be successful.

A systematic review of the MEDLINE database was performed in February 2017 using the PubMed interface. A search was performed using a combination of the terms: "high tibia osteotomy," "high tibial osteotomy," "tibia osteotomy," "cartilage regeneration," "microfracture," "abrasion arthroplasty," "subchondral drilling," "chondrocyte implantation," "chondroplasty," "mosaicplasty," and "stem cell therapy knee." Clinical studies with an HTO being the primary surgical procedure (with or without adjunct cartilage restoration procedures) were included for the review.

Cartilage Regeneration after High Tibial Osteotomy

High tibial osteotomy only

It has been thought that an HTO allows for the correction of abnormal biomechanical forces, thereby allowing the affected compartment of the joint to be offloaded,[39] and for articular cartilage to recover. Though limited, there are studies which looked into the effect of HTO on cartilage regeneration on second-look arthroscopy. Studies by Kanamiya *et al*.,[34] Koshino *et al*.,[35] Jung *et al*.[36] and Wakabayashi *et al*.[37] are prime examples of this and are described below [Table 1].

In 2002, in their study of 58 knees in 47 patients undergoing lateral closing wedge HTO, Kanamiya *et al*.[34] found partial or even coverage with cartilage in 55% of knees operated on, white scattering of fibrocartilage in 34%, and no repair in 11%, at 18 months after surgery. Mean age at second-look arthroscopy was 63.4 years. In contrast, in the same year, Wakabayashi *et al*.[37] demonstrated that lateral closing wedge HTO had a greater effect on repair with more severe damage in their study of 73 patients with mean age of 64 years (during arthroscopy 1 year after surgery, in the group with more severe chondral injury preoperatively, incidence of cartilage repair on both the femoral and tibial surfaces was significantly higher than in the group with fibrillated cartilage surfaces preoperatively). Histology showed that the cartilage repair was fibrocartilage, indicating that while HTO did not promote hyaline cartilage regeneration, it prevented deterioration. It also demonstrated that even in severe chondral lesions down to bare bone, HTO was able to promote cartilage recovery in a significant proportion of patients.

In 2003, Koshino *et al*.[35] performed lateral closing wedge HTO using the Koshino blade plate, on 146 knees in 115 patients with a mean age of 65 years. Followup with arthroscopy 2 years later showed that in 132 patients with postoperative valgus angulation of 5° or more, 86 knees showed no or partial regenerative findings and 46 showed a total coverage with regenerated cartilage. Conversely, 13 knees with correction to 4° valgus or less showed no or partial regeneration and one showed complete regeneration. Correction to 5° valgus or more was significant in predicting complete cartilage regeneration.

Niemeyer *et al*.[40] studied outcomes in 69 patients with a mean age of 46.73 years, using the International Knee Documentation Committee (IKDC) and Lysholm scores, and found a significant continuous increase in IKDC score from 47.25 points preoperatively to 72.72 points 3-year post-MOWHTO. They also found that degree of chondral injury preoperatively in the medial and lateral compartments was not significant in predicting improvement in clinical outcome scores used, but degree of anterior compartment chondral injury was significant in influencing improvement in IKDC scores.

In 2014, Jung *et al*.[36] reported good outcomes in their study of 159 knees undergoing MOWHTO. On arthroscopy at 2 years following surgery (mean age at second-look arthroscopy was 60.2 years), 16 patients without adequate correction to revarization (0° or less)

Table 1: Effect of high tibial osteotomy as a standalone procedure

Author	Year	Manuscript title	Journal	HTO technique	Cartilage restoration technique	Clinical outcome measure and results
Kanamiya *et al*.	2002	The influences of biomechanical factors on cartilage regeneration After HTO for knees with medial compartment Osteoarthritis: Clinical and arthroscopic observations	Arthroscopy: The Journal of Arthroscopic and Related Surgery	Closing wedge HTO	-	Second-look arthroscopy approximately 18 months postoperatively showed partial or even coverage with cartilage in 55% of knees operated on, white scattering of fibrocartilage in 34%, and no repair in 11%, at 18 months after surgery
Wakabayashi *et al*.	2002	A comparison of the healing potential of fibrillated cartilage Versus eburnated bone in osteoarthritic knees after high Tibial osteotomy: An arthroscopic study With 1-year followup	Arthroscopy: The Journal of Arthroscopic and Related Surgery	Closing wedge HTO	-	Second-look arthroscopy 1 year postoperatively showed a higher incidence of cartilage repair on both the femoral and tibial surfaces in patients with cartilage fibrillation as compared to patients with eburnated bone. Further, histologic findings showed most of the nonrepaired joint surface of fibrillated cartilage appeared to be hyaline cartilage, but repair tissues of eburnated bone were mainly fibrocartilage
Koshino *et al*.	2003	Regeneration of degenerated articular cartilage after high tibial valgus osteotomy for medial compartmental osteoarthritis of the knee	The Knee	Closing wedge HTO	-	Second-look arthroscopy at an average of 2 years postoperatively showed no regenerative findings in 8.9%; partial regeneration with fibrocartilaginous tissue in the previous degenerated area in 58.9%; and total coverage by newly regenerated fibrocartilage or hyaline-like cartilage in 32.2%. Mature regeneration was observed more frequently in the knees with increased width of the medial joint space after HTO and in knees with more than 5° of anatomical valgus angulation after HTO
Niemeyer *et al*.	2010	Open wedge osteotomy using an internal plate fixator in patients with medial compartment gonarthritis and varus malalignment: 3-year results with regard to preoperative arthroscopic and radiographic findings	Arthroscopy: The Journal of Arthroscopic and Related Surgery	Closing wedge HTO	-	Significant improvements were observed in IKDC and Lysholm scores at 36 months after HTO

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Table 1: Contd...

Author	Year	Manuscript title	Journal	HTO technique	Cartilage restoration technique	Clinical outcome measure and results
Jung *et al*.	2014	Second-look arthroscopic assessment of cartilage regeneration after medial opening wedge HTO	Arthroscopy	MOWHTO	-	Second-look arthroscopy at an average of 2 years postoperatively showed that cartilage regeneration was achieved in the medial femoral condyle articular cartilage in 92% of knees and in the medial tibial plateau articular cartilage in 69% of knees. Maturation of the cartilage regeneration was found in the medial femoral condyle articular cartilage in 4% of knees and in the medial tibial plateau articular cartilage in 1% of knees

HTO=High tibial osteotomy, MOWHTO=Medial opening wedge high tibial osteotomy, IKDC=International Knee Documentation Committee

reported improvement in Knee Society Score (KSS) from 64.6 to 88.1 points, 19% did not show cartilage regeneration, 75% showed white scattering with fibrocartilage or partial or even coverage, and 6% showed mature regeneration. One hundred and thirty three patients with ideal correction (1°–5° valgus) reported KSS improvement from 68.7 to 93.8 points, and 95% showed partial or even cartilage regeneration and 3% showed mature regeneration. Ten patients with overcorrection (6° or more valgus) reported KSS improvements from 72.8 to 81.9 points, and 90% showed partial or even cartilage regeneration while 10% showed mature regeneration.

These studies indicate that a correction of malalignment of the knee is beneficial for the recovery and maintenance of articular cartilage, even without additional cartilage restoration procedures. As such, it has been thought that correction of malalignment of the knee is closely related to the success of cartilage restoration procedures of the knee. It is with this concept that various studies have been conducted to investigate the functional outcomes and success of cartilage restoration techniques when intrinsic malalignment of the knee has been corrected in the same setting. The wide-ranging types of cartilage restoration procedures set the premise for interesting studies based on various permutations of such techniques along with an HTO.

High tibial osteotomy in combination with microfracture, abrasion arthroplasty, or subchondral drilling

The combination of HTO and chondral resurfacing has been found to be effective and involves debridement of unstable cartilage, exposing the subchondral bone, followed by the procedure to stimulate the underlying bone marrow. Early studies seem to suggest that cartilage regeneration appears to be augmented after correction of the malalignment of the knee joint.

In 1997, Akizuki *et al*.[41] reported on 84 knees treated with HTO as compared to HTO with abrasion arthroplasty. At 1 year postoperatively, they found a significantly higher incidence of Outerbridge Grade II repair (a smooth articular surface and small fissures) and a lower incidence of Grade IV repair (full thickness cartilage loss) in the abrasion arthroplasty group on both the femoral and tibial joint surfaces. Histology revealed that 64% of the regenerated tissue consisted of fibrocartilage [Table 2].

Nearly a decade later, Matsunaga *et al*.[42] investigated outcomes in 51 knees in 45 patients undergoing closing wedge HTO with abrasion arthroplasty (mean age 64.6 years), compared to 26 knees in 25 patients undergoing HTO with MFX (mean age 65 years). They found 94% of patients in the abrasion arthroplasty group to have Outerbridge Grade II or III repair 1 year postoperatively and 58% of patients with MFX to have Grade II or III repair. There was no significant difference with respect to the development of hyaline cartilage as compared to fibrocartilage. Schuster *et al*.[43] reported similar findings in their study of 91 knees in 85 patients (mean age 50.4 years) undergoing MOWHTO with combined abrasion arthroplasty and MFX. They found a survival rate of 95.2% at 5 years, with the improvement of IKDC scores from 45.1 to 67.2 points. Arthroscopy at a mean of 1.5 years showed good cartilage regeneration in 50.0% and excellent in 25.8% on the tibial side and in 48.1% and 39.0% on the femoral side.

Table 2: Effect of various cartilage restoration techniques as an adjunct to high tibial osteotomy as procedure

Author	Year	Manuscript title	Journal	HTO technique	Cartilage restoration technique	Clinical outcome measure and results
Akizuki *et al*.	1997	Does arthroscopic abrasion arthroplasty promote cartilage regeneration in osteoarthritic knees with eburnation? A prospective study of HTO with abrasion arthroplasty versus HTO alone	Arthroplasty	HTO	Abrasion arthroplasty	Second-look arthroscopy 1 year postoperatively showed that patients in the abrasion arthroplasty group had greater cartilage regeneration on both the femoral and tibial joint surfaces. Histology revealed that 64% of the regenerated tissue consisted of fibrocartilage
Matsunaga *et al*.	2007	Repair of articular cartilage and clinical outcome after osteotomy with microfracture or abrasion arthroplasty for medial gonarthrosis	The Knee	Closing wedge HTO	Abrasion arthroplasty, microfracture	Second-look arthroscopy 1 year postoperatively showed better repair of the femoral and tibial condylar cartilage in the abrasion arthroplasty group when compared to the microfracture and HTO alone group
Schuster *et al*.	2015	Open wedge HTO and combined abrasion/ microfracture in severe medial osteoarthritis and varus malalignment: 5-year results and arthroscopic findings after 2 years	Arthroscopy	MOWHTO	Combined abrasion arthroplasty and microfracture	Second-look arthroscopy at a mean of 1.5 years postoperatively in 87.9% of knees showed good cartilage regeneration in 50.0% and excellent in 25.8% on the tibial side and good cartilage regeneration in 48.1% and excellent in 39.0% on the femoral side The survival rate was 95.2% at 5 years Subjective IKDC scores remained significantly higher after 5 years
Jung *et al*.	2015	Comparison of results of medial opening wedge HTO with and without subchondral drilling	Arthroscopy	MOWHTO	Subchondral drilling	Second-look arthroscopy at an average of 2 years postoperatively showed even coverage with fibrocartilage in 10%, partial coverage with fibrocartilage in 57%, and white scattering with fibrocartilage in 33% in the group with subchondral drilling, compared to even coverage with fibrocartilage in 3%, partial coverage with fibrocartilage in 55%, and white scattering with fibrocartilage in 35% and no formation of fibrocartilage in 7% in the group with HTO alone KSS scores were not significantly different between the 2 groups

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Table 2: Contd...

Author	Year	Manuscript title	Journal	HTO technique	Cartilage restoration technique	Clinical outcome measure and results
Bauer *et al*.	2012	Knee joint preservation with combined neutralising HTO and MACI in younger patients with medial knee osteoarthritis: A case series with prospective clinical and MRI followup over 5 years	The Knee	Closing wedge HTO	ACI	There were significant improvements in the KOOS and MRI results (with good quality infill found in 33% of patients) Histological investigation of one knee demonstrated full-thickness hyaline-like
Bode *et al*.	2013	A nonrandomized controlled clinical trial on ACI in cartilage defects of the medial femoral condyle with or without HTO in patients with varus deformity of<5°	Archives of Orthopaedic and Trauma Surgery	MOWHTO	ACI	Survival was significantly higher in the group receiving both ACI and HTO compared to ACI alone (89.5% compared to 58.33%) KOOS was not statistically significant
Ferruzzi *et al*.	2014	Cartilage repair procedures associated with HTO in varus knees: Clinical results at 11 years followup	The Knee	MOWHTO	ACI, microfracture	HSS Knee and WOMAC scores were significantly higher in the groups receiving HTO and ACI, and HTO alone, as compared to the group receiving HTO and microfracture
Minzlaff *et al*.	2013	Osteochondral autologous transfer combined with valgus HTO: Long term results and survivorship analysis	The American Journal of Sports Medicine	58.1% closing wedge HTO, 41.9% MOWHTO	Osteochondral autologous transfer	Patients experienced a significant improvement in the Lysholm and VAS scores. There was a 90.1% graft survival rate at 8.5 years postoperatively
Matsushita *et al*.	2017	HTO combined with cancellous bone graft and osteochondral autograft transplantation in a patient with massive osteochondral defects in the medial femoral condyle	Journal of Orthopaedic Surgery	MOWHTO	Osteochondral autologous transfer	Second-look arthroscopy 2 years postoperatively showed a well-covered bone graft site with cartilaginous tissue and a well-integrated osteochondral plug in this patient
Wakitani *et al*.	2002	Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees	Osteoarthritis Cartilage	Dome osteotomy	Stem cell therapy	Relook arthroscopy 42 weeks postoperatively showed chondral defects to be covered with white soft tissue in the stem cell-recipient group, and metachromasia was observed in almost all areas of the sampled tissue and hyaline cartilage-like tissue was partially observed. Arthroscopic and histological grading score was better in the cell transplanted group than in the cell free control group

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Table 2: Contd...

Author	Year	Manuscript title	Journal	HTO technique	Cartilage restoration technique	Clinical outcome measure and results
Wong *et al*.	2013	Injectable cultured bone marrow derived mesenchymal stem cells in varus knees with cartilage defects undergoing HTO: A prospective, randomized controlled clinical trial with 2 years followup	Arthroscopy	MOWHTO	Stem cell therapy	The stem cell-recipient group showed significantly higher improvements in Tegner, Lysholm and IKDC scores. MRI scans performed 1 postoperatively showed significantly better MOCART scores for the cell-recipient group
Koh *et al*.	2014	Comparative outcomes of open wedge HTO with platelet rich plasma alone or in combination with mesenchymal stem cell treatment: A prospective study	Arthroscopy	MOWHTO	Combination of stem cell therapy and PRP	Second-look arthroscopy at a mean of 19.8 months postoperatively showed partial or even fibrocartilage coverage was achieved in 50% of the stem cell PRP group patients but in only 10% of the patients in the PRP only group The patients in the stem cell PRP group showed significantly greater improvements in the KOOS subscales for pain and symptoms, and VAS pain scores compared to the PRP only group
Saw *et al*.	2015	HTO in combination with chondrogenesis after stem cell therapy: A histologic report of 8 cases	Arthroscopy	MOWHTO	Stem cell therapy	Second-look arthroscopy at a mean of 25.9 months postoperatively showed satisfactory healing of the regenerated cartilage. Histologic analysis showed significant amounts of proteoglycan and type II collagen. The total ICRS Visual Assessment Scale II histologic scores comparing the regenerated articular cartilage with normal articular cartilage indicated that the repair cartilage score approached 95% of the normal articular cartilage score

MACI=Matrix-induced autologous chondrocyte implantation, ACI=Autologous chondrocyte implantation, PRP=Platelet rich plasma, IKDC=International Knee Documentation Committee, KSS=Knee Society Score, KOOS=Knee Injury and Osteoarthritis Outcome Score, MRI=Magnetic resonance imaging, HSS=Hospital for Special Surgery, VAS=Visual analog scale, MOCART=Magnetic resonance observation of cartilage repair tissue, IVRS=International Cartilage Repair Society, HTO=High tibial osteotomy, MOWHTO=Medial opening wedge high tibial osteotomy, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

Jung *et al*.[44] investigated the effectiveness of subchondral drilling as an adjunct to MOWHTO in 30 knees and compared this to HTO alone in 31 knees. They found that patients with subchondral drilling had more coverage with fibrocartilage, but improvement in KSS was not significantly different.

These studies indicate a better outcome in patients who underwent HTO together with abrasion arthroplasty or MFX but not with subchondral drilling.

High tibial osteotomy with autologous chondrocyte implantation

The use of ACI in promoting cartilage regeneration was first analyzed in animal models and found to be effective. In 1994, Brittberg *et al*.[45] were the first to report the use of ACI in patients and outcomes from this procedure have been promising [Table 2].

In 2002, as a followup to the prior study by Brittberg *et al*.[45] in 1994, Peterson *et al*.[46] performed a histologic evaluation

of articular cartilage regeneration on femoral condyle and patella lesions managed with ACI in 11 out of 61 patients at a mean of 54.3 months after surgery, and regeneration was graded good or excellent in 89% of patients with femoral condyle chondral lesions after 2 years. Of these patients, 10.52% had had an HTO before ACI. Similarly, in patients with osteochondritis dissecans, grading was good or excellent in 86% of patients, but 7.14% of patients with osteochondritis dissecans had had a previous HTO as well. The prior HTO in these patients may have contributed to the good outcome of ACI in these cases. Mean age of these patients was 30.4 years in the group with femoral condyle lesions and 26.9 years in the group with osteochondritis dissecans. Subsequently, in 2010, Peterson *et al*.[47] conducted a review of clinical outcomes of ACI to determine durability of the implantation after surgery and found significant improvements in clinical outcome that remained high after 10–20 years. However, 9.38% of the patient population had a previous or concurrent HTO at the time of ACI, and again, this might have contributed to the good outcome.

In 2012, Bauer *et al*.[48] performed a combined lateral closed wedge HTO and ACI in 18 patients with a mean age of 47 years and that while clinical outcomes with regard to all domains of KSS except "symptoms" were significantly maintained at 5 years, outcomes with regard to magnetic resonance imaging (MRI) scan findings were fair and good at 2 years but were unsatisfactory at 5 years after surgery. Histological examination was only carried out in one patient who died 20 months after surgery, and histology demonstrated successful cartilage implantation.

In 2013, in a nonrandomized controlled clinical trial, Bode *et al*.[49] studied outcomes of MOWHTO and ACI in 43 patients (mean age 39.14 years) and found a higher graft survival rate of 89.5% in the combined treatment group based on MRI findings and the need for revision surgery (compared to 58.3% in the ACI alone group).

In their review of the literature, Perera *et al*.[50] found that ACI had a higher chance of success if there was normal alignment in the affected knee and thus recommended a concomitant HTO to correct any malalignment present. In a review article, Bentley *et al*.[51] drew similar conclusions as well. Similarly, in a systematic review of the existing literature, De Windt *et al*.[52] found a lower failure and conversion rate to TKA (2.5%–6.5% of patients) for HTO with ACI (compared to 20%–50% for HTO alone).

In 2014, in their study of 56 patients, Ferruzzi *et al*.[53] compared outcomes for MOWHTO with ACI (mean age 51 years) as compared to MFX (mean age 53 years). They found significantly higher improvements in the modified Hospital for Special Surgery (HSS) knee assessment instrument (35–69 points in the ACI group compared to 35–59 points in the MFX group) and Western Ontario and McMaster Universities Arthritis Index rating score (31–70 points in the ACI group, compared to 35–62 points in the MFX group), and lower radiographic progression of osteoarthritis in patients who underwent HTO with ACI (6 patients with Kellgren-Lawrence Grade IV preoperatively to seven patients at 2 years in the ACI group, compared to eight patients with Grade IV preoperatively to 12 patients at 2 years in the MFX group).

These studies indicate that ACI is a useful adjunct to HTO in promoting cartilage regeneration and improving clinical outcomes.

High tibial osteotomy with osteochondral autograft transfer system or mosaicplasty

The use of autografts has also proven beneficial in the treatment of chondral lesions, both in OATS and mosaicplasty. HTO allows weightbearing forces to be directed away from the graft area, thereby increasing the chance of graft survival and improving clinical outcomes when combined with an autograft transfer.

In 2013, Minzlaff *et al*.[54] performed HTO (58.1% lateral closing wedge HTO, 41.9% MOWHTO) with OATS in 86 patients (mean age 38 years) and found an improvement in the Lysholm score from 40 to 73 points, decrease in pain score (visual analog scale decreased from 7.5 to 2.7 points), and a 90.1% graft survival rate at 8.5 years after surgery.

In 2017, Matsushita *et al*.[55] reported on a single case (aged 46 years) with osteonecrosis of the medial femoral condyle with a varus deformity and chondral lesion following trauma, in which an MOWHTO was performed with OATS. Second-look arthroscopy at 2 years showed complete coverage of the chondral lesion with regenerated cartilage and a well-integrated osteochondral plug, with an area of fibrillation. Lysholm scores improved from 41 to 95 points at 3 years [Table 2].

Unfortunately, further literature regarding combined HTO and OATS or mosaicplasty is lacking, and further study is needed to determine the objective effect that this combined procedure has on cartilage regeneration.

High tibial osteotomy with stem cell therapy

Stem cells are unique in that they have the potential to differentiate into other mesenchymal lineages, with the one of interest here being chondrocytes. In recent years, there have been several studies investigating the use of stem cell therapy to aid in chondrogenesis, as an adjunct to HTO, with promising results.

In 2002, Wakitani *et al*.[56] published results of using dome HTO with human autologous culture expanded bone marrow mesenchymal stem cells (MSCs) in 12 patients, with a further 12 patients as a control group (HTO alone). Mean age was 63 years. At a mean of 6.7 weeks after surgery, a second-look arthroscopy showed that cartilage regeneration was significantly better in the cell-recipient group (graded

on a scale modified from one previously described by the author). Using the HSS knee-rating scale, the cell-recipient group reported better improvement (65–81.3 points compared to 66.3–79.2 points in the control group). In a followup long term outcomes study, the author demonstrated the safety of MSC as none of their patients went on to develop surgical site infections or malignancies of the joint .

In 2013, Wong *et al*.[57] conducted a prospective randomized controlled clinical trial as the first of its kind investigating HTO and the use of stem cells as an adjunct. Twenty eight patients underwent an MOWHTO with MSC injections (with 28 other patients as a control group undergoing HTO alone), and median age was 51 years, ranging from 24 to 54 years. The cell-recipient group reported significantly better improvements of 7.65 points for IKDC score, 7.61 points for Lysholm scores, and 0.64 points for Tegner scores. MRI scans performed 1 year after surgery showed significantly better results in the cell-recipient group, with 32% who had complete coverage of the chondral lesion (compared to none in the control group), and 36% in the cell-recipient group with >50% cartilage coverage (compared to 14% in the control group) [Table 2].

In 2014, Koh *et al*.[58] analyzed outcomes in 21 patients with a mean age of 54.2 years (MSC recipients) and 52.3 years (control group) undergoing MOWHTO with the use of MSC and platelet-rich plasma (PRP) (MSC-PRP group), compared with a control group of 20 patients undergoing HTO with PRP injections (control group). The MSC-PRP group showed significantly better Knee Injury and Osteoarthritis Outcome Score subscales for pain (control group: 74.0 points, compared to MSC-PRP group: 81.2 points) and symptoms (control group: 75.4 points, compared to MSC-PRP group: 82.8 points) at last followup (mean 24.4 months). Second-look arthroscopy at a mean of 19.8 months after surgery showed that in the MSC-PRP group, 14.3% had even fibrocartilage coverage, 38.1% had partial fibrocartilage coverage Grade 3, 42.9% had white scattering with fibrocartilage, and 4.8% did not show any regenerative changes, compared to the control group, of which 4.3% had partial fibrocartilage coverage, 47.8% had white scattering with fibrocartilage, and 47.8% did not show any regenerative changes.

In 2015, Saw *et al*.[59] performed a study to investigate the effect peripheral blood stem cells (PBSCs) had on chondrogenesis as an adjunct to an HTO. Eight patients with a mean age of 52.9 years underwent an MOWHTO with PBSC injections. Second-look arthroscopy (mean 25.9 months after surgery) and histological examination of a chondral core biopsy performed in all patients showed smooth regenerated articular cartilage with excellent integration and International Cartilage Repair Society scores approaching 95% of normal articular cartilage.

These studies indicate a positive outcome on cartilage recovery as an adjunct to HTO.

Conclusion

Malalignment of the knee with osteoarthritis can have an adverse impact on a patient's functional status, especially if the patient is young and active. An HTO offers a safe and effective approach to overcoming this difficult issue, with good relief of symptoms and return to an active and pain-free lifestyle.

In our review of the literature, we have found an HTO to have good outcomes, with good regeneration of cartilage. Based on the above review of the current literature, it appears that cartilage restoration procedures performed in conjunction with HTO can lead to improved cartilage regeneration, with some studies suggesting excellent outcomes. However, greater study into this new field of treatment is required. There are also several studies currently being conducted to assess cartilage injury and recovery on a cellular and histological level, and how an HTO affects this recovery process.In addition, the beneficial role of MSCs injection as an adjunct to HTO is a developing field with initial promising results. Further study is needed to investigate on long term functional outcome. This may hold the key to effective treatment of malalignment and resultant osteoarthritis in younger patients. Future areas of study should address the shortfall of clinical data pertaining to the long term outcomes of HTO, especially when coupled with adjuvant cartilage regeneration procedures. Failure in terms of the need for conversion to joint replacement and when this happens postoperatively should also be analyzed, perhaps with a large multicenter study.

In conclusion, HTO is an effective technique in correcting malalignment and managing osteoarthritis, especially when cartilage restoration procedures are used as an adjunct. When used in combination, clinical outcome seems to be better compared to isolated procedures alone.

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Conflicts of interest

There are no conflicts of interest.

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