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DIAGNOSTIC ADVANCES

Clinical applications of advanced magnetic resonance imaging techniques for arthritis evaluation

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Abstract

Magnetic resonance imaging (MRI) has allowed a comprehensive evaluation of articular disease, increasing the detection of early cartilage involvement, bone erosions, and edema in soft tissue and bone marrow compared to other imaging techniques. In the era of functional imaging, new advanced MRI sequences are being successfully applied for articular evaluation in cases of inflammatory, infectious, and degenerative arthropathies. Diffusion weighted imaging, new fat suppression techniques such as DIXON, dynamic contrast enhanced-MRI, and specific T2 mapping cartilage sequences allow a better understanding of the physiopathological processes that underlie these different arthropathies. They provide valuable quantitative information that aids in their differentiation and can be used as potential biomarkers of articular disease course and treatment response.

Key words: Magnetic resonance imaging; Joint; Diffusion weighted imaging; Dynamic contrast enhanced; Musculoskeletal system; Cartilage; DIXON; Arthritis

Core tip: New magnetic resonance imaging (MRI) techniques, successfully applied in other anatomical areas, can help to improve the diagnostic accuracy for arthritis evaluation. Advanced fat suppression techniques like DIXON or functional sequences such as cartilage imaging, diffusion weighted imaging or dynamic contrast enhanced-MRI are showing promising results for arthritis assessment. These techniques provide both morphological and functional information in several clinical scenarios including infection, degenerative or inflammatory arthritis.

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INTRODUCTION

Joint diseases are first evaluated through conventional plain radiography, although this technique is limited in that only late subchondral and bony abnormalities in arthropathies can be detected. Bone scintigraphy has been used to detect the presence of active disease[1]. Ultrasound (US) with Doppler capabilities plays a complementary role in the evaluation of soft tissue involvement for active synovial inflammation assessment without use of radiation or administration of exogenous contrast agents[2]. However, US is limited by operator-dependency and lack of visualization of deep joints. Computed tomography (CT) can help to better define bone involvement in specific joints, particularly when the diagnosis is questionable based on other imaging techniques[3]. A major drawback of CT is its use of ionizing radiation, which limits its use in pediatric population.

The introduction of magnetic resonance imaging (MRI) for joint assessment has overcome several limitations of conventional imaging techniques due to its higher tissue contrast, the ability to obtain multiplanar acquisitions, and the absence of ionizing radiation. Furthermore, MRI sequences permits an early detection of cartilage changes, better depiction of bone and soft tissue edema, and the characterization of synovial involvement[4]. Also, several disease-specific scales based on MRI changes have been proposed to measure arthritis related changes in clinical practice and have been applied in research trials to increase reproducibility[5].

Currently, several new functional MRI techniques have been translated from the brain to the musculoskeletal system which provide physiopathological information of normal tissue and disease. The DIXON sequence allows for very homogeneous fat-suppression in large and small joints, leading to improved detection of bone edema, synovial enhancement, and subchondral involvement. The Dixon sequence also is able to quantitatively define the fat and water content of a tissue, which can be useful in treatment monitoring of arthropathies. Diffusion-weighted imaging (DWI) evaluates the movement of the free water within tissues, allowing for an indirect estimation of cellularity and cell membrane integrity which enables discrimination between hypercellular lesions, such as malignant and inflammatory processes, from normal tissues. DWI can evaluate arthritis in a quantitative manner while avoiding the use of contrast agents.

Dynamic-contrast enhanced MRI (DCE-MRI) exploits differences in tissue vascularization. In this manner, this technique has been used to differentiate the etiology of synovial involvement in arthropathies according to the enhancement pattern and other quantitative derived biomarkers. The use of T2 mapping, which acquires different echo times (TE) within the same sequence, has been shown to aid in the early detection and quantification of cartilage abnormalities based on changes in water content, which indirectly reflects collagen content and collagen fiber orientation in the extracellular matrix. T2 mapping has been primarily used for early detection of osteoarthritis in the knee, as areas of initial cartilage degeneration show longer T2 values.

This review visits the technical basis and quantitative biomarkers provided by all these new advanced MRI techniques in the assessment of arthropathies and succinctly analyze their clinical applications.

ADVANCED MRI SEQUENCES FOR ARTHRITIS EVALUATION

Fat suppression techniques

The detection of bone edema is considered, along with synovial involvement, as the key feature in assessing joint involvement in arthropathies. The presence of bone edema has been demonstrated to correlate with overall patient outcome, preceding the existence of bone erosions and joint deformity[6,7]. Given its excellent tissue contrast, MRI is considered the single modality able to properly assess the presence, location, and extension of bone edema[8]. Edema imaging is mainly based on fat-suppressed T2-weighted sequences, as the higher water content of involved bone marrow is better depicted against a background of suppressed fat signal. Several sequences have been classically used for evaluation of bone marrow edema, including short inversion time recovery (STIR), spectral presaturation with inversion recovery (SPIR) and spectral adiabatic inversion recovery (SPAIR)[9,10]. Table 1 summarizes the main physical properties of these techniques and their clinical applications.

Bone marrow edema is also well detected on T1-weighted imaging, specifically with chemical shift imaging (CSI). This gradient-echo (GE) based technique exploits the different resonance frequencies of fat and water. In CSI, two different TE are acquired, providing an image where fat signal is subtracted from water signal (opposed-phase image) and another where the signal of water and fat are added (in-phase imaging)[5,6]. CSI has shown potential to differentiate true bone replacement from red bone marrow in different locations, and helps to better identify the presence of bone edema and its extension[11,12].

Chemical shift and DIXON

Several types of advanced sequences have emerged as a technical optimization of chemical shift based on the DIXON technique. This technique acquires several TE at the same time and combines them to obtain, not only an "in phase" or "opposed phase" imaging, but also "fat only" and "water only" maps[13,14]. In this manner, time

Table 1 Fat suppression techniques in musculoskeletal system

	In phase-out of phase	Fat saturation (CHESS)	Water excitation	DIXON	STIR	SPIR	SPAIR
Physical basis	Change of TE	Selective RF pulse that suppresses fat	Selective RF pulse that excites water	Different TEs, mathematic post-processing	Selective inversion of short T1 tissues	Spectrally selective RF pulse that suppresses fat	Spectrally adiabatic selective RF pulse that suppresses fat
Advantages	Fast High SNR	High SNR Contrast enhanced studies	Fast 3D acquisition	Four images in one acquisition Quantification Less prone to B0 and B1	Less prone to B0 and B1	Pre- and post-contrast studies	Insensitive to B1
Drawbacks	Sensitivity to B0	Sensitivity to B0 and B1 at large FOV	Sensitivity to B0	Acquisition time	Suppress all short T1 structures	Sensitivity to B0	Sensitivity to B0
Clinical applications	Detection of bone infiltration	Bone edema evaluation in joints MR-arthrography	Cartilage evaluation	All in one technique High SNR Less metal induced artifacts	Large FOV (spine) Multiple interfaces (fingers, toes, metal)	Postcontrast imaging of inflammatory or neoplastic conditions	Large FOV and high SNR needed: thigh or MR-neurography

CHESS: Chemical Shift Selective; STIR: Short inversion time recovery; SPIR: Spectral presaturation with inversion recovery; SPAIR: Spectral adiabatic inversion recovery; TE: Time of echo; RF: Radiofrequency; SNR: Signal noise ratio; FOV: Field of view.

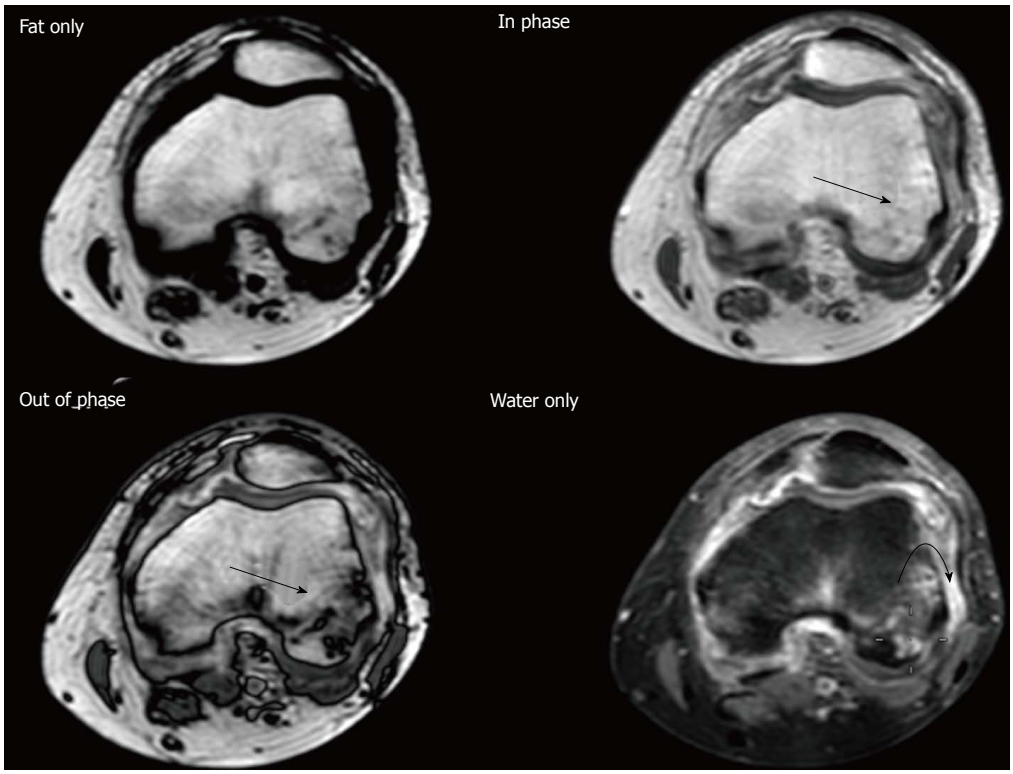

Figure 1 DIXON. Thirty-two years old woman with knee pain and suspected rheumatoid arthritis. Post-contrast DIXON study was performed. Opposed-phase image shows large hypointense areas in both condyles (arrows), which are hardly seen on the in-phase image, consistent with bone marrow edema. Note the presence of bone erosions and synovitis (curved arrow) better depicted on water only imaging.

can be saved by obtaining several stacks of images from only one acquisition (Figure 1).

The DIXON sequence is suitable for routine MRI to evaluate soft tissue and bone disorders and is compatible with a wide variety of pulse sequences, shcu as Turbo Spin Echo (TSE) and GE, and weightings (T2-weighted, T1-weighted or proton density images). The insensitivity of DIXON imaging to B0 and B1 heterogeneity offers robust fat suppression with higher SNR than other fat-suppressed techniques. Furthermore, the use of DIXON improves image quality in areas traditionally challenging for obtaining homogeneous fat-suppression, such as in regions of high magnetic susceptibility (*i.e.*, metallic implants) or in small anatomic areas, such as toes and fingers. DIXON sequences can be especially helpful in patients who cannot tolerate uncomfortable positions, particularly the pediatric and elderly populations[14,15], saving time in the acquisition of other sequences. Finally, DIXON provides quantitative parameters about water and fat

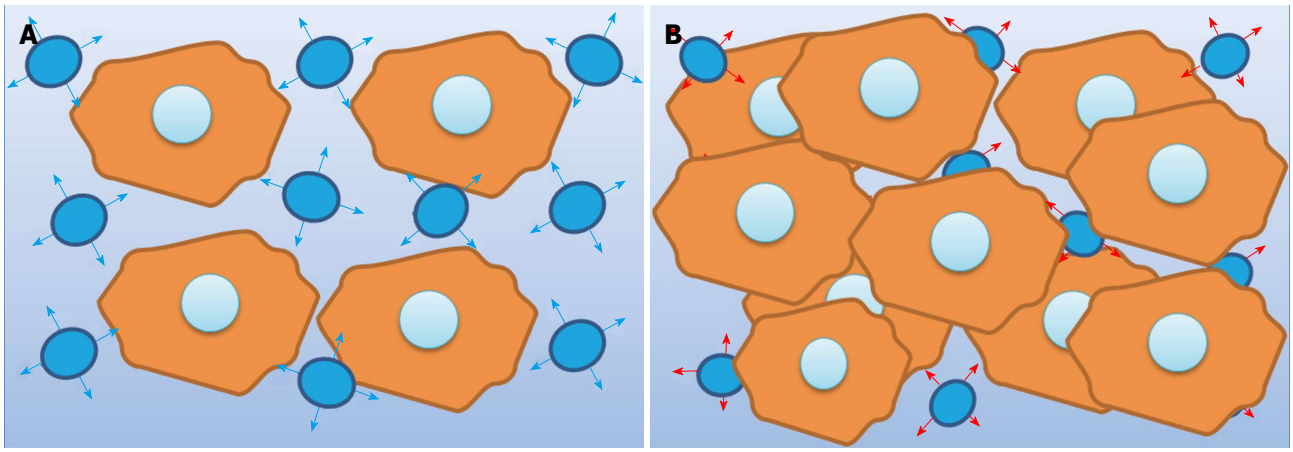

Figure 2 Diffusion-weighted imaging. A: Free water diffusion. The diagram represents the free motion of water molecules in the extracellular space between cells in normal tissue; B: Restricted water diffusion. The diagram represents the restricted motion of water molecules in the extracellular space due to hypercellularity. Another condition that leads to a decrease in the extracellular space is the presence of cytotoxic edema, while the presence of debris and detritus as in the case of abscesses may result also in restricted diffusion.

content of bone marrow and other tissues, including the percentage of signal loss between in phase and opposed phase images (fat fraction), which may provide potential biomarkers for treatment monitoring of arthritis[12,16]. Water only GE T1-weighted images provide high quality fat-suppression, which can be especially useful in dynamic postcontrast series or high-resolution late post-contrast studies, thereby improving the detection of subtle areas of enhancement[17].

DWI

DWI evaluates the movement of free water within biological tissues. This property indirectly estimates cellularity and cell membrane integrity and allows for discrimination between hypercellular lesions and normal tissues[18] (Figure 2). DWI provides quantitative information through the Apparent Diffusion Coefficient (ADC) that represents the exponential decay of a single component of diffusion signal. DWI improves detection of malignant lesions which show reduced water motion secondary to the occupancy of the interstitial space by malignant cells. Furthermore, it has been proposed as an important oncological biomarker due to its ability to discriminate between malignant and benign lesions[19]. In a similar fashion, infection and inflammation demonstrate reduced water motion and restriction of diffusion. In this manner, DWI and ADC have demonstrated its ability for lesion characterization and treatment monitoring in musculoskeletal applications[20].

Specific technical adjustments are necessary to perform DWI in musculoskeletal radiology. Most commonly, DWI is performed using a single shot-echo planar imaging (SS EPI) sequence, which is prone to susceptibility and motion artifacts, that are usual in joint evaluation, especially in fingers and toes, due to air-bone-soft tissue interfaces. For bone evaluation, as well as for other anatomical regions, multi-channel or surface coils are usually needed for parallel imaging in order to obtain adequate SNR and reduce artifacts[21].

DWI provides a qualitative and quantitative assessment of arthritis in a relative short scan time and without need for exogenous contrast[22]. Normal bone marrow demonstrates low signal intensity on DWI images with low ADC values due to its low cellularity and scarce free water content and dominance of fatty tissue, especially in yellow (fatty) marrow. Characteristically, active arthritis will appear as areas of high signal on highly-weighted diffusion images, also known as high b values images, with concomitant decreased signal on ADC maps. As mentioned previously, one benefit of DWI is that the use of contrast agents is not required. This is particularly important for patients with joint diseases, as it is not uncommon for these patients to have an underlying systemic disease with renal function impairment. In this population, the administration of gadolinium chelates should be taken with caution to decrease the potential risk of develop nephrogenic systemic fibrosis. Also, children with juvenile idiopathic arthritis have inherent drawbacks for intravenous puncture[23]. In this setting, DWI can be considered as an alternative to contrast-enhanced sequences.

For articular disease assessment, DWI may also be used for soft tissue evaluation, particularly for synovial involvement, joint effusion characterization, and bone marrow edema detection thanks to its ability to assess the water molecules movement.

DCE MRI

Conventional delayed postcontrast T1-weighted sequences only provide morphological information about areas of enhancement. DCE-MRI goes beyond conventional postcontrast MRI by providing pathophysiological information of the inflammatory processes themselves. DCE-MRI is usually based on a 3D gradient echo sequence with high temporal resolution, applying a dynamic scan faster than 4 s per dynamic[24]. This approach with high temporal resolution has shown several advantages over conventional multi-phase DCE-MRI (temporal resolution

Table 2 Main parameters derived from dynamic contrast enhanced-magnetic resonance imaging studies

Parameter	Biological meaning
Area under the curve	The integral in a plot of concentration of contrast agent in blood plasma against time
Maximum (relative) enhancement	The maximum signal difference between the signal intensity at its maximum and baseline
Time to peak	Time elapsed between the arterial peak and the end of the steepest portion of enhancement
Wash in rate	The maximum slope between the time of onset of contrast inflow and the time of peak enhancement on the time intensity curve
Wash out rate	The clearance rate of contrast agent
K^{trans}	Volume transfer constant between blood plasma and EES
K^{ep}	Rate constant between EES and blood plasma
Ve	Volume of EES per unit of volume of tissue

EES: Extravascular extracellular space.

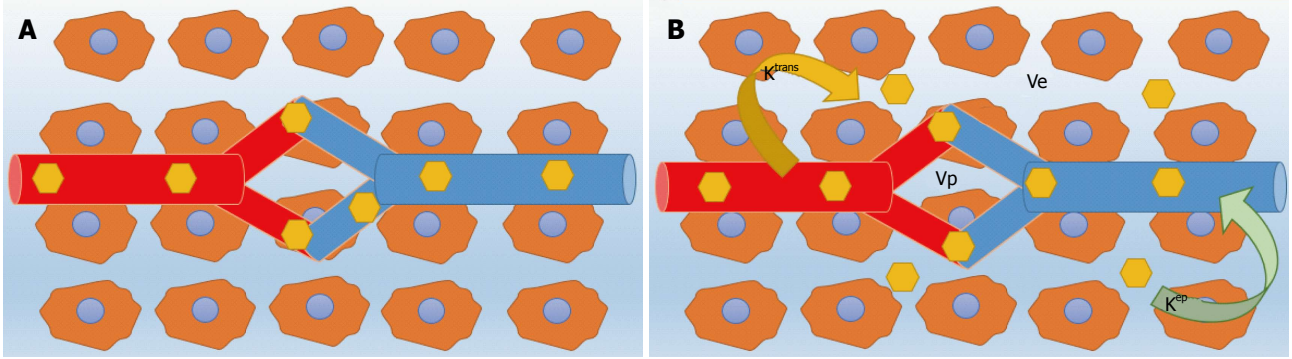

Figure 3 Dynamic-contrast enhanced-magnetic resonance imaging. Dynamic-contrast enhanced-magnetic resonance imaging analysis may be performed using a monocompartmental or a bicompartmental model. A: Diagram represents a monocompartmental model in which only vascular space is considered for distribution of gadolinium chelate; B: Diagram represents a bicompartmental model in which, besides the vascular space, the extracellular extravascular space with leakage and recirculation of gadolinium molecules are also considered. The main parameters derived for those models are detailed in Table 2.

between 12 to 20 s) with improved assessment of the dynamic enhancement process (Figure 3). New 4D acquisitions that combine high temporal and spatial resolution are able to provide simultaneous assessment of both structural and vascular properties[25]. This technique also permits MR-angiography reconstructions of regional vasculature.

In joint disease, the target structure on DCE-MRI is the synovium. DCE-MRI helps to understand the specific and complex physiopathological process that underlies each specific type of arthritis. The differential diagnosis may be narrowed based on the enhancement characteristics of the synovium, along with bone edema pattern and its distribution. The most helpful features for distinguishing the etiology of the joint process is the steepness and speed of enhancement during the first phases of DCE-MRI. For example, significant differences have been found in relative enhancement rate (RER), not in the first phases, but at delayed acquisition 15 min after Gad injection, with greater RER in rheumatoid arthritis (RA) than in psoriatic arthritis (PA). These results are a reflection of histopathology of synovitis in RA which presents higher cellularity and greater number of vessels compared with PA[26].

The analysis of DCE-MRI images has been classically performed using regions of interest (ROI). ROI-based analysis provides an average of all data included on a usually freehand drawn area[27,28]. Although widely used, this method is prone to sample errors. Other semi-automatic analysis methods have been proposed, using pixel by pixel maps of signal intensity data recorded on DCE-MRI studies[28,29].

Several types of time-intensity curves (TIC) have been described depending on the morphology and shape of the enhancement curve[30,31]. Type Ⅰ TIC is no enhancement, type Ⅱ curve reflects a slowly and progressively rising enhancement. Type Ⅲ TIC has a fast wash-in phase followed by a plateau and Type Ⅳ curve demonstrates fast wash-in and an early wash-out phase, usually linked to inflammatory activity. Finally, type Ⅴ is related to a fast wash-in with later progressive enhancement[27,32].

Parameters derived from monocompartmental or bicompartmental models of analysis of DCE studies are being considered as potential biomarkers for arthritis evaluation[33]. These biomarkers may predict aggressiveness of the arthritis and potentially aid in treatment monitoring[34]. Table 2 summarizes the main parameters derived from DCE-MRI studies and its biological meaning.

Cartilage imaging

Imaging of cartilage is one of the primary goals for MRI of the joints. The loose of the normal physiologic

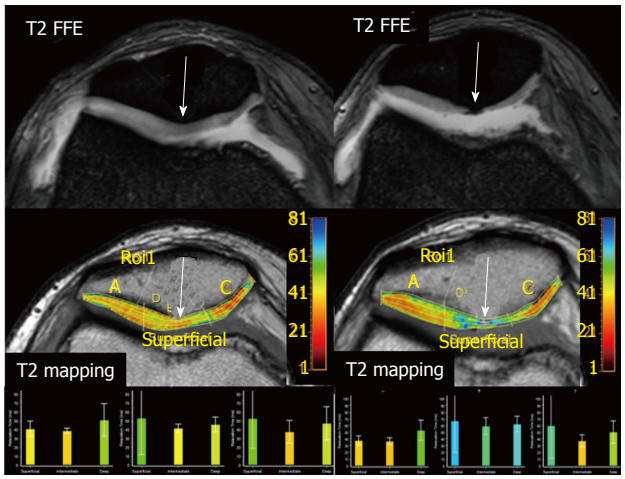

Figure 4 Osteoarthritis progression. A 49-year-old woman with knee pain is studied with two consecutive MRI studies. The first MRI (left images) shows a moderate joint effusion with patchy areas of increased signal intensity on T2 FFE sequence within the patellar cartilage. T2 mapping demonstrates diffuse increase in T2 relaxation times, more conspicuous at the patellar apex (arrows) consistent with early cartilage damage. Follow-up MRI performed 15 mo later (right images), demonstrates severe cartilage thinning, especially at patellar apex, that correlates with a severe increase in T2 relaxation times on the T2 mapping study. This clinical example demonstrates how T2 mapping can help to detect patients with evidence of early OA. MRI: Magnetic resonance imaging; OA: Osteoarthritis.

extracellular matrix precedes the development of bone damage and joint deformity. Articular hyaline cartilage has been classically evaluated with MRI using a morphological approach, which is limited due to the absence of pathophysiological information. In the last two decades, several functional sequences have been developed to allow a better understanding of cartilage structure. Functional MRI provides a qualitative and quantitative leap in early cartilage damage detection and treatment monitoring.

Nowadays, the most commonly applied functional technique for assessment of cartilage damage is T2 mapping. To obtain these images, multiple TE are acquired within the same sequence, computing the T2 relaxation time for each of those acquisitions. A voxel-based parametric map is generated showing the T2 relaxation time of cartilage, which can be assessed visually (qualitative analysis) or quantitative (ROI-based analysis)[35]. T2 relaxation time depends on the amount of water and the integrity of extracellular matrix, mainly secondary to collagen fiber density. The chemical interaction of collagen fibers with water protons results in a shortening of T2 relaxation time of the normal cartilage (Figure 4). There is a direct correlation between T2 values and water content and an inverse correlation with collagen concentration[36]. In this manner, areas of injured cartilage show a decrease in extracellular matrix (mainly collagen and proteoglycans) and increased water content. By increasing the TE, T2 mapping can detect these areas of early injury.

CLINICAL SCENARIOS

Infectious arthritis

The most frequent cause of septic arthritis is direct invasion through a skin defect/ulcer or haematogenous spread. In other cases, the infection is related to previous joint replacement surgery. Clinical and biochemical criteria are usually enough for an appropriate diagnosis, however in many cases, imaging is needed in order to evaluate the extent of the infection, particularly to evaluate for bone involvement. MRI has demonstrated a high accuracy for septic arthritis assessment[37,38]. As will be discussed in the next section, the introduction of functional MRI sequences may improve the specificity of the diagnosis, especially in evaluating the physiologic characteristics of the synovium, joint fluid, and neighboring bone.

DWI has shown potential for assessing joints and synovial fluid. One of the most useful applications of DWI in joint assessment is the evaluation of joint fluid and periarticular collections, in particular for depiction of infectious synovitis. In inflammatory fluid, hyaluronidases disrupt hyaluronic chains (that confer fluid viscosity) resulting in an increase in ADC values[39] (Figure 5). On the other hand, in septic arthritis, the presence of inflammatory cells, detritus, and pus produces an increase in viscosity which results in lower ADC values[40] (Figure 6). Thus, DWI is able to determine the nature of synovial fluid without the need for contrast agent injection and may also obviate the need for arthrocentesis, reducing potential complications such as infection and haemorrhage.

DWI has also demonstrated high accuracy in the differentiation between synovial thickening and reactive joint effusion, with high signal intensity at synovium on high b values due to hypercellularity. In cases of synovial thickening, intermediate ADC values (1.3-2.2 × 10^{-3} mm^2/s) may be found due to increased vascularization and associated perfusion-related effects in the synovium[20,40].

In cases of reactive bone involvement, there will be an increase in signal intensity on high b value DWI with concomitant high ADC values compared with normal bone due to the increase in water content of the damaged subchondral bone. When subchondral bone is affected by septic arthritis (osteomyelitis), involved areas will show hyperintensity at high b values with low ADC values due to the presence of pus and inflammatory cells[41].

DCE-MRI is also able to discriminate between synovial thickening and effusion and allows for the assessment of soft tissue involvement, synovitis (Figure 7), and necrotic areas in severe septic arthritis[42].

Postcontrast fat suppressed T1-weighted sequences usually help in the detection of bone marrow involvement as areas of increased enhancement. Normal yellow marrow will show no significant change in signal intensity after contrast injection compared to baseline. Involved bone in joints with septic arthritis will show a characteristic TIC (type II curve), with an intense early enhancement and later slight progressive increase of the enhancement slope compared to baseline marrow, without evidence of delayed washout[43]. Perfusion of epiphysis of involved bone has been shown to be lower

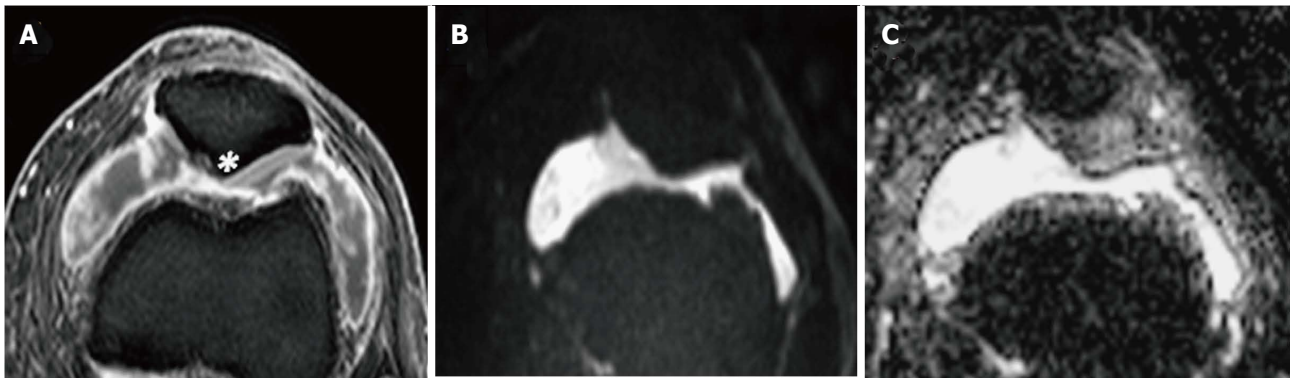

Figure 5 Synovial fluid evaluation with diffusion-weighted imaging. In a 42-year-old woman with RA and knee swelling. A: Axial post contrast fat-suppressed TSE T1-weighted sequence shows articular fluid and synovial enhancement; B, C: DWI with a b value of 900 s/mm^2 and corresponding ADC map confirm the presence of an effusion without significant restriction of free water motion (ADC: 2, 8 × 10^{-3} mm^2/s) consistent with transudate due to rheumatoid arthritis, as confirmed by arthrocentesis. In this case, DWI helps to exclude infection. Note the presence of a prominent chondral erosion near to patellar apex (asterisk on A). DWI: Diffusion-weighted imaging; RA: Rheumatoid arthritis; ADC: Apparent diffusion coefficient.

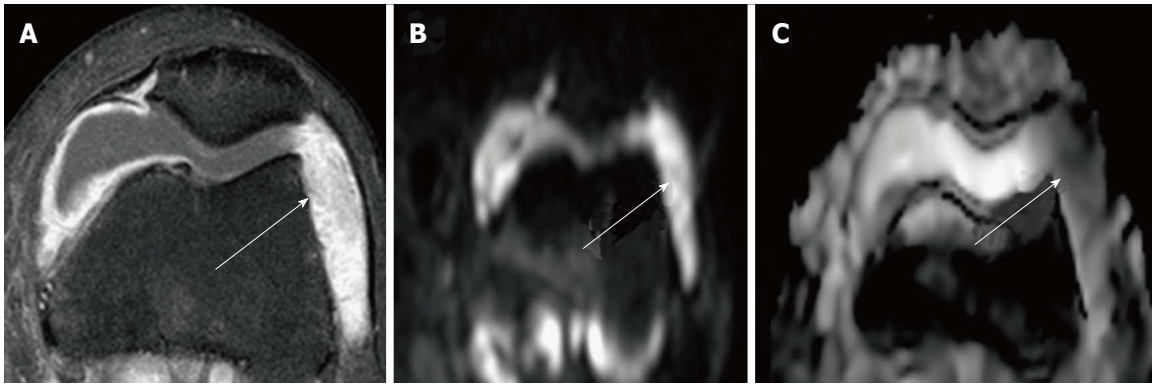

Figure 6 Septic synovitis. Magnetic resonance imaging findings in a 22-year-old man with knee pain and fever. A: Axial post contrast fat-suppressed TSE T1-weighted image shows a large joint effusion with synovial thickening and intense enhancement; B, C: DWI with a b value of 800 s/mm^2 and corresponding ADC map demonstrate areas of severely restricted diffusion (ADC: 1, 8 × 10^{-3} mm^2/s) within the articular fluid at the lateral patellar recess consistent with exudate, as proven by arthrocentesis. DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient; TSE: Turbo spin echo.

than expected on the initial phases of DCE-MRI likely due to an increase in hydrostatic pressure or possibly septic thrombosis of epiphyseal vessels. Furthermore, these changes may lead to avascular necrosis[44].

Inflammatory arthritis

Sacroiliitis: For sacroiliitis (SI) evaluation, conventional fat suppression techniques have high accuracy but a relative lack of specificity in the discrimination between early acute and sub-acute disease. Recently, several reports have focused on the potential of DWI to assess the sacroiliac joints, given its ability to detect subchondral bone edema with similar accuracy to fat suppressed contrast-enhanced T1-weighted images[45]. This may determine the degree of activity in acute sacroiliitis, although with lesser SNR than fat suppressed T2-weighted sequences[46]. In active sacroiliitis, areas of high signal intensity will be detected on high b value images in the subchondral bone but with higher ADC values than normal bone marrow, reflecting the presence of an inflammatory process. In chronic sacroiliitis, due to fatty changes, the involved joint will show lower signal intensity on high b value images and lower ADC values than normal bone marrow (Figure 8)[47].

DWI has also been shown to increase the conspicuity of bone subchondral edema, likely related to a proper suppression of background signal, and thus may increase the specificity of these changes in patients with early SI. Higher ADC values (0.5-1.5 × 10^{-3} mm^2/s) have been found in affected subchondral bone compared with control groups (0.2-0.6 × 10^{-3} mm^2/s)[48].

Post contrast fat suppression T1-weighted images as well as DCE-MRI have demonstrated its usefulness for SI detection with higher accuracy of the latter for detection of active disease even in the earliest phases[49].

Rheumatoid arthritis: Rheumatoid arthritis (RA) pathogenesis starts with an autoimmune inflammatory reaction against antigens located at the synovium that usually results in eventual joint destruction. As in SI, MRI has demonstrated to be superior to conventional imaging for detection of RA even in early phases[2].

Detection and characterization of synovitis and subchondral bone edema are the primary focus of MRI,

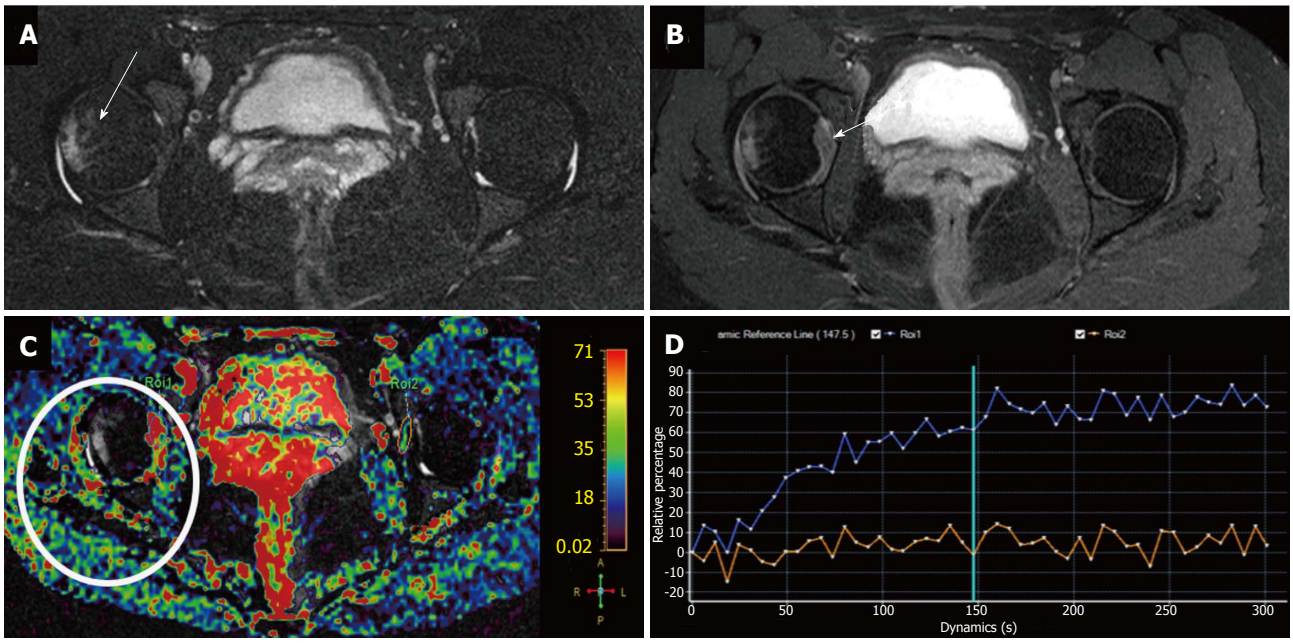

Figure 7 Evaluation of inflammatory arthritis with dynamic-contrast enhanced-magnetic resonance imaging in a 42-year-old woman with rheumatoid arthritis and right hip pain. A: Axial STIR shows mild articular effusion in the right hip with subtle signs of subchondral bone edema (arrow); B: Axial post-gadolinium SPIR GE T1-weighted image demonstrates moderate synovial thickening and enhancement especially at the medial articular surface (arrow); C: Relative enhancement map; D: Dynamic-contrast enhanced-magnetic resonance imaging demonstrate a type I TIC (blue curve) in the right hip, with progressive enhancement, compared to absence of significant enhancement in the contralateral hip (orange curve). This finding helps to confirm the inflammatory involvement of right hip. STIR: Short inversion time recovery.

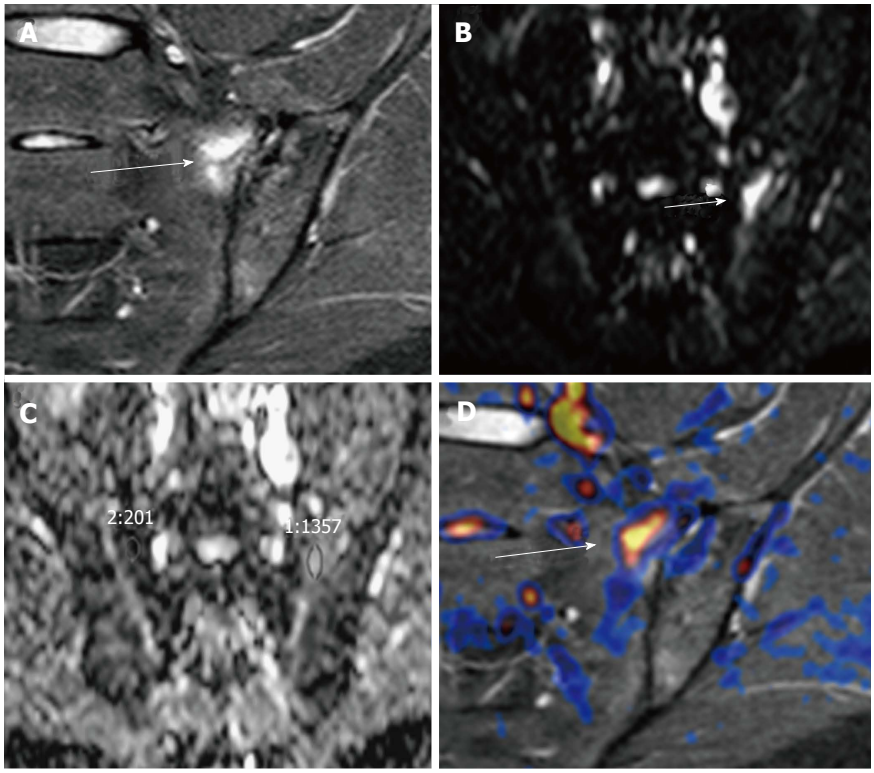

Figure 8 Acute sacroiliitis in a 32-year-old woman with left hip pain. A-C: Coronal STIR shows a focus of subchondral bone edema in the left hemisacrum (arrow, A), which appears hyperintense on (B) high *b* value DWI, with (C) significantly higher ADC values than contralateral bone marrow (1.3×10^{-3} mm^2/s *vs* 0.2×10^{-3} mm^2/s); D: Fused DWI and STIR images allow a better depiction of bone edema. STIR: Short inversion time recovery; DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient.

as these features have been demonstrated to be the strongest predictors of early RA and bone erosions, respectively[50]. These characteristics have been included in a MRI scoring system for RA evaluation (RAMRIS),

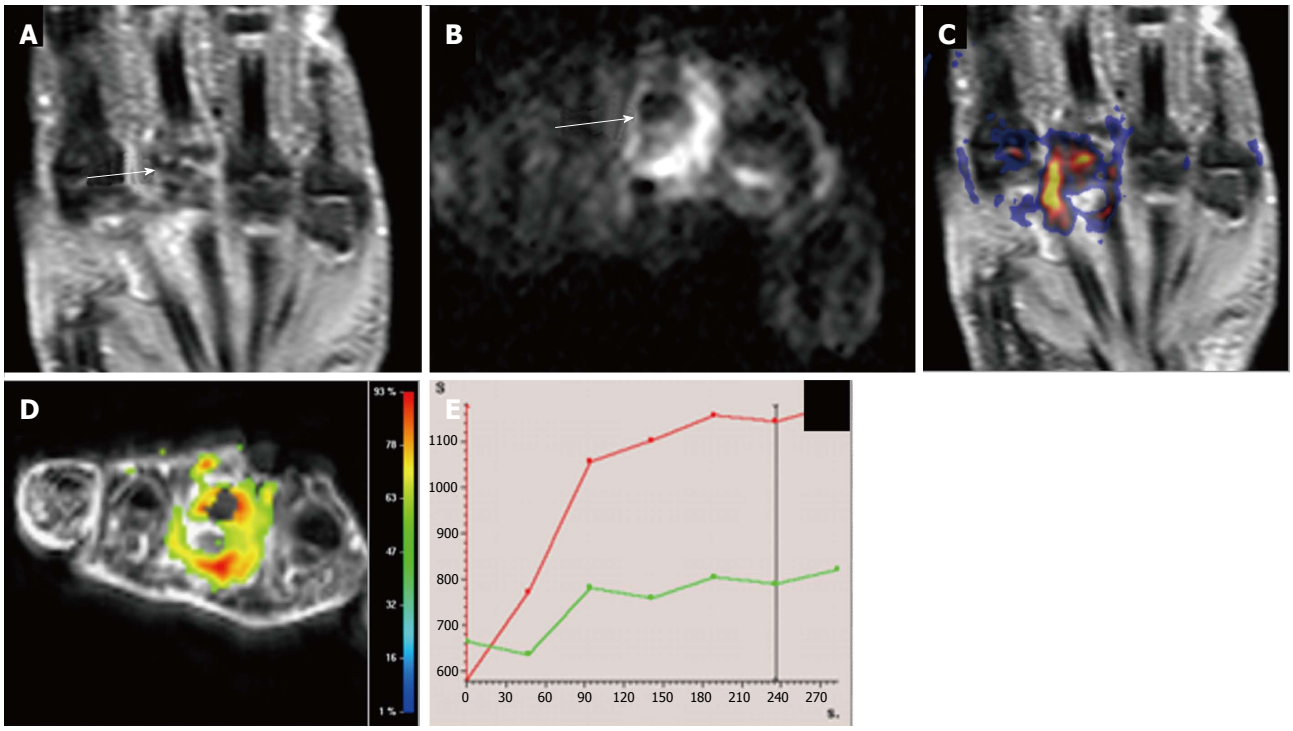

Figure 9 Multiparametric evaluation of rheumatoid arthritis in a 40-year-old woman with hand involvement. A: Coronal STIR shows severe articular surface erosions with subchondral edema and synovial hypertrophy at the 3rd metatarsal-phalangeal joint (arrow); B: Axial DWI b800 demonstrates markedly restricted diffusion within this joint (arrow, B) with good correlation on (C) STIR and DWI b 800 fused image; D, E: (D) DCE-MRI relative enhancement map shows increased enhancement and (E) TIC of the involved joint (red curve) shows an initial fast enhancement which becomes more progressive and slow in late phases in comparison to the adjacent normal joint (green curve). STIR: Short inversion time recovery; DWI: Diffusion-weighted imaging; MRI: Magnetic resonance imaging; DCE: Dynamic contrast enhancement.

as indicator of disease activity[51]. Fat suppression techniques have improved the ability of MRI for bone edema detection as discussed previously.

Functional sequences like DWI and DCE-MRI have also contributed to the increase in overall accuracy of MRI for RA assessment, providing several quantitative parameters which may be used as biomarkers of RA activity[2]. DWI has demonstrated a high accuracy for synovitis detection in the wrist and hand, especially in the metacarpophalangeal and proximal phalangeal joints, in patients with RA[52]. Synovial infiltration by inflammatory cells may affect the mobility of water molecules (Figure 9). Furthermore, the inherent background suppression of surrounding tissues increases the sensitivity and specificity of DWI over other MRI techniques for synovitis and bone edema detection, which have been linked to rapid radiographic progression in patients with early signs of RA[51,52]. One downside of DWI is the susceptibility to inhomogeneities in the magnetic field and low SNR, limiting its application in assessment of the hands and feet.

The interest of applying DCE-MRI studies for the evaluation of RA, particularly in the assessment of synovitis, is rising nowadays, as it has demonstrated a high correlation with clinical, biochemical, and histological markers of disease activity[33]. The steepness of the TIC in cases of active disease, usually demonstrating a fast initial enhancement phase and later plateau or washout, better reflects the physiopathological process behind synovitis than the single use of pre and post-gad T1 sequences. Semi-quantitative parameters such as maximum enhancement (ME) and rate of early enhancement (REE) may be used as potential biomarkers and allow the detection of changes in synovial vasculature before changes in synovial volume or bone edema occur[53].

Besides clinical and biochemical criteria, DCE-MRI has demonstrated the ability to discriminate between RA and psoriatic arthritis (PA), as previously discussed. A significant difference is in the relative enhancement rate (RER), at delayed acquisition 15 min after gadolinium injection has been reported between both entities. These results are a reflection of histopathology of synovitis in RA which has a higher cellularity and a greater number of recruited vessels compared with PA[26].

Juvenile idiopathic arthritis: Juvenile idiopathic arthritis has also been successfully evaluated with classical morphological MRI sequences, and more recently with functional imaging with promising results for the assessment of knee, wrist, and hip involvement[54,55]. DWI has several advantages in the depiction of bone edema and synovitis in young patients, including the lack of ionizing radiation, the ability to assess active and subclinical synovitis in patients with a difficult clinical examination, the identification of high-risk patients, and ultimately, in treatment monitoring[20].

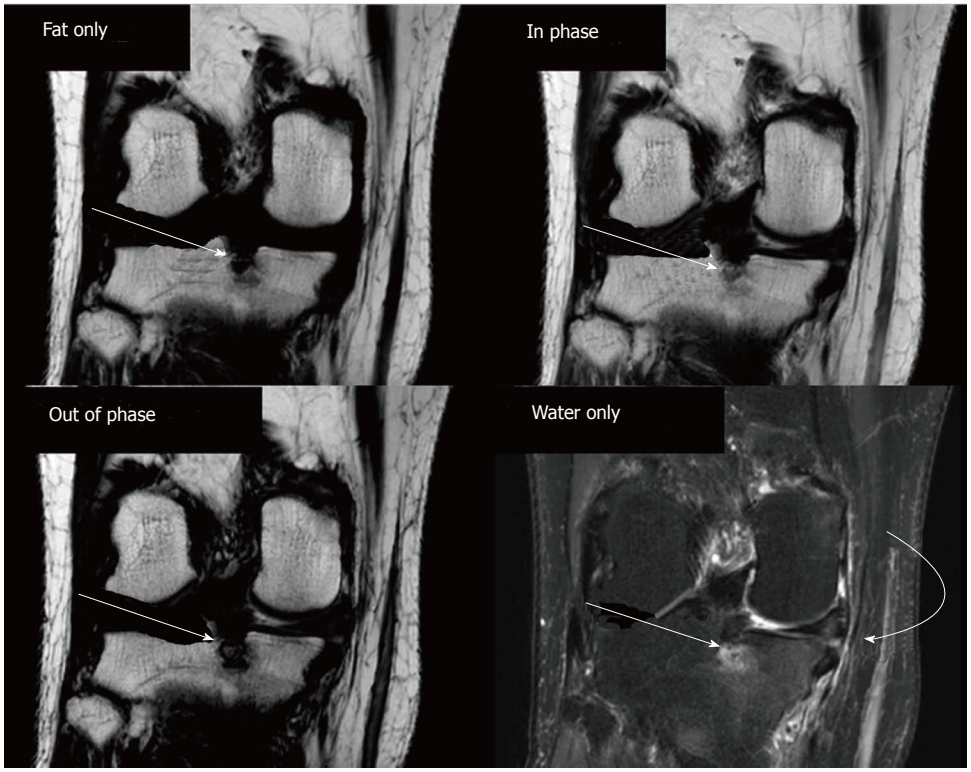

Figure 10 DIXON for evaluation of osteoarthritis in a 56-year-old woman with chronic knee pain. A subchondral geode is identified at the medial aspect of the medial tibial plateau (arrow), which is more conspicuous in the opposed-phase image than in the in-phase image suggesting edematous changes, as confirmed in the water-only acquisition. The water only image also shows soft tissue edema at the body of the medial meniscus and medial collateral ligament (curved arrow).

Finally, DCE-MRI has been proposed as a potential biomarker in children with juvenile idiopathic arthritis and wrist involvement demonstrating an association between clinical active disease and derived-parameters such as maximum relative enhancement[56].

Osteoarthritis

The active erosive changes that occur in the first phases of osteoarthritis (OA) may be studied by functional MRI sequences. If treatment is introduced in this phase, before reparative changes occur, the course of the disease may be altered enough to avoid joint deformities.

Based on DCE-MRI, differences between RA and OA can be found that reflects the different physiopathology of RA (inflammatory) and OA (degenerative). OA shows higher semi-quantitative (REE) and quantitative (K^{trans}, K^{ep}) values than control subjects, but lower ones than those in RA, likely due to an inferior angiogenic potential and decreased permeability of synovium in OA[57].

Joint imaging requires multiple planes and several fat-suppression sequences, factors that prolong the total scan time. Some studies have demonstrated that CSI and DIXON techniques, through in-phase and out of phase sequences as well as through the use of water only images, can accurately assess subchondral bone thickness while reducing the scan time (Figure 10)[58].

Early detection of cartilage damage may allow the treatment of patients with potentially better outcomes than in advanced OA stages[59]. As previously discussed, T2 mapping techniques are able to detect areas of elevated T2 values within normal-appearing hyaline cartilage on morphological sequences[60,61]. In OA, cartilage damage is usually present at high pressure points, unlike in RA and other inflammatory arthritis whereas can be seen at any area of cartilage joint surface[62].

Therapy monitoring

Functional MRI techniques for joint evaluation can be also used in treatment monitoring. As drugs used for modulation of articular disease progression in SI and other inflammatory arthritis have non-negligible adverse side effects, these advanced MRI sequences may accurately determine the effectiveness of treatment. Normalization of ADC values and signal intensity on DWI is related to proper treatment response, while the presence of high ADC values after treatment may reflect persistence of inflammatory signs[63]. For example, for SI, DWI has demonstrated the potential to be a tool for therapy monitoring of active sacroiliitis[47,63,64]. In inflammatory arthritis, the response to steroid and non-steroid anti-inflammatory drugs can be assessed by reduction of angiogenesis in DCE- derived parameters[65]. In a similar manner, in septic arthritis, DCE-MRI can aid in the assessment of response to antibiotherapy (Figure 11). Parameters derived from pharmacokinetic models, such as K^{trans} and K^{ep}, are also elevated in patients with RA, reflecting the increase in perfusion, extravascular space, and permeability in synovitis. Their reduction after successful treatment provides a mechanism for noninvasive

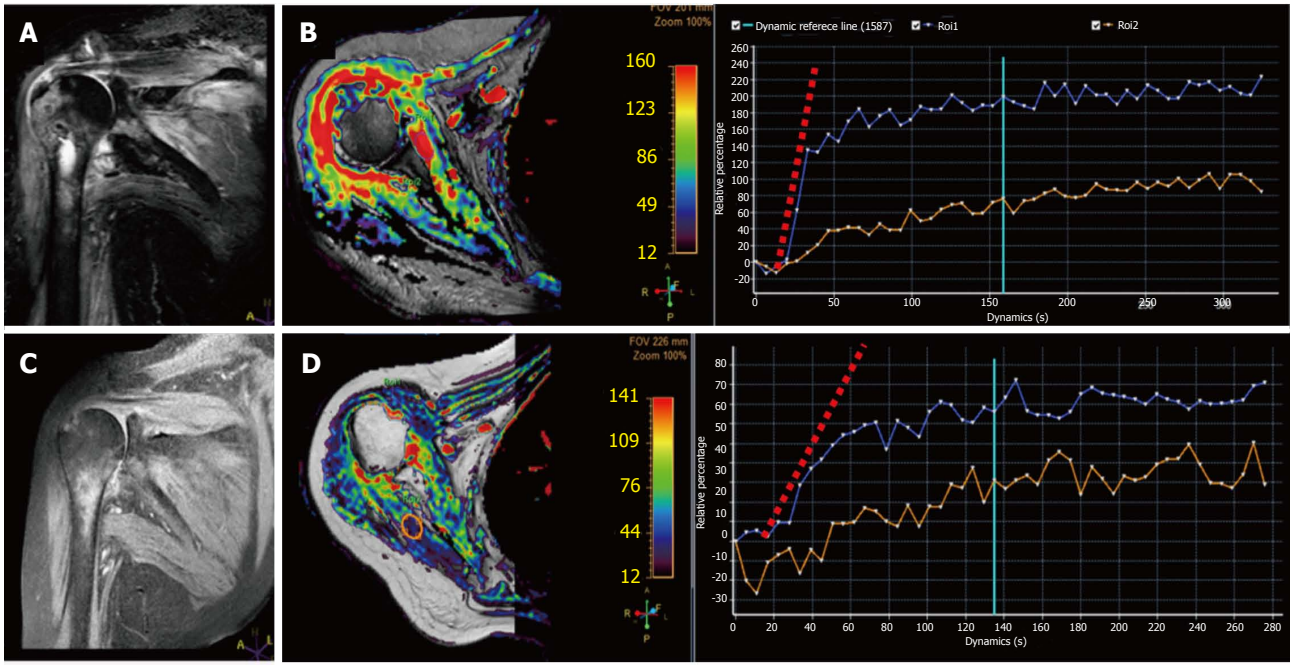

Figure 11 Magnetic resonance follow-up of septic arthritis in a 58-year-old woman with shoulder pain, fever, and swelling. A: Coronal STIR shows severe edema within the proximal humerus as well as in the surrounding soft tissues with minimal intraarticular fluid; B: DCE-MRI relative enhancement map demonstrates extensive enhancement in the synovium and the humeral head; C, D: Follow-up MRI study 3 wk after intravenous antibiotic therapy demonstrates adequate response to treatment with reduction of edema on STIR and enhancement on DCE-MRI. Note also the change in the initial slope of the blue TIC (synovial enhancement) between pre and post-treatment studies. The orange TIC shows healthy muscle contrast enhancement as an internal reference. STIR: Short inversion time recovery; DWI: Diffusion-weighted imaging; MRI: Magnetic resonance imaging; DCE: Dynamic contrast enhancement.

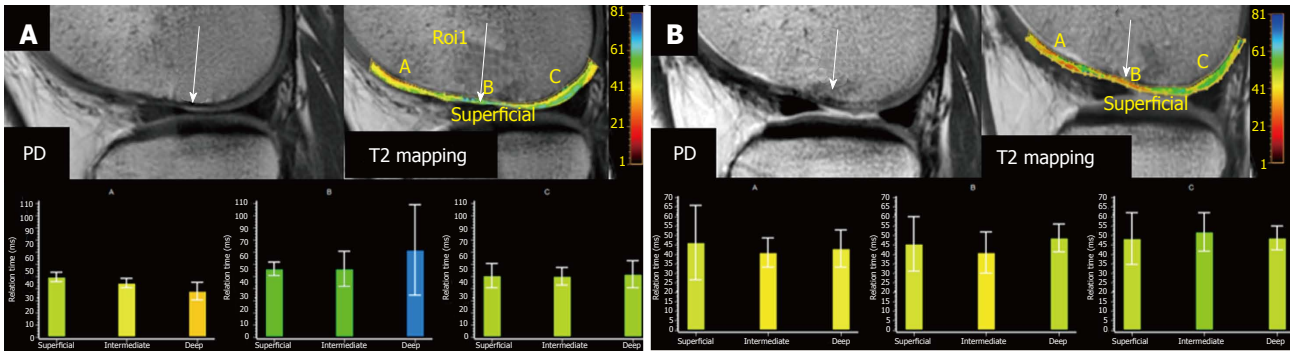

Figure 12 Treatment monitoring with magnetic resonance imaging in a 26-year-old gymnast with knee pain. Initial MRI (A) shows mild cartilage thinning at the medial femoral condyle with subchondral damage PD image. A moderate increase in T2 relaxation values (arrow) confirms the loss of collagen fibers in this area. Patient underwent MTX therapy and a follow-up MRI performed 3 mo later (B) demonstrates moderate chondral irregularity with focal areas of increased signal intensity on PD. T2 mapping demonstrates normalization of T2 relaxation time values compared with the pre-treatment study due to the generation of new fibrous cartilage. MRI: Magnetic resonance imaging; MTX: Microfracturing therapy; PD: Proton-density images.

treatment monitoring[31]. These parameters also allow for the discrimination between patients with active disease from inactive disease and healthy persons[66].

In a similar manner, for OA treatment monitoring, new specific drugs and cartilage repairing techniques have been developed trying to slow, or even revert, the progression of OA. Thus, accurate imaging biomarkers that can provide an earlier diagnosis of OA and can detect immediate signs of progression during treatment monitoring are crucial. The effectiveness of these treatments is closely related to their early introduction at the first stages of OA. Surgical techniques in patient with chondromalacia such as microfracturing therapy (MTX) and matrix autologous chondrocyte transplantation (MACT) are now used in clinical practice, and functional MR sequences may be able to assess the success or failure of the surgical intervention[67]. T2 values of the repaired tissue after MTX is initially lower than after MACT due to the presence of repairing fibrous cartilage rather than hyaline cartilage (Figure 12). However, during long-term follow-up, T2 values of the repaired cartilage in patients treated with MTX tend to normalize in comparison to the rest of cartilage. If this normalization does not occur, a therapy failure may

be considered[68].

CONCLUSION

The introduction of MRI for joint evaluation has improved the assessment of arthropathies. However, in many cases, conventional MRI studies are insufficient for a specific diagnosis and limited in their assessment of treatment success. A wide range of advanced MRI techniques are now available in musculoskeletal radiology and can be applied for evaluating arthritis. Technical improvements in fat suppression sequences such as DIXON enable a faster and better detection of bone involvement. DWI and DCE-MRI provide pathophysiological information regarding the cellularity and vascularization of bone and soft tissue in joint diseases, which can aid in determining the specific type of arthritis, the extent of disease, and the success or failure of treatment. T2 mapping allows the evaluation of early cartilage damage before conventional sequences, leading to earlier, and thus potentially more successful, treatment. Integration of these functional techniques within conventional protocols should be considered not only for diagnostic purposes but also for treatment monitoring of arthropathies.

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MINIREVIEWS

Mesenchymal stem cells for cartilage regeneration in osteoarthritis

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Abstract

Osteoarthritis (OA) is a slowly progressive disease where cartilage of the synovial joint degenerates. It is most common in the elderly where patients experience pain and reduce physical activity. In combination with lack of conventional treatment, patients are often left with no other choices than arthroplasty. Over the last years, multipotent stromal cells have been used in efforts to treat OA. Mesenchymal stem/progenitor cells (MSCs) are stromal cells that can differentiate into bone, fat, and cartilage cells. They reside within bone marrow and fat. MSCs can also be found in synovial joints where they affect the progression of OA. They can be isolated and proliferated in an incubator before being applied in clinical trials. When it comes to treatment, emphasis has hitherto been on autologous MSCs, but allogenic cells from healthy donors are emerging as another source of the cells. The first adaptations of MSCs revolved in the use of cell-rich matrix, delivered as invasive surgical procedure, which resulted in production of hyaline cartilage and fibrocartilage. However, the demand for less invasive delivery of cells has prompted the use of direct intra-articular injections, wherein a large amount of suspended cells are implanted in the cartilage defect.

Key words: Intra-articular injection; Mesenchymal stem cells; Osteoarthritis; Regeneration; Cartilage

Core tip: There are several published reviews of the role of multipotent stromal cells in osteoarthritis (OA) of the knee. However, there is also need for additional current therapeutic options and clinical trials of multipotent stromal cells for OA. We review additional therapeutic potentials of mesenchymal stem cells in knee OA using either autogenous or allogenic cells. Direct intra-articular injections of cells in suspension become a delivery method, being both relatively simple and cost effective compared to major surgical procedures. The amount of

cells injected is a critical factor; higher numbers of cells resulting in greater pain reduction and increased cartilage volume.

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INTRODUCTION

Increases in life expectancies and an ageing population results in rise of chronic and degenerative diseases which are becoming a major public health concern. Osteoarthritis (OA) is characterized by degeneration of articular cartilage, leading to articular cartilage damage, subchondral cysts, joint space narrowing, subchondral sclerosis, osteophyte formation at the joint margin, and synovitis[1]. Known risk factors include advancing age, genetics, obesity, mechanical stress and joint trauma[2]. Predominantly occurring in the elderly, OA can afflict any joints even nonweight-bearing ones. Major weight-bearing joints or joints under repetitive stress, including hands, hips and knees are in particular risk of developing OA[3]. Conservative treatment options do not stop the onset of OA and are mainly focused on pain control. They include physiotherapy, rehabilitation, pain relief with acetaminophen and non-steroidal anti-inflammatory agents, as well as intra-articular injection of hyaluronic acid (IA-HA). Although these therapeutic strategies may be helpful in reducing symptoms, they are no longer considered effective. Due to lack of compelling medical treatments, advance-stage OA patients often undergo total joint arthroplasty. Surgical procedures come with risks of failure and infection as well as the cost of hospital care, physiotherapy, and rehabilitation. The lack of conventional treatment, combined with risks and high costs of joint replacement surgery has driven researchers towards application of multipotent stromal cells for the repair of full thickness articular cartilage.

Mesenchymal stem/progenitor cells (MSCs) are multipotent stromal cells first identified and described in 1966 by Alexander Fridenstein[4]. MSCs from bone marrow (BM) have been demonstrated to exhibit differentiation potentials for mesodermal cell lineage, including osteo-, adipo-, chondro- and myogenic potentials[5]. MSCs are partly responsible for the maintenance and healing of connective tissues and Karp *et al*[6] indicated that MSCs could migrate from their reservoirs following tissue injury or inflammation.

MSCs are adult stem cells present in various parts of our body, for instance BM, peripheral blood, umbilical cord blood, fatty tissues, skeletal and cardiac muscles, Wharton's Jelly of umbilical cord, facet joints, interspinous ligaments, and ligamentum flavum[7-10]. They are primarily isolated from the BM, with major harvesting sites being the iliac crest, tibia and femur. MSCs are then separated from the rest of the marrow cells and expanded to obtain sufficient amounts. Adipose tissues are also rich in MSCs, even more so than BM with up to 1000 times more MSCs per gram of fatty tissues contrasted with that of BM[11]. Therefore, a sufficient amount of cells can be obtained from adipose tissues without the need of culture expansion, resulting in minimum manipulation of cells. MSCs grown under standard culture conditions feature a fibroblast like phenotype, exhibit plastic adherent property and are capable of giving rise to a cell colony derived from a single cells called colony-forming fibroblast unit[12], nonetheless only a fraction of the population remains clonogenic. The plasticity of MSCs has made them a promising candidate for various tissue engineering applications to treat several diseases including immune-mediated disorders, genetic abnormalities, and OA[13].

The publications reviewed here were collected manually from NCBI PubMed (https://www.ncbi.nlm.nih.gov/pubmed) from 1966 until December 2016. The following keywords or combination of keywords were used in the search engine to achieve the articles presented in this review: MSCs, OA, intra-articular injection, tissue engineering, and regeneration. Initial selection was done by screening titles and abstracts. No special screening process was applied, even though restrictions were utilized to select exclusively human investigation and the English language. Preference was given to clinical studies. Articles featuring pioneering methods or vast improvements of existing methods according to the author opinions were selected for this review. Figure 1 illustrates the flowchart and the assortment step.

MSCs AND OA

Synovial joints consist of number of different tissues and MSCs have been isolated from most of them although their functions within the joints are not yet fully understood. It has been suggested that they act as a source of cells which are able to be stimulated for the repair and reconstruction or regeneration of the joints. Moreover, they might also be involved in the suppression of T-cells to reduce inflammation within the joint[14]. Although chondrocytes are the predominant cell type within cartilage, MSCs have also been found to have no capability for cartilage regeneration after articular cartilage damage. Since MSCs are progenitors of young and mature chondrocytes, chondrogenic progenitor cells may help restore the superficial zone with lubricating glycoprotein to lessen friction in the articular cartilage (Figure 2)[15].

Murphy *et al*[16] revealed that MSCs isolated from end-stage OA patients showed impaired differentiation capacity as well as reduced proliferation activity *in vitro*. They compared BM-derived MSCs (BMSCs) from patients who underwent total knee arthroplasty

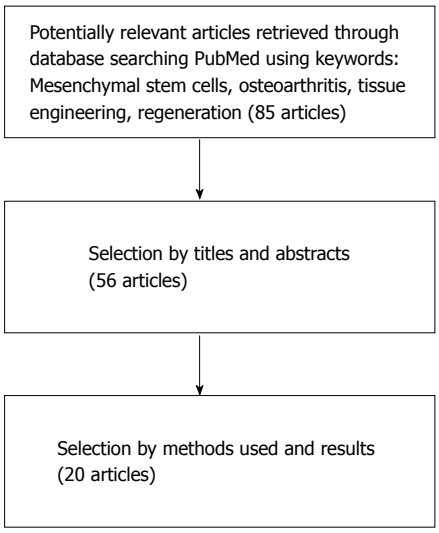

Figure 1 Flow chart representing the search and selection of articles for review.

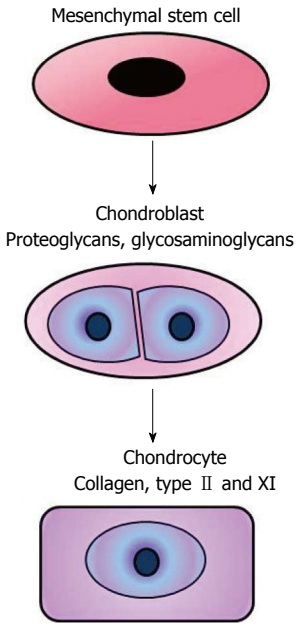

Figure 2 The way in which mesenchymal stem cells contribute to cartilage repair still remains unknown. Paracrine signalling and chondrogenic differentiation most likely play a crucial role.

(TKA) with cells isolated from healthy individuals. They reported that a significantly lower amount of MSCs could be isolated from OA patients and that they had reduced proliferation activity. Interestingly, they also observed the MSCs having altered differentiation profiles, favouring osteogenic differentiation, whilst having reduced adipogenic and chondrogenic potentials. Another study found that patients' age and stage of OA also affected the differentiation capability and expression of stemness genes of localized adipose-derived MSCs[17]. More shockingly, recent study reported that synovial fluid from OA patients inhibited the *in vitro* chondrogenic differentiation in MSC cultures of healthy donors[18]. Albeit, these functional deficiencies can be ameliorated by culture media supplementation with growth factors[19].

CELL BASED THERAPIES FOR CARTILAGE REPAIR

Cell based tissue engineering for OA have been used with varying results for over two decades. Autologous chondrocyte implantation (ACI) is a cell based technology wherein the cultured chondrocytes are applied on the injured area for regenerating and repairing cartilage[20]. This method has evinced promising outcomes in subjects with a variety of articular cartilage lesions that had responded poorly to prior treatments. However, the results have been conflicting[21] and the self-renewal rate and activity of chondrocytes is low, leading to slow an inadequate healing. Additionally, arthroscopy is required to obtain healthy cartilage from unaffected non-weight bearing joints and implanted during an open knee surgery, resulting in high costs, morbidity at donor sites and increased stress for patients. Reductions in pain, improvements in the joint function and the formation of functional hyaline cartilage have all been reported. The destruction of articular cartilage is irreversible in OA and does not relieve symptoms. Patients are often left with no other choice than total joint replacement. Consequently, autologous chondrocyte implantation may not be a favourable surgical procedure for subjects with OA. In addition, this method faces challenges with cartilage tissues having a limited capacity for repair. Accordingly, MSCs are emerging as a potential substitute or alternate cellular materials for more durable treatment of cartilage defects.

MICROFRACTURE AND MSCs

Microfracture is a well-established and studied surgery technique that stimulates migration of cells from the BM to cartilage lesions. Small holes are drilled at the target site into the subchondral BM which then bleeds into the lesion and forms a clot of marrow cells, including BMSCs[22]. This technique has given good results on small lesions but comes with limitations. BMSCs are only a portion of total cells within the BM and a relatively few BMSCs are recruited through microfracture being inadequate treatment for bigger cartilage lesions. Researchers have focused on isolating and expanding cells before applying them to the target area and a number of studies illustrated successful BMSC treatment for repairing focal chondral defects. Knowledge on MSC extraction, chondrogenic capacity, and tissue engineering has encouraged scientists and surgeons to test clinical potentials of MSCs to stop and reverse onset of OA, as well using their plastic adherent ability to resurface large cartilage lesions and facilitate osteochondral integration within the affected joints (Figure 3).

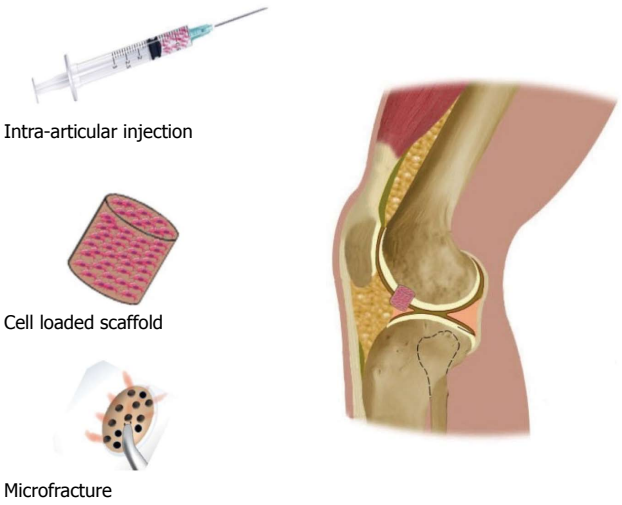

Figure 3 There are 3 major methods in which mesenchymal stem cells can be applied: Intra-articular injection of mesenchymal stem cell suspension, implantation of cell-mixed composite scaffold, and microfracture through articular cartilage and subchondral bone.

Buda *et al*[23] established a one-step surgical procedure which employs BMSCs to heal osteochondral lesions of the knee. The procedure was completed in a single setting where BM aspiration and concentration were accomplished in the same operating room as knee arthroscopy. The BM aspirate concentrate was fixed in hyaluronic acid blended membranes before being transplanted to the site where it was applied with autogenous platelet-rich-fibrin glue, providing growth factors to further stimulate the healing process. All of the patients treated with this technique showed significant improvements for parameters measuring the severity of OA and pain scores. Moreover, magnetic resonance imaging (MRI) showed that the cartilage lesion was fully covered in at least 70% of the subjects. This method was both feasible and effective for treating most of the patients enrolled and the whole process could be completed within a day. Furthermore, it did not require any cell expansion or manipulation, reducing costs and risks involved. Nevertheless, as only a fraction of BM cells are MSCs, one may speculate that the quantity of MSCs recruited this way was somewhat unsatisfactory. Another major contributing factor might have been growth factors embedded in the platelet-rich-fibrin glue produced from the peripheral blood of the subjects. Gobbi *et al*[24,25] reported a similar "one-step cartilage repair" technique in 2011 and 2014. The advantage of the one-step approach is that it only requires one surgery and it involves no long-term cell expansion, resulting in fewer visits to the clinic. However, it is nearly impossible to estimate the number of MSCs recruited in this process making standardized treatment with reproducible results challenging.

INTRA-ARTICULAR INJECTION OF MSCs

In 2008, Centeno *et al*[26,27] reported two male patients with knee OA. MSCs were harvested from the posterior superior iliac spine and simultaneously venous blood was harvested to prepare platelet lysate (PL) containing growth factors to facilitate the repair. The first subject received an injection of one milliliter of phosphate-buffered saline (PBS) consisting of 2.2×10^7 MSCs. The second subject received 4.6×10^7 MSCs suspended in one milliliter PBS. Both cases then received one milliliter of 10% PL in PBS one and 2 wk after the initial injections. Additionally, after one week, the subjects obtained intra-articular injection of dexamethasone as low-dose dexamethasone treatment has been demonstrate to stimulate chondrogenic differentiation[12]. Modified visual analogue scale (VAS) scores have been utilized to estimate pain followed by MRI to evaluate cartilage volume. Both subjects showed improvements in VAS scores and cartilage volume following 3 and 6 mo follow-up with up to 28.6% cartilage volume increase. While a decrease was also observed in the latter patient, it was not considered significant since it was below the measurement error. These studies revealed that increased cartilage volume and reduction in pain could be achieved with minimum invasive measures and is a promising treatment for OA. However, a major weakness in these cases was the short follow up time consisting of 6 mo for the first and 3 mo for the second patient. Besides, long-term follow-up results are unavailable.

In recent years, Wong *et al*[28] examined the outcomes of BMSC injection following a microfracture and medial opening-wedge high tibial osteotomy (HTO). The study was a randomised controlled trial that included 56 patients with unicompartmental osteoarthritic knees. The participants were classified into two groups, all received HTO combined with microfracture, and 3 wk later the intervention group received an intra-articular injection of 1.5×10^7 autologous BMSCs suspended in hyaluronic acid, while the control group obtained exclusively hyaluronic acid. The observed time spanned two years, during which both groups showed improvements in the International Knee Documentation Committee scores as well as Tegner and Lysholm scores. Interestingly, the intervention group showed significantly better improvements in all parameters. Moreover, MRI performed 1 year following injections, found cartilage thickness to be significantly greater in the intervention group. In this study, MSCs were recruited for cartilage repair by two means, such as microfracture in both groups and intra-articular injections in the intervention group. In conclusion, the postoperative injection of culturally expanded MSCs, significantly improved the treatment outcome and rate of cartilage regeneration. Additionally, the MSCs could be collected during operation and proliferated in culture to achieve sufficient numbers before the patients return to the hospital. Although microfracture and HTO are an effective means to treat OA, they are still major surgical procedures with high cost and risk.

Table 1 Summary of studies using mesenchymal stem cells for cartilage regeneration in osteoarthritis

Ref.	Type of study	Type of cells	Significance
Wakitani *et al*[33]	Case and control study	Autologous BMSCs from Iliac crest	Autologous BMSCs cell implants are effective for treating OA cartilage defects in humans, producing hyaline like cartilage
Centeno *et al*[26]	Case study	Autologous BMSCs from Iliac crest	Autologous BMSCs can be introduced by intra-articular injections into an osteoarthritic knee promotes cartilage regeneration and reduction pain
Buda *et al*[23]	Case series	Autologous BMSCs from Iliac crest	One-step repair technique utilising bone-marrow concentrate is a simple and time-efficient way to treat large chondral defects
Koh *et al*[34]	Case and control study	Autologous AMSCs from infrapatellar fat pad	Intra-articular injections of AMSCs are a safe treatment option, reducing pain and improving the function of knee OA patients
Wong *et al*[28]	Randomized control trial	Autologous BMSCs from Iliac crest	Postoperative intra-articular injections of autologous BMSCs improves the MOCART outcomes of patients with varus knees undergoing HTO and microfracture
Vangsness *et al*[30]	Randomized, double-blind, controlled study	Allogenic BMSCs from 18-30 years old donors	Postoperative intra-articular injections of allogenic BMSCs contribute to meniscus regeneration and reduction in pain following medial meniscectomy
Jo *et al*[29]	Cohort study	Autologous AMSCs from abdominal subcutaneous fats	Cartilage regeneration and pain reduction is significantly improved when high amounts of AMSCs are injected into OA knees compared with low amounts
Sekiya *et al*[35]	Therapeutic study	Autologous synovial MSCs	Localized synovial MSCs can be used to treat cartilage defects resulting in hyaline like cartilage and improved pain scores

AMSCs: Adipose-derived MSCs; BMSCs: Bone marrow-derived MSCs; HTO: High tibial osteotomy; MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue; MSCs: Mesenchymal stem cells; OA: Osteoarthritis.

DETERMINATION OF THE OPTIMAL DOSE

In 2014, Jo *et al*[29] investigated the dose effects of MSCs in OA treatment. Their phases Ⅰ/Ⅱ clinical trial consisted of 18 patients suffering from knee OA who received injections of adipose-derived MSCs. In phase Ⅰ, patients were divided into 3 groups receiving either low dose (1.0×10^7), mid dose (5.0×10^7) or high dose (1.0×10^8) injections of MSCs. Whereas in phase Ⅱ, the high dose treatment was given to 9 patients. The MSCs were harvested from abdominal subcutaneous fats *via* liposuction before being suspended in 3 mL of saline and injected into the knee joints. During the 6 mo follow up period, the high dose group showed a significant reductions in Western Ontario and McMaster Universities Arthritis Index scores, VAS pain scores and improvements were also observed in the low and mid dose groups. Although, pain improvements were observed in the low dose group, the size of the cartilage defect increased, whereas in the mid and high dose groups it showed significant reduction in size. Arthroscopy and histological staining further revealed the presence of hyaline-like cartilage covering the site in the high dose group. No adverse effects were observed during the follow-up time and the researchers concluded that the high dose treatment reduced pain, was safe and improved the knees function by forming hyaline-like cartilage.

ALLOGENIC MSCs FOR TREATMENT

The first randomised, double blinded control study was reported in 2014 when Vangsness *et al*[30] treated 55 patients with allogenic MSCs. Furthermore, it was the first study investigating the safety, effectiveness and clinical outcome of intra-articular injections of non-matched human leukocyte antigen (HLA) allogenic BMSCs. Patients were blindly divided into 3 groups, and all groups underwent partial medial meniscectomy. Afterwards, group A received 5.0×10^7 cells and group B 1.5×10^8 cells in 5 mL injections of HA, whereas the control group received only HA. Patients were evaluated before and 2 years post-treatment using MRI to measure cartilage volume and VAS scores for measuring level of pain. The MRI revealed a significant increase in cartilage volume, with group A showing the best outcome. Pain reduction was observed for groups A and B, whilst no pain reduction was recorded in the control group. Even though cartilage growth was not observed in all patients, the study confirmed the effectiveness and safety of using non-matched HLA allogenic BMSCs. Several reports have since demonstrated the successful treatment of cartilage regeneration using MSCs in OA (Table 1). Recent evidences have highlighted the importance of MSCs from development to postnatal joint homeostasis and OA[31]. Possible mechanisms of MSCs in the treatment of OA may be attributed to the ability of MSCs to initiate the repair process by promoting cartilage regeneration[32]. Further research efforts will be needed to better understand the exact role of MSCs in the treatment of OA.

CONCLUSION

In summary, these studies show that MSCs can be employed successfully to treat mild to moderate OA through various ways. They provide alternative treatment options and treatment can start early during progression of OA. The traditional major surgeries used to treat late stages are expensive and come with risks. The less invasive techniques outlined in this minireview

have revealed good outcomes, but the field merits further investigation. Superior outcome was evident with greater quantity of MSCs injected. Allogenic cells from healthy young donors can also be utilized. These findings have further empowered researchers to investigate the potentials of MSCs for tissue engineering and a number of clinical trials are now underway. Most of the emphasis on minimally invasive therapeutic alternatives including intraarticular injections of MSCs, aim to cut out cost and risks of major surgeries. Additional investigations are warranted to validate the safety and efficiency of different application before a standardized treatment regimen can be established.

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ORIGINAL ARTICLE

Basic Study

Electron probe microanalysis of experimentally stimulated osteoarthrosis in dogs

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Abstract

AIM

To develop methods of articular cartilage preparation for X-ray-electron probe microanalysis and to study its elements content in experimental osteoarthrosis.

METHODS

Twenty dogs aged 2-8 years were divided in research (aged 2 years, induction of osteoarthrosis - IOA) and intact group. Intact group included three subgroups (aged 2, 5 and 8 years). Samples of cartilage after araldite saturation and pouring were partially cut into semithin sections stained with methylene blue and with methylene blue-basic fuchsin. Their smooth surfaces were investigated by X-ray-electron probe microanalysis. Spatial distribution of sulfur, calcium and phosphorus and their concentrations (weight %) were investigated.

RESULTS

X-ray electron probe microanalysis revealed non-uniform

sulfur distribution in cartilage of intact animals: Its content increases from superficial zone to deep one, this regularity was preserved in animals with IOA. Differences of IOA with spontaneous chondropathy were revealed. Spontaneous aging was characterized by calcium and phosphorus storage in deep and calcified zones and compensatory increase of sulfated glycosaminoglycans in intermediate and deep cartilage zones as evidenced by the metachromatic reaction and microanalysis data. Unlike spontaneous chondropathy connected with aging in experimentally stimulated osteoarthrosis more intensive storage of calcium but minor phosphorus in intermediate zone were marked. In IOA the calcified cartilage thinning and osteoclastic resorption are apparent with few changes of elements composition; the only difference from control is minority phosphorus content.

CONCLUSION

The obtained results demonstrate specific tricks of X-ray electron probe microanalysis and its possibility in the research of mechanisms of articular cartilage alterations in osteoarthrosis.

Key words: Osteoarthrosis; Articular cartilage; Dog; X-ray electron probe microanalysis

Core tip: In this basic study we present the development of methods of articular cartilage preparation for X-ray-electron probe microanalysis and elements content in articular cartilage in animal experimentally induced (IOA) osteoarthrosis and during spontaneous animal aging (SA). SA was characterized by calcium and phosphorus storage in deep and calcified articular cartilage zones and compensatory increase of sulfated glycosaminoglycans in intermediate and deep zones. In IOA more intensive storage of calcium but few phosphorus in intermediate zone were marked. As for Sulphur content, all zones of uncalcified cartilage in two-year-old animals with IOA were comparable with cartilage of five-year-old intact animals.

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INTRODUCTION

Osteoarthrosis (OA) has great social impact in terms of disability, pain, illness and treatment costs. Pathogenesis of OA involves the structures of the whole joint especially subchondral bone and synovium but is characterized predominantly by articular cartilage destruction[1]. Cartilaginous tissues possess relatively few amounts cells (chondrocytes) that account 1%-5% of volume[2] and large amounts of extracellular matrix that constitutes the bulk of tissue and protects chondrocytes from mechanical overloading.

Cartilage destruction in osteoarthrosis is multifactorial cascade process in which participate both cells and extracellular matrix, especially sulfated glycosaminoglycans. These last are included in proteoglycans and play the leading role in support of tissue homeostasis, architectonics and mechanical stability, cellular mitogenic activity, receptive functions and intercellular relations[3].

Mineralization of cartilage has been associated with OA progression and cartilage destruction[4] but some authors consider it as primarily an effect of aging[5].

A lot of biochemical and microscopical methods are used in modern researches of cartilage content and structure but X-ray-microprobe analysis was performed very rare though it permit to evaluate glycosaminoglicans and mineral content by corresponding chemical elements.

To develop the optimal methods of articular hyaline cartilage sample preparation for X-ray-electron probe microanalysis and to compare its elements content in intact animals and in animals with experimentally induced osteoarthrosis.

MATERIALS AND METHODS

Twenty healthy adult mongrel dogs of either sex, aged 2-8 years, weighing 18-25 kg, were used in this study. All animals have received human care in compliance with the protocol approved by the Institutional Ethical Committee. The animals were acclimatized to laboratory conditions for one month prior experimentation. Dogs were housed in individual cages (floor area 4.5 m^2) and were provided water three times daily and food two times daily with a measured volume. Animals were divided in research (aged 2 years) and intact group (control). Intact group included three subgroups (aged 2, 5 and 8 years). In research group modelling of primary gonarthrosis was performed by reduction of limb blood supply and knee immobilization[6]. So, dogs of research group were operated. Anesthesia was first induced with intramuscular injections of atropine, dimedrol and xylazine and then maintained with intravenous injection sodium pentobarbital (30 mg/kg *i.v.*). Briefly, each femoral artery was freed from surrounding tissues and after proximal and distal ligation was resected. Each knee joint were immobilized with external fixation apparatus. After 28 d of immobilization dogs of research group were euthanized. Dogs of intact group were also euthanized by barbiturate overdose (intravenous injection, 150 mg/kg pentobarbital sodium) for tissue collection.

Samples of cartilage were harvested from lateral femoral condyles - presented in Figure 1A. Samples consisted of slices 2-3 mm thick, 5-6 mm long and 2-3 mm wide were cut with a scalpel tangentially within

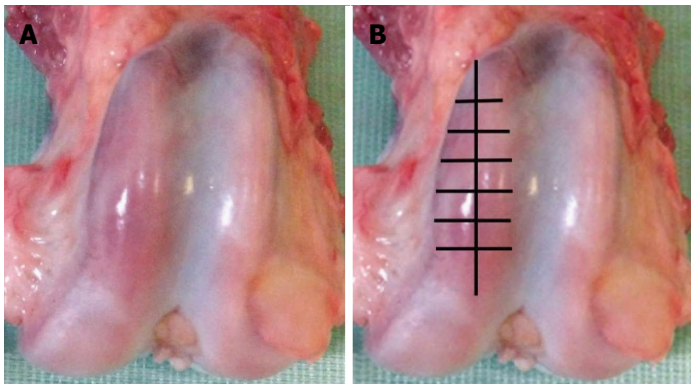

Figure 1 Condyles of canine thigh bone after experimental modelling of osteoarthrosis (A), scheme of articular cartilage harvesting (B).

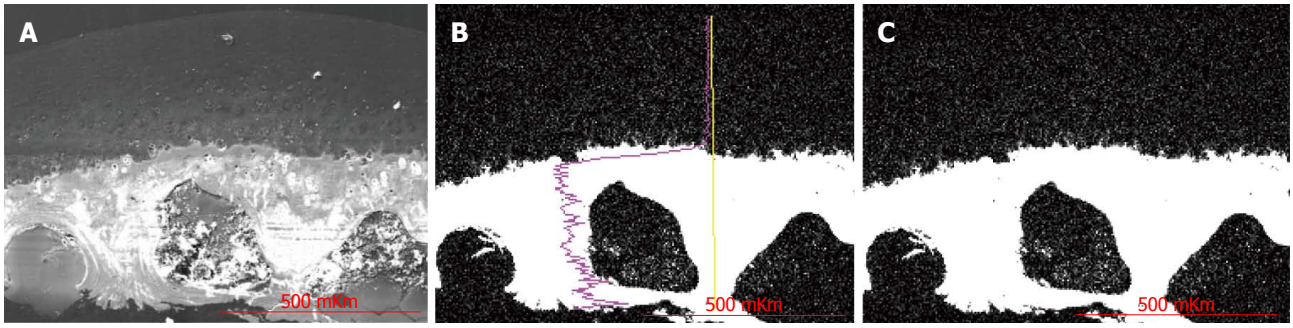

Figure 2 X-ray electron probe microanalysis of articular cartilage in intact dog. A: SEM micrograph of articular cartilage and subchondral zone; B: Scanning line regimen, graph shows calcium distribution on line; C: Scanning area regimen shows calcium distribution on the sample surface. Instrumental magnification × 110.

articular cartilage - presented in Figure 1B. Samples were fixed in glutaraldehyde-paraformaldehyde mixture excluding postfixation in tetraoxide osmium because X-ray peaks of heavy metals may mask and overlap on rays of analyzed elements[7,8]. Taking into consideration very high water content in cartilage[2] the specimens were dehydrated with smooth transition from ethanol to aceton according to known methods[9] but with increasing of exposition in 70%-96% ethanol to within the hour. Stages of araldite saturation and pouring were performed according to recently described method[10]. Increased density of cartilage matrix in araldite in comparison with native material decrease volume of X-ray excitation and provide the increase of microanalysis sensitivity.

Further investigation included two stages. At the first stage epoxy blocks were partially cut into semithin (1 mkm) sections with a glass knife using ultramicrotome "Nova" (LKB, Sweden). Slices were stained with methylene blue (metachromatic reaction for sulfated glycosaminoglycans) and with methylene blue-basic fuchsin (for detection of matrix basophily). Histology slides were examined using the "Opton-3" photomicroscope (Germany).

At the second stage smooth surfaces of epoxy blocks resulting from semithin slices cutting were investigated by X-ray-electron probe microanalysis. This technique prevents artifacts and saves the sample preparation time excluding the stage of grinding and polishing.

Three blocks was selected randomly from each animal. They were attached to polished clean aluminium discs with current-conducting adhesive. Surfaces of epoxy blocks were exposed to silver deposition using Eico IB-6 ion coater and JEOL JEE-4X vacuum evaporator. The investigation of element composition was performed using scanning electron microscope JSM-840 (JEOL, Japan) equipped with energy dispersive X-ray analyser (INCA 200, Oxford Instruments).

Results were obtained as smart maps, showing spatial distribution of elements and quantitative data in weight per cents. Spatial distribution of sulfur, calcium and phosphorus and their concentrations (ωS, ωCa, ωP - weight %) were investigated. For standard results equipment was calibrated by comparison templet made of wollastonite (CaO: SiO_2). Two regimens were used for collecting X-ray spectra: Scanning line and scanning area - presented in Figure 2. In the second regimen strict longitudinal alignment of parallel scanning rows without overlapping fields provided the most representative total sample.

Statistical analysis

For quantitative data analysis the unpaired Student *t* test and Mann-Whitney *U* test were used (software package Attestat Program, version 9.3.1, developed by I.P. Gaidyshev, Certificate of Rospatent official registration No. 2002611109). If the *P*-value was less than 0.05, the data was considered statistically significant.

RESULTS

In 2 years-aged intact group metachromatic reaction in

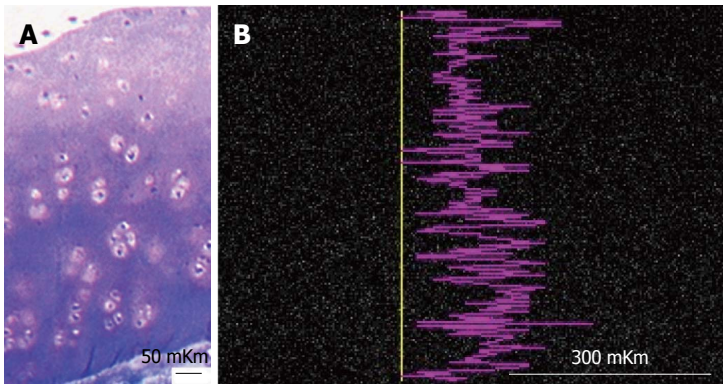

Figure 3 Articular cartilage of intact dog. A: Semithin section, methylene blue stain. Ob. -6.3 x; oc. -12.5 x; B: Smart map shows sulphur distribution on scanned line. Instrumental magnification 170.

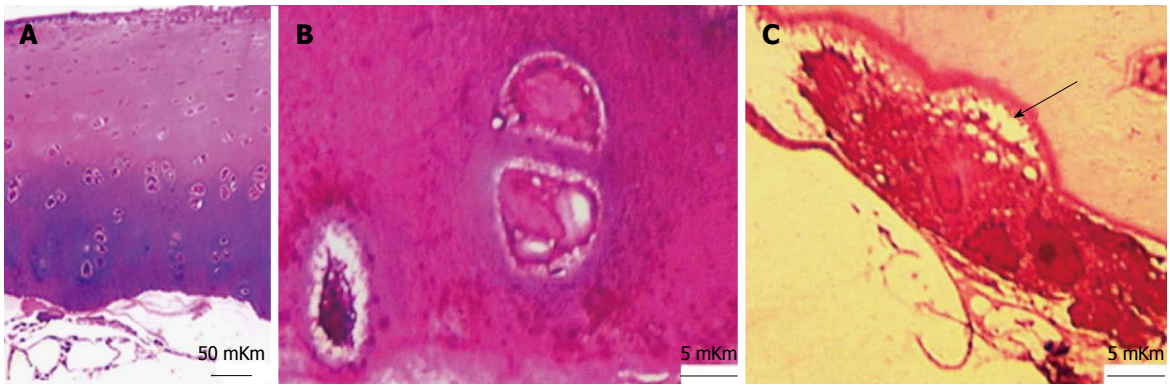

Figure 4 Articular cartilage in dog with experimentally induced osteoarthrosis. Methylene blue - basic fuchsin staining. A: General appearance. Ob. - 6.3 x, oc. - 12.5 x; B: Focal basophilia of intercellular matrix in deep zone. Ob. - 100 Ol, oc. - 12.5 x; C: Osteoclast, resorbing the ground substance of calcified cartilage. Howship lacuna (arrow). Ob. - 100 Ol, oc. - 12.5 x.

interterritorial matrix of superficial zone was moderate but in territorial matrix of intermediate and deep zones it was highly intensive - presented in Figure 3A. X-ray electron probe microanalysis revealed nonuniformity of Sulphur zonal distribution - presented in Figure 3B.

In IOA (induced osteoarthrosis) group metachromatic reaction was localized, its intensity was lowered and accompanied with fibrillation of matrix in superficial zone. Intensively basophilic matrix was revealed in intermediate and deep zones and presented in Figure 4A and B. The calcified cartilage zone was thinned or absolutely absent in some areas (Figures 4A and 5). At the borderline between calcified cartilage and subchondral bone the osteoclastic resorption was marked - presented in Figure 4C.

In 5 years-aged intact group histochemical reaction for sulfated glycosaminoglycans was weak, metachromasy was focal (Figure 6A), matrix of superficial zone was basophilic, many of cells had signs of destruction.

In 8 years-aged intact group metachromatic reaction was also focal, locuses of intensive metachromasy were revealed in intermediate and deep zones (Figure 6B), cartilaginous cells had increased sizes, light homogeneous nuclei and basophilic cytoplasm. Territorial matrix of deep zone was basophilic.

In IOA group ωS were decreased in all of cartilage zones besides calcified, but its distribution with maximal meanings in intermediate and deep zones was the same as in two-year-old intact group. In five-year-old intact group in comparison with two-year-old intact group ωS was decreased in superficial, intermediate and deep zones, but increased in calcified cartilage. In eight-year-old intact group in comparison with two-year-old intact group ωS was increased in intermediate, deep and calcified cartilage zones, but not in superficial zone - presented in Table 1.

In IOA group in comparison with two-year-old intact group ωCa was increased in all zones of cartilage besides the calcified. In five-year-old intact group ωCa was increased only in superficial zone and in calcified cartilage. In eight-year-old intact group more expressed increase in deep and calcified zones were marked (Table 1).

Changes of ωP were differently directed. In IOA it was increased in intermediate and deep zones but decreased in calcified cartilage. In 5 years-aged and especially in 8 years-aged intact groups ωP was increased in all zones including calcified cartilage - presented in Figure 7 and Table 1.

DISCUSSION

So, X-ray electron probe microanalysis revealed non-uniform serum distribution in cartilage of intact animals: its content increases from superficial to deep zone,

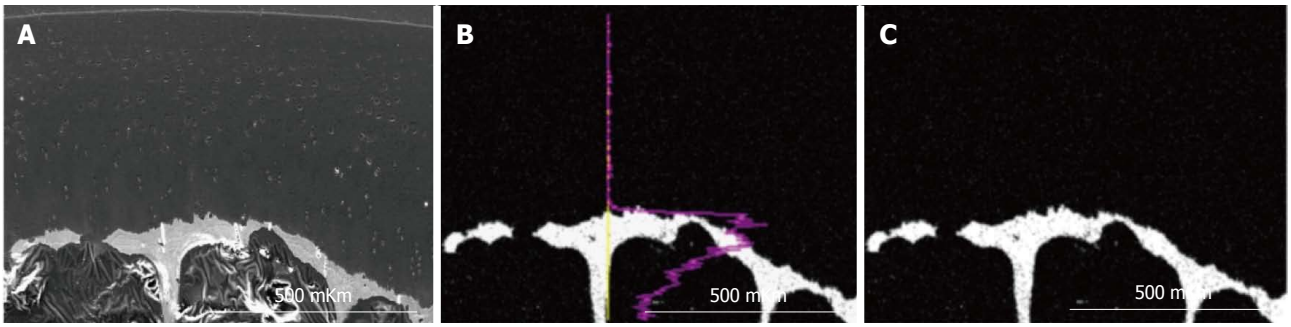

Figure 5 X-ray electron probe microanalysis of articular cartilage in dog with experimentally induced osteoarthrosis. A: SEM micrograph of articular cartilage and subchondral zone; B: Scanning line regimen, graph shows calcium distribution on line; C: Scanning area regimen shows calcium distribution on the sample surface. Instrumental magnification 100.

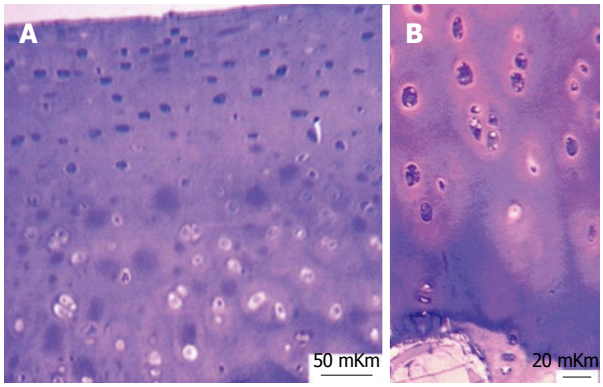

Figure 6 Age-related changes of articular cartilage in intact group. Semithin section. Methylene blue - basic fuchsin staining. A: Focal metachromasy of articular cartilage in five year old dog. Ob. -6,3 x; oc. - 12,5 x; B: Intensive metachromasy in intermediate and deep zones of articular cartilage in eight year old dog. Ob. -16 x; oc. - 12,5 x.

this regularity was preserved in animals with induced experimental osteoarthrosis. The obtained data are in agreement with literature: The aggrecan content in superficial zone is lower than in others[11]. It is known that metabolism of sulfated glycosaminoglycans changes in the early stages of articular cartilage damage[12].

Recently we obtained histological characteristics of articular cartilage in experimentally induced osteoarthrosis[13,14] corresponding to grade 1-3 according to OARSI classification[15]. It was revealed[14] that in this experimental model chondrocytes of intermediate zone were the most vulnerable: More than 50% cells had signs of necrosis or apoptosis. It is known that apoptotic bodies contain alkaline phosphatase and precipitate calcium promoting cartilage calcification[16].

According to other authors hypertrophic chondrocytes of osteoarthrotic cartilage produce large amounts of collagen X, matrix proteinase 12 and alkaline phosphatase influencing calcification[17]. Ohira and Ishikawa[18] (1986) found precipitates of hydroxiapatite crystals around degenerated chondrocytes.

In current research substantial difference of experimentally induced osteoarthrosis from spontaneous chondropathy were revealed. Spontaneous aging characterizes by calcium and phosphorus storage in deep and calcified zones and compensatory increase of sulfated glycosaminoglycans in intermediate and deep cartilage zones as evidenced by the metachromatic reaction and microanalysis data. Unlike spontaneous chondropathy connected with aging in experimentally reduced osteoarthrosis more intensive storage of calcium but minor phosphorus in intermediate zone were marked. The revealed contradistinction is in agreement with research of human aging, which leads to suggest that phosphorus exuded from bones storages in arteries and cartilage tissue[19].

In experimentally induced osteoarthrosis the calcified cartilage thinning and osteoclastic resorption are apparent with few changes of elements composition; the only difference from control is minority phosphorus content.

Preparation of biologic samples for X-ray electron probe microanalysis perform according the same principles as preparation for electron microscopy but possess its own specific tricks; peculiar properties of research object also must be taken into consideration. The obtained results demonstrate definitely the possibility of X-ray electron probe microanalysis in the research of mechanisms of articular cartilage alteration in osteoarthrosis, these changes is documented and assessed quantitatively.

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COMMENTS

Background

Multiple biochemical and microscopic methods are used in modern researches of cartilage content and structure in normal and diseased human and animal beings but X-ray-microprobe analysis was performed very rare though it permit to evaluate glycosaminoglicans and mineral content by corresponding chemical elements. The optimal methods of articular hyaline cartilage sample preparation for X-ray-electron probe microanalysis and comparison of its elements content in intact animals of different ages and in animals with experimentally induced osteoarthrosis were not investigated.

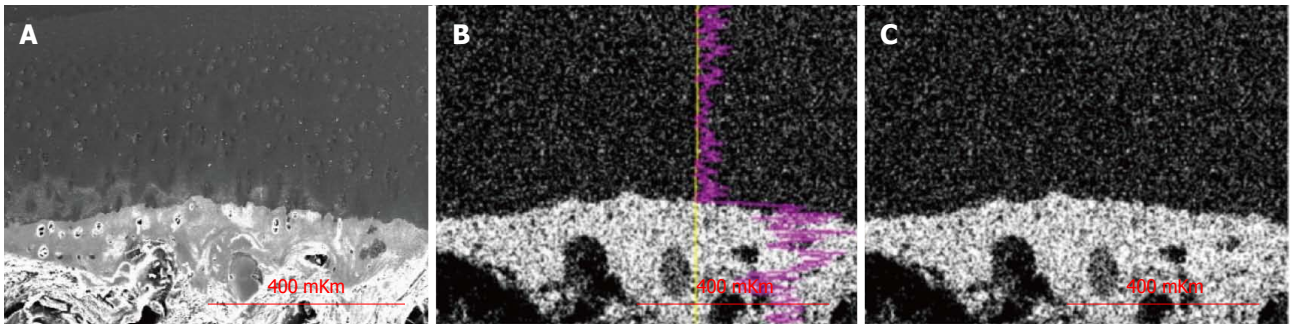

Figure 7 X-ray electron probe microanalysis of articular cartilage in intact five years old dog. A: SEM micrograph of articular cartilage and subchondral zone; B: Scanning line regimen, graph shows phosphorus distribution on line; C: Scanning area regimen shows phosphorus distribution on the sample surface. Instrumental magnification 120.

Table 1 Content of chemical elements in canine articular cartilage

Cartilage zones/groups	Superficial zone	Intermediate zone	Deep zone	Zone of calcified cartilage
ωS (mean ± SD, weight%)				
IOA in 2 yr	0.18 ± 0.04[a]	0.23 ± 0.02[a]	0.28 ± 0.03[a]	0.13 ± 0.02
Intact				
2 yr (control)	0.35 ± 0.01	0.42 ± 0.04	0.52 ± 0.02	0.14 ± 0.02
5 yr	0.20 ± 0.02[a]	0.28 ± 0.04[a]	0.34 ± 0.02[a]	0.28 ± 0.04[a]
8 yr	0.33 ± 0.03	0.52 ± 0.01[a]	0.63 ± 0.04[a]	0.41 ± 0.07[a]
ωCa (mean ± SD, weight%)				
IOA in 2 yr	0.04 ± 0.02	0.08 ± 0.02[a]	0.15 ± 0.02[a]	9.72 ± 0.03
Intact				
2 yr (control)	< 0.01	0.04 ± 0.01	0.09 ± 0.01	13.93 ± 0.02
5 yr	0.04 ± 0.01	0.05 ± 0.03	0.10 ± 0.02	16.16 ± 1.04[a]
8 yr	0.03 ± 0.02	0.05 ± 0.03	0.22 ± 0.02[a]	21.16 ± 3.04[a]
ωP (mean ± SD, weight%)				
IOA in 2 yr	< 0.02	0.03 ± 0.01	0.08 ± 0.01	4.74 ± 0.02[a]
Intact				
2 yr (control)	< 0.01	< 0.01	< 0.01	6.89 ± 0.01
5 yr	< 0.02	0.07 ± 0.01[a]	0.09 ± 0.02[a]	7.44 ± 1.47[a]
8 yr	0.04 ± 0.02[a]	0.09 ± 0.02[a]	0.11 ± 0.02[a]	9.44 ± 1.29[a]

[a]$P < 0.05$, *vs* control.

Research frontiers

Previous research have already proved that in this experimental model of primary osteoarthrosis chondrocytes of intermediate zone were the most vulnerable and that apoptotic bodies promote cartilage calcification.

Innovations and breakthroughs

This is the first study evaluating substantial difference of experimental gonarthrosis induced by reduction of limb blood supply and knee immobilization from spontaneous age-related chondropathy. The optimized methods of articular hyaline cartilage sample preparation for X-ray-electron probe microanalysis are described.

Applications

In experimentally induced osteoarthrosis the uncalcified cartilage was characterized with minority Sulphur content, calcium and phosphorus storage in comparison with intact animals of corresponding age. The calcified cartilage thinning and osteoclastic resorption in induction of osteoarthrosis are apparent with few changes of elements composition; the only difference from control is minority phosphorus content.

Terminology

Experimentally stimulated osteoarthrosis in used biological model histologically corresponds to grade 1-3 according to OARSI classification.

Peer-review

Stupina *et al* developed methods of articular cartilage preparation for X-ray-electron probe microanalysis and to study its elements content in experimental osteoarthrosis. It is well designed and written manuscript. It is a potential important study to the fields of osteoarthrosis research, diagnosis and therapy.

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ORIGINAL ARTICLE

Basic Study

Benefits of Ilizarov automated bone distraction for nerves and articular cartilage in experimental leg lengthening

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Abstract

AIM

To determine peculiarities of tissue responses to manual and automated Ilizarov bone distraction in nerves and articular cartilage.

METHODS

Twenty-nine dogs were divided in two experimental groups: Group M - leg lengthening with manual distraction (1 mm/d in 4 steps), Group A - automated distraction (1 mm/d in 60 steps) and intact group. Animals were euthanized at the end of distraction, at 30th day of fixation in apparatus and 30 d after the fixator removal. M-responses in gastrocnemius and tibialis anterior muscles were recorded, numerical histology of peroneal

and tibialis nerves and knee cartilage semi-thin sections, scanning electron microscopy and X-ray electron probe microanalysis were performed.

RESULTS

Better restoration of M-response amplitudes in leg muscles was noted in A-group. Fibrosis of epineurium with adipocytes loss in peroneal nerve, subperineurial edema and fibrosis of endoneurium in some fascicles of both nerves were noted only in M-group, shares of nerve fibers with atrophic and degenerative changes were bigger in M-group than in A-group. At the end of experiment morphometric parameters of nerve fibers in peroneal nerve were comparable with intact nerve only in A-group. Quantitative parameters of articular cartilage (thickness, volumetric densities of chondrocytes, percentages of isogenic clusters and empty cellular lacunas, contents of sulfur and calcium) were badly changed in M-group and less changed in A-group.

CONCLUSION

Automated Ilizarov distraction is more safe method of orthopedic leg lengthening than manual distraction in points of nervous fibers survival and articular cartilage arthrotic changes.

Key words: Limb lengthening; Articular cartilage; Nerve; Histomorphometry; Dog

Core tip: Limb lengthening developed by Ilizarov is now well accepted method for correction of orthopedic problems but in some cases it is complicated with nerve and joint malfunctions or disturbances. In this animal study we present the comparative analysis of quantitative indices of nerves and articular cartilage structural reorganization during lengthening with manual and automatic Ilizarov bone distraction. Results of the study have indicated the benefits of automatic distraction.

Shchudlo N, Varsegova T, Stupina T, Shchudlo M, Saifutdinov M, Yemanov A. Benefits of Ilizarov automated bone distraction for nerves and articular cartilage in experimental leg lengthening. *World J Orthop* 2017; 8(9): 688-696 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i9/688.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i9.688

INTRODUCTION

The technology of gradual limb lengthening developed by Ilizarov is now well accepted method for correction of limb length discrepancy, short stature or treatment of bone defects, resulting from trauma, congenital abnormality or oncologic resection. Distraction osteogenesis is an effective method for new bone tissue creation but in some cases is complicated with nonunion, neurovascular disturbances, muscle contractures and joint stiffness. Using manual circular distractor and specially developed automatic device, Ilizarov[1] investigated various rates and rhythms of distraction and have concluded that "rate of 1.0 mm/d led to the best results". He also reported that "the greater the distraction frequency, the better the outcome" comparing the automatic distraction (1 mm/d in 60 steps) with manual (1 mm/d in 4 steps). This conclusion has been confirmed in clinical practice[2] but automatic distraction is not widely implemented method because of its technical difficulties and costs.

There are few research groups dealing with automatic distraction. Nakamura *et al*[3] have found less damage in knee cartilage in automatically distracted group (1 mm/d in 120 steps) compared with manual group (1 mm/d in two steps). In goats undergoing leg lengthening with automated distractor producing one, four or 720 increments per day it was found that "the intensity and dispersion of degenerative changes in muscles were in reverse proportion to the frequency of distraction"[4]. Distraction mode 1 mm/d in 1440 steps in comparison with 1 mm/d in 3 steps resulted in better range of motion and somatosensory evoked potentials, though muscle histology was the same[5]. Aarnes *et al*[6] reported that high frequency of distraction improved tissue adaptation during leg lengthening in humans. In recent research there was no difference in time to union or in the incidence of complications in comparison with manual low-frequent distraction[7].

Taking into account discrepancies in results it is important to revise experimental leg lengthening series from the points of quantitative histological and physiological methods. Such data is absent in global literature. The safety of automatic Ilizarov distraction for muscles, nerves and cartilage[8-11] was substantiated in Russian articles, but peculiarities of structural response to manual and automatic Ilizarov bone distraction in nerves and articular cartilage were not revealed.

The aim of our research - comparative analysis of structural changes in leg nerves and knee cartilage during experimental leg lengthening with manual (1 mm/d in four steps) and automatic (1 mm/d in 60 steps) distraction.

MATERIALS AND METHODS

Experiments were carried out in accordance with Principles of Laboratory Animal Care (NIH Publication No. 85-23, revised 1985). Twenty-nine mongrel adult dogs (weight 20-25 kg, 18-20 cm leg length) were used. Five animals formed the intact group and 24 were operated.

Surgery and experimental design

Anesthesia with intramuscular injections of atropine, dimedrol and xylazine was maintained with sodium pentobarbital (30 mg/kg *i.v.*) intravenously. Mid-diaphyseal osteoclasis and osteosynthesis by Ilizarov were performed. In M-group (n = 12) the lengthening

protocol involved a 5-d latent period, and then manual movement of graded traction nodes at the rate of 1 mm/d in 4 steps was performed for 28 d. In A-group (n = 12) protocol was the same as in M-group, but distraction rate was 1 mm/d in 60 steps. The animals were euthanized at three time-points: D28 - the end of distraction (15% increase the initial leg length in both groups), F30 - 30 d of fixation in apparatus (bone regenerate consolidation in all animals of A-Group, but in M-Group consolidation was evident only in three animals), WA30 - 30 d without apparatus (full weight bearing of the operated limb in M-Group, but in A-Group it was noted immediately after the apparatus removal).

Neurophysiologic evaluation

Intramuscular EMG was performed after anesthesia also at D 28, F 30 and WA 30. M-responses in gastrocnemius and tibialis anterior muscles were recorded using a digital EMG-system DISA-1500 (DANTEC, Denmark). Bio potential leads were monopolar with modified needle electrodes. The active recording electrode was inserted percutaneously in muscle belly and the reference electrode - in its tendon. M-responses were recorded after supramaximal electrical stimulation of sciatic nerve through para neural needle electrodes using rectangular wave pulses of 1-ms duration. Muscle action potential amplitudes were measured from the top of the negative peak to the top of maximal positive peak.

Morphological evaluation

Histologic analysis was performed in 19 animals (all intact and seven from each experimental group). Animals were euthanized. Nerves and cartilage samples were fixed in mixture of 20 g/L solutions of glutaraldehyde and paraformaldehyde in phosphate buffer (pH 7.4) adding 1 g/L picric acid and then were partially embedded in paraffin. Paraffin sections were cut on "Reichert" microtome (Austria) and mounted in glasses with poly-L-lysin for reaction with ki-67 according protocols of producing company using the visualization system RE7140-K (Novocastra, Great Britain). Another parts were post-fixed in 1 g/100 mL tetraoxide osmium solution with 1.5 g/100 mL potassium ferricyanide and embedded in araldite. Transverse semi-thin sections (thickness 0.5-1.0 μm) were made with glass knives using the Nova ultratome LKB (Sweden), mounted on glass slides and then stained with toluidine blue and methylene blue-basic fuchsin. For numerical analysis the semi-thin epoxy sections of enlarged area (4-8 mm^2 instead of standard 1 mm^2) were used. Such technology provided the cellular details visualization in the light microscope and the sample representativeness[12]. Two calibrated experts conducted numerical analysis. True-color images were digitized using the stereomicroscope "AxioScope.A1") with camera "AxioCam" (Carl Zeiss MicroImaging GmbH, Germany). Histomorphometry was performed with "VT-Master-Morphology" program (VideoTest, Russia, St. Petersburg). In 3 total sections (magnification 32 ×) nerves areas and summary areas of nerve fascicles with perineurium were determined. In 25 nonoverlapping fields of the endoneurial compartment (magnification 1250 ×), collected in a systematic random order, the numerical densities of endoneurial vessels were evaluated. About 400 samples of myelinated fibres for each nerve site were made, and morphometric parameters-diameters of myelinated nerve fibers, their axons and myelin sheath thickness-were measured. Per cent of degenerated myelinated nerve fibers in the samples were calculated.

Cartilage depth and volumetric chondrocytes density in 30 digital images were estimated, per cents of isogene groups and empty lacunas in random selection of 100 chondrocytes were calculated. Surfaces of epoxy blocks were exposed to silver deposition using Eico IB-6 ion coater and JEOL JEE-4X vacuum evaporator. The investigation of element composition was performed using scanning electron microscope JSM-840 (JEOL, Japan) equipped with energy dispersive X-ray analyzer (INCA 200, Oxford Instruments). Using accelerated voltage 20 kV concentrations of sulfur (ωS, weight %) and calcium (ωCa, weight %) were assessed. Results were obtained as smart maps, showing spatial distribution of elements and quantitative data in weight per cents. For SEM-micrographs cartilage samples were dehydrated in alcohols of ascending concentrations, permeated with camphene according to original method[13], air dried and coated with silver.

Statistical analysis

Statistical treatment of numerical data was performed in software package Attestat Program (version 9.3.1, developed by I. P. Gaidyshev, Certificate of Rospatent official registration No. 2002611109), the paired and unpaired Student t tests, Mann-Whitney U test and Fisher exact test were used at 0.05 significance level.

RESULTS

EMG changes

M-responses amplitudes were badly changed in all animals especially in m. tibialis anterior of M-group. At D28 and F30 the intramuscular EMG revealed fibrillations and sporadic positive sharp waves in both groups. At WA30 they disappeared. Table 1 shows that in m. gastrocnemius M-response amplitudes at D28 tended to be lower in A-group than in M-group, but at F30 and WA 30 the parameters of A-group became better than of M-group. In m. tibialis anterior they were better in A-group at all t-points.

Changes of nerves sheaths

Pathologic conditions of epineurium, subperineurial space and endoneurium were more prominent in M-group. Table 2 shows that at F30 the thickening of Tn was noted in A-group and the thinning of Pn - in M-group. The first

Table 1 M-response amplitudes in leg muscles

t-points of EMG-testing	M. gastrocnemius		M. tibialis anterior	
	mean ± SE (mV)	Difference *vs* initial (%)	mean ± SE (mV)	Difference *vs* initial (%)
Initial (before experiment)	32.0 ± 2.9	-	22.6 ± 1.3	-
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	13.4 ± 3.1	-58.1	8.8 ± 1.9	-61.1
30 d of fixation	10.6 ± 4.6	-66.9	8.3 ± 1.3	-63.3
30 d without apparatus	16.3 ± 5.8	-49.1	8.9 ± 0.1	-60.6
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	12.0 ± 1.7	-62.5	12.7 ± 1.6[a]	-43.8
30 d of fixation	11.9 ± 1.2[a]	-62.8	10.5 ± 0.5[a]	-53.5
30 d without apparatus	18.3 ± 4.6[a]	-42.8	14.0 ± 2.0[a]	-38.1

[a]$P < 0.05$ *vs* group M.

Table 2 Areas of nerves histologic transverse sections (A_n)

Nerves/group and *t*-points	Tibial nerve		Peroneal nerve	
	(mean ± SD) (10^4 mKm^2)	Difference *vs* contra-lateral (%)	(mean ± SD) (10^4 mKm^2)	Difference *vs* contra-lateral (%)
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	353.7 ± 34.8	3	41.6 ± 9.4	-2
30 d of fixation	291.6 ± 26.2	-4	63.6 ± 1.1	-11[a]
30 d without apparatus	248.7 ± 29.2	3	53.3 ± 8.8	-3
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	287.3 ± 60.0	-2	56.2 ± 3.4	-1
30 d of fixation	306.8 ± 76.7	15[a,c]	75.8 ± 16.3	-1[c]
30 d without apparatus	224.8 ± 31.1	10[c]	46.5 ± 1.1	1

[a]$P < 0.05$ *vs* contralateral; [c]$P < 0.05$ *vs* group M.

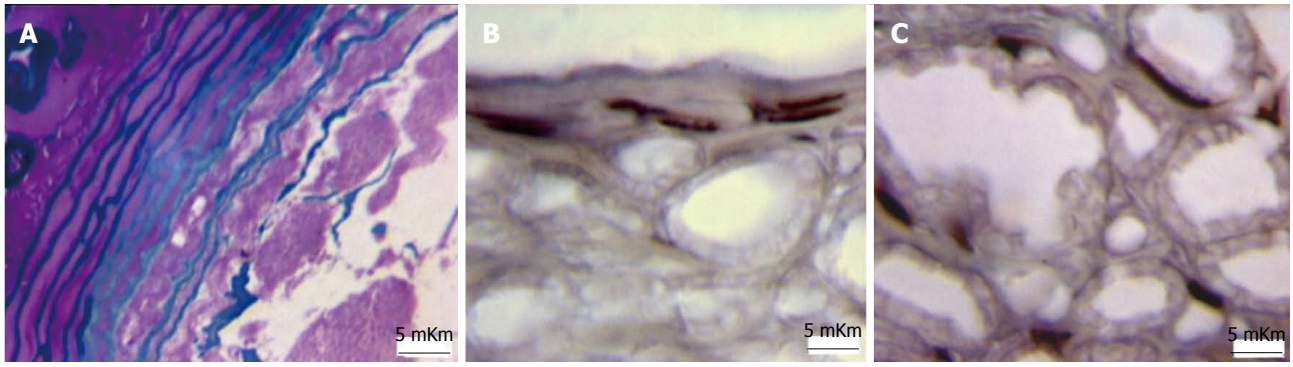

Figure 1 Peroneal nerve, F30, M-group. A: Perineurium, fragment of transverse semithin section, methylene blue - basic fuchsin stain; B: Proliferating cells in perineurium; C: Proliferating cells in endoneurium; fragments of paraffin-embedded sections stained using antibodies to Ki-67. Magnification 1250 ×.

was determined by thickening and hypervascularity of epineurium, the second - by fibrotic changes of epineurium with marked loss of adipocytes. Laminated cellular structure of perineurium in lengthened nerves was maintained in both groups - presented in Figure 1A. In M-group the signs of subperineurial edema were noted - also visible in Figure 1A. Numerosity of perineurial cells nuclei was increased, fibrillar interlayers were thickened. In perineurial cells nuclei the high expression of ki-67 was noted - presented in Figure 1B.

Table 3 shows that at D28 the summary fascicular areas in transverse histologic sections of lengthened nerves were decreased compared to corresponding contralateral ones. Fascicular thinning was more prominent in Pn than in Tn. Extent of it in corresponding nerves in M and A-groups was approximately equal. At WA30 nerves restored their fascicular areas in A-group, in M-group nerve fascicles were thickened because of endoneural fibrosis.

The level of ki-67 expression in endoneurial cells was increased especially at F30 - presented in Figure 1C. Table 4 shows that in M-group the numerical density of endoneural microvessels in lengthened Tn was increased only at F30, Pn nerve - at all *t*-points

Table 3 Summary fascicular areas (A_f) in transverse histologic sections of nerves

Nerves/group and *t*-points	Tibial nerve		Peroneal nerve	
	(mean ± SD) (10^4 mKm^2)	Difference *vs* contra-lateral (%)	(mean ± SD) (10^4 mKm^2)	Difference *vs* contra-lateral (%)
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	68.7 ± 6.9	-8	18.8 ± 8.1	-15
30 d of fixation	73.5 ± 5.8	-7	40.1 ± 2.3	-1
30 d without apparatus	54.2 ± 4.8	9[a]	27.8 ± 9.5	14[a]
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	83.7 ± 13.5	-9[a]	25.7 ± 2.5	-16[a]
30 d of fixation	86.8 ± 13.5	-4	29.6 ± 7.0	1
30 d without apparatus	82.0 ± 6.4	5	25.9 ± 0.6	0[c]

[a]$P < 0.05$ *vs* contralateral; [c]$P < 0.05$ *vs* group M.

Table 4 Numerical densities of microvessels (N_{Amv}) in endoneurium

Nerves/group and t-points	Tibial nerve		Peroneal nerve	
	mean ± SE (mm^{-2})	Difference *vs* intact (%)	mean ± SE (mm^{-2})	Difference *vs* intact (%)
Intact	182 ± 22	-	141 ± 8	-
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	180 ± 11	-1.1	192 ± 47[a]	36.17
30 d of fixation	203 ± 3[a]	11.54	157 ± 36	11.35
30 d without apparatus	187 ± 10	2.75	197 ± 52[a]	39.72
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	135 ± 21[a]	-25.8[c]	164 ± 8[a]	16.31[c]
30 d of fixation	181 ± 30	-0.5[c]	171 ± 29[a]	21.28[c]
30 d without apparatus	219 ± 22[a]	20.3[c]	164 ± 28[a]	16.31[c]

[a]$P < 0.05$ *vs* intact; [c]$P < 0.05$ *vs* group M.

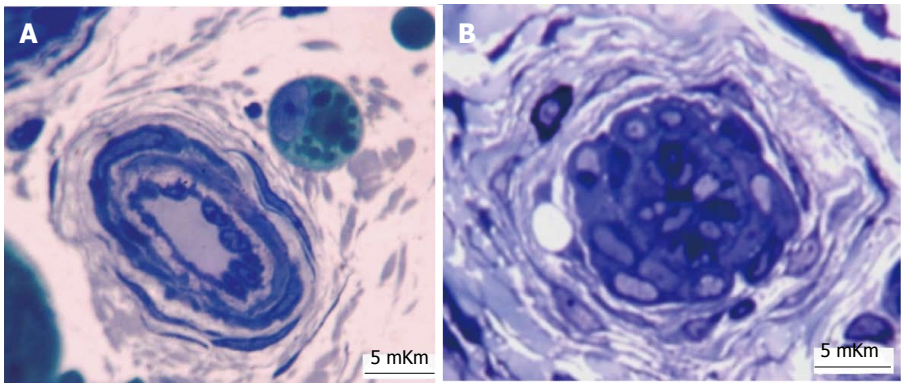

Figure 2 Fragments of canine Pn semithin sections. WA30, M-group. Toluidine blue stain. A: Normal condition of artery in epineurium; B: Epineural artery with closed lumen. Magnification 1250 ×.

especially at D28 and WA30. In A-group the numerical density of endoneural microvessels in Tn were decreased at D28 compared with intact nerve, at F30 it was approximately equal to parameter of intact nerve and at WA 30 endoneurium of Tn was highly vascularized. The numerical densities of endoneural vessels in Pn in A-group were increased at all *t*-points.

Nerve fibers changes

Majority of nerve fibers in lengthened nerves survived but shares of nerve fibers with atrophic and degenerative changes were bigger in M-group.

In two cases (one for each group) massive nerve fibers degeneration (more than 40% of nerve fibers with signs of demyelination, axonal or Wallerian degeneration) was revealed in Pn on the background of epineurial vessels obliteration or closing - presented in Figure 2. In all the rest animals of M-group the shares of degenerated myelin fibers overcame the corresponding indexes of intact nerves and of nerves in A-group at all *t*-points of experiment - presented in Tables 5 and 6. The shares of degenerated myelinated nerve fibers in Tn of A-group at F30 and WA30 were even smaller than in intact nerves.

Table 5 Average morphometric parameters of tibial myelinated nerve fibers (mean ± SE)

Parameters/group and *t*-points	Share of degenerated nerve fibers (%)	Nerve fibers diameters (mKm)	Axonal diameters (mKm)	Myelin sheath thickness (mKm)
Intact control	1.6 ± 0.2	6.75 ± 0.01	4.63 ± 0.13	1.06 ± 0.02
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	5.0 ± 0.7[a]	6.91 ± 0.17	4.57 ± 0.19	1.16[a] ± 0.01
30 d of fixation	4.0 ± 0.9[a]	6.77 ± 0.47	4.44 ± 0.28[a]	1.17 ± 0.10
30 d without apparatus	4.4 ± 2.4	6.61 ± 3.19	4.37 ± 2.10[a]	1.12 ± 0.64
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	2.4 ± 0.7[b]	6.29 ± 0.13	4.63 ± 0.10	0.83 ± 0.02[a]
30 d of fixation	0.5 ± 0.2[a,c]	6.88 ± 0.11	4.99 ± 0.10[a]	0.95 ± 0.12
30 d without apparatus	0.9 ± 0.1[a,c]	7.26 ± 0.13[a]	5.05 ± 0.09[a]	1.11 ± 0.05

[a]$P < 0.05$ *vs* intact; [c]$P < 0.05$ *vs* group M.

Table 6 Average morphometric parameters of peroneal myelinated nerve fibers (mean ± SE)

Parameters/group and t-points	Share of degenerated nerve fibers (%)	Nerve fibers diameters (mKm)	Axonal diameters (mKm)	Myelin sheath thickness (mKm)
Intact control	1.9 ± 0.3	6.46 ± 0.07	4.39 ± 0.08	1.04 ± 0.04
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	6.0 ± 1.4[a]	5.37 a ± 0.41	3.69 ± 0.29[a]	0.84 ± 0.09[a]
30 d of fixation	4.3 ± 1.3[a]	6.09 ± 0.63	4.44 ± 0.57	0.98 ± 0.06
30 d without apparatus	4.2 ± 0.4[a]	5.90 ± 0.43	4.10 ± 0.10[a]	0.90 ± 0.17[a]
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	4.0 ± 0.8[a,c]	5.56 ± 0.26[a]	3.70 ± 0.53[a]	0.92 ± 0.13
30 d of fixation	3.3 ± 0.1[a,c]	5.62 ± 0.07[a]	3.91 ± 0.09[a]	0.85 a ± 0.07
30 d without apparatus	2.4 ± 0.6[c]	6.17 ± 0.45	4.14 ± 0.16	1.01 ± 0.06

[a]$P < 0.05$ *vs* intact; [c]$P < 0.05$ *vs* group M.

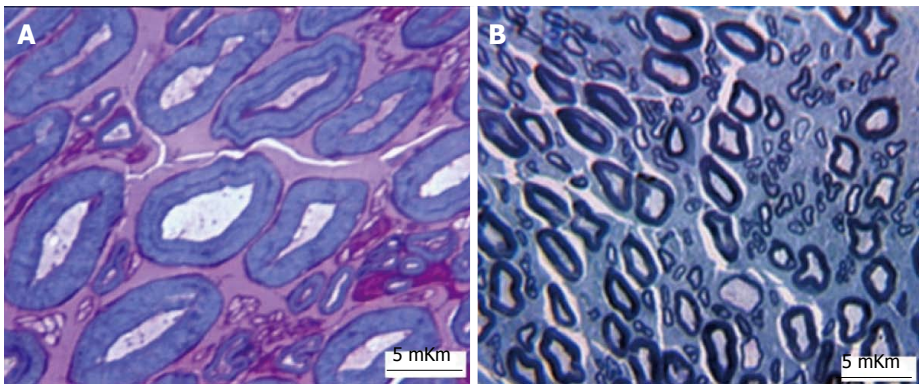

Figure 3 Fragments of canine Tn semithin sections, WA30. A: Some large myelinated nerve fibres has visibly thinned axons and thickened myelin sheaths, M-group, methylene blue - basic fuchsin stain, magnification 1250 ×; B: Two large nerve fibers (in the lower part of the image) are hypomyelinated; A-group, toluidine blue stain, magnification 500 ×.

In comparison with intact nerves the average axonal diameter of Tn myelinated nerve fibers in M-group was decreased, the average myelin thickness increased. These changes are consistent with findings of myelinated fibers with signs of axonal atrophy and hypermyelination - presented in Figure 3A. In A-group the average axonal diameter in Tn at D28 was comparable with intact nerve, but the average myelin thickness was decreased. At subsequent t-points the average axonal diameter was bigger than in intact Tn nerve, the average myelin thickness was restored, although some nerve fibers were hypomyelinated at the end of experiment - presented in Figure 3B. In Pn the average axonal diameter was decreased in both groups at D28 and F30, but at the end of experiment this parameter didn't significantly differed from intact nerve (Table 6). Restoration of all morphometric indices was evident only in Group A. In Group M the average diameter of nerve fibres and the average myelin thickness remained decreased.

Articular cartilage changes

Alteration of morphometric parameters and mineral contents developed in both groups - more prominently

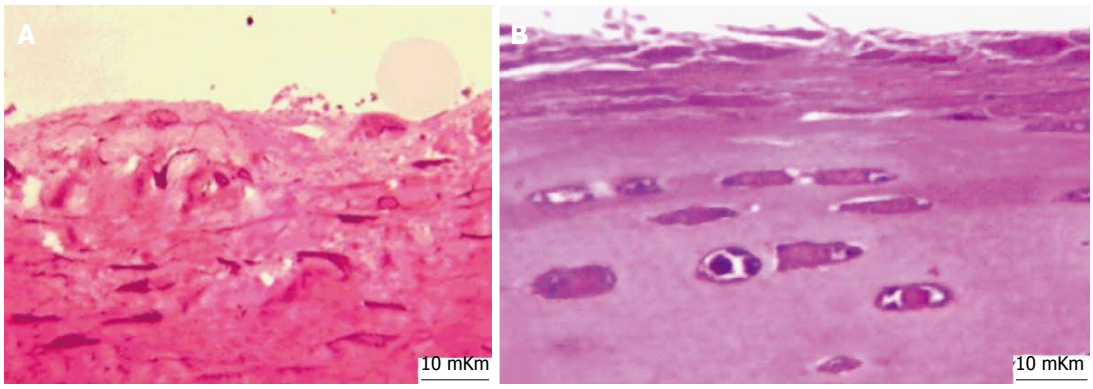

Figure 4 Superficial zone of articular cartilage at D28 in semithin sections. A: M-group; B: A-group. Methylene blue - basic fuchsin stain. Magnification 500 ×.

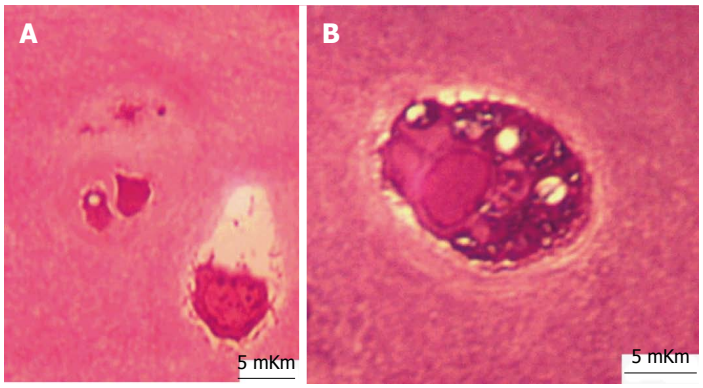

Figure 5 Chondrocytes of intermediate cartilage zone at F30. A: In the left lacuna there are two degenerated chondrocytes, in the right lacuna - chondrocyte shrinkage, chromatin condensed on periphery of caryolemma, M-group; B: Chondrocyte with well-developed functionally active vacuolated cytoplasm occupies the whole lacuna. A-group. Semithin sections. Methylene blue - basic fuchsin stain. Magnification 1250 ×.

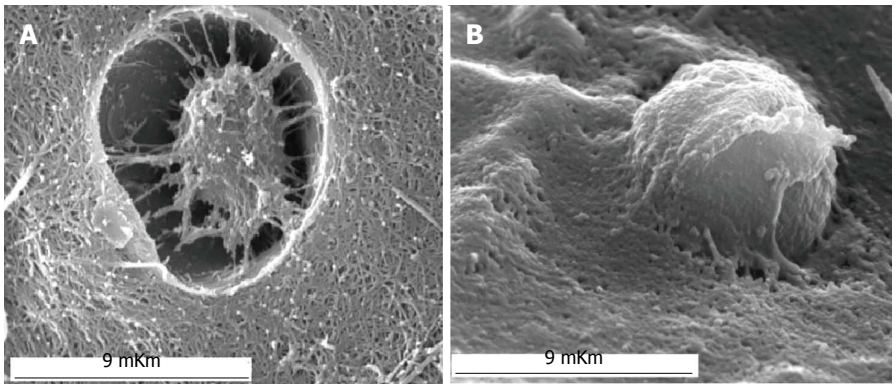

Figure 6 Chondrocytes in SEM at F30. A: Cellular shrinkage. M-group; B: Rounded cell. A-group. Magnification 5500.

in M-group. At D28 injuries of superficial cartilage zone were revealed - presented in Figure 4. More intensive separation of collagen network with usuras formation was noted in M-group. At F30 some chondrocytes of intermediate zone were with signs of apoptosis or necrotic death ranged mainly in M-group - presented in Figure 5A. In A-group many of chondrocytes were functionally active. They occupied the whole lacuna, had homogenic nuclei and well developed vacuolated cytoplasm - example of such cell presented in Figure 5B. Chondrocytes shrinkage and rounding of functionally active chondrocytes were also revealed by SEM - presented in Figure 6. At WA30 restoration of cellular cartilage architectonics was noted only in A-group. Cartilage thickness changes were divergent in studied groups - presented in Table 7. In M-group parameter increased at D28 and decreased at F30 and WA30 - compared with intact control. In A-group the thickness of cartilage decreased at D28 and at F30, but recovered at WA30. In both groups chondrocytes with signs of destruction were revealed mainly in superficial and deep cartilage zones. Maximal indices of empty lacunas and

Table 7 Average morphometric parameters of articular cartilage (mean ± SD)

Parameters/group and *t*-points	Cartilage thickness (mKm)	Chondrocytes volumetric density (%)	Isogenic groups	Empty lacunas
			(% of chondrocyte sample)	
Intact control	475.5 ± 1.31	9.03 ± 1.51	14.5	13.6
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	710.3 ± 7.16[a]	4.13 ± 0.28[a]	24.7	29.97
30 d of fixation	421.1 ± 4.81[a]	5.1 ± 0.27[a]	20.18	20.85
30 d without apparatus	416.9 ± 4.37[a]	5.6 ± 0.19[a]	16.1	21.12
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	356.45 ± 1.55[a,c]	8.34 ± 0.48[a,c]	25.6	24.3
30 d of fixation	392.7 ± 2.12[a,c]	6.8 ± 0.45[a,c]	28.8	16.3
30 d without apparatus	464.6 ± 6.51[c]	7.96 ± 0.37[a,c]	29.9	15.4

[a]$P < 0.05$ *vs* intact; [c]$P < 0.05$ *vs* group M.

Table 8 Content of sulfur and calcium in articular cartilage (mean ± SD, weight %)

Parameters/group and t-points	ωS	ωCa
Intact control	1.26 ± 0.02	0.15 ± 0.02
M-group - manual distraction (1 mm/d in 4 steps)		
28 d of distraction	0.71 ± 0.01[a]	0.19 ± 0.02[a]
30 d of fixation	0.96 ± 0.02[a]	0.39 ± 0.03[a]
30 d without apparatus	0.94 ± 0.02[a]	0.27 ± 0.02[a]
A-group - automatic distraction (1 mm/d in 60 steps)		
28 d of distraction	0.79 ± 0.01[a]	0.16 ± 0.01[c]
30 d of fixation	1.09 ± 0.02[a,c]	0.18 ± 0.02[c]
30 d without apparatus	1.15 ± 0.02[c]	0.20 ± 0.02[a,c]

[a]$P < 0.05$ *vs* intact; [c]$P < 0.05$ *vs* group M.

utmost decrease of chondrocytes volumetric densities were noted in M-group. Compensatory increase of isogenic clusters index was more prominent in A-group. In all experimental animals ωCa increase and ωS decrease were marked - more prominently in M-group presented in Table 8.

DISCUSSION

So, better restoration of M-response amplitudes in leg muscles in group with automatic distraction was consistent with less structural alterations of nerves and articular cartilage. Adaptive growing processes in nerve sheaths were marked with ki-67-positive cells in both groups but probably the smaller incremental length (0, 017 mm in group with automatic distraction instead of 0, 25 mm in group with manual distraction) was associated with fewer disturbances in nerves sheaths. Subperineurial edema and fibrosis were evident only in group with manual distraction and restoration of nerve fascicles summary area was achieved only in group with automatic distraction. Per cents of degenerated nerve fibers were smaller in group with automatic distraction than in group with manual distraction at all time points of experiment. Being expressed in per cents this difference seems to be rather small, but in absolute figures it means that in group with automatic distraction thousands neurons don't lose their connections with periphery and survive. Thousands neurons with degenerated axial cylinders in M-Group enter into regenerative status and create new outgrowths but such active changes may lead to death many of them. As for morphometric parameters of survived myelinated nerve fibers population, in peroneal nerve all of them were restored at the end of experiment only in group with automatic distraction. Automatic distraction prevented axonal atrophy and absolute myelin thickening in tibial nerve. Such changes were evident in group with manual distraction and even in conditions without distraction - after experimental shin bone fracture[14]. Increased axonal diameters in tibial nerves in group with automatic distraction were associated with better nerve fibers survival because shares of degenerated nerve fibers were smaller even in comparison with intact nerves. Limitation of our study - we have not study endoneurial circulation and axonal transport with special methods. But restoration of fascicular areas, smaller per cents of degenerated nerve fibers and bigger axonal diameters in group with automatic distraction bear indirect evidence that more discrete (high frequent) mode of automatic distraction resulted in fewer disturbances of endoneurial fluid and axoplasmic flow.

Articular cartilage alterations also depended on distraction frequency. All quantitative parameters (cartilage thickness, volumetric densities of chondrocytes, percentages of isogenic clusters and empty cellular lacunas, contents of sulfur and calcium) were less

changed in group with automatic distraction.

And thus, automated distraction developed by Ilizarov (1 mm/d in 60 steps) is more advantageous because few alterations of nerves and cartilage structure than in manual mode (1 mm/d in 4 steps) provide better initial functional recovery and better functional prognosis.

ACKOWLEDGMENTS

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COMMENTS

Background

Comparative study of the effects of manual low-frequent and automated high-frequent distraction on the results of orthopedic limb lengthening at clinics is problematic. The safety of automatic Ilizarov distraction for nerve, cartilage and muscles changes in experimental animal leg lengthening was substantiated in Russian articles but careful multiparametric comparative analysis has not been done.

Research frontiers

It was stated that for a definite rate of distraction the higher frequent distraction improve bone formation and consolidation. Previous experimental researches have proved that automatic distraction is safer for nerves ultrastructures and cartilage relief than manual.

Innovations and breakthroughs

Special technology of tissue semi thin sections of enlarged shear provided representative histomorphometric data. This is the first study evaluating substantial difference of peroneal and tibial nerves adaptability to conditions of orthopedic leg lengthening. Complex research of articular cartilage histomorphometry, scanning electron microscopy and X-ray electron probe microanalysis revealed fewer alterations in group with automatic distraction.

Applications

Better nerve fibers survival and less arthrotic cartilage changes in conditions of automatic distraction are critically important for good functional prognosis of orthopedic leg lengthening. Development of axonal atrophy and degenerative myelin sheath thickening in tibial nerve fibers evident in group with manual distraction was effectively prevented in group with automatic distraction.

Terminology

Ilizarov method is one of the most clinically implemented distraction osteogenesis procedures. Ilizarov discovered that gradual tension stress maintain the regeneration and growth of living tissues. He was the first who developed the automated high frequent distraction. Different tissue responses on distraction with various frequencies may be revealed in standard experimental models, when groups differ in only one experimental condition - the frequency of distraction. Subtle differences in tissue structures may be of critical importance for functional prognosis.

Peer-review

The topic is interesting and the study may have a point.

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ORIGINAL ARTICLE

Retrospective Study

Lumbar ganglion cyst: Nosology, surgical management and proposal of a new classification based on 34 personal cases and literature review

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Abstract

AIM

To analyze different terms used in literature to identify lumbar extradural cysts and propose a common scientific terminology; to elaborate a new morphological classification of this pathology, useful for clinical and surgical purposes; and to describe the best surgical approach to remove these cysts, in order to avoid iatrogenic instability or treat the pre-existing one.

METHODS

We retrospectively reviewed 34 patients with symptomatic lumbar ganglion cysts treated with spinal canal decompression with or without spinal fixation. Microsurgical approach was the main procedure and spinal instrumentation was required only in case of evident preoperative segmental instability.

RESULTS

The complete cystectomy with histological examination was performed in all cases. All patients presented an improvement of clinical conditions, evaluated by Visual Analogic Scale and Japanese Orthopaedic Association scoring.

CONCLUSION

Spinal ganglion cysts are generally found in the lumbar spine. The treatment of choice is the microsurgical cystectomy, which generally does not require stabilization.

The need for fusion must be carefully evaluated: Pre-operative spondylolisthesis or a wide joint resection, during the operation, are the main indications for spinal instrumentation. We propose the terms "ganglion cyst" to finally identify this spinal pathology and for the first time its morphological classification, clinically useful for all specialists.

Key words: Synovial cyst; Lumbar spine; Instability; Surgery; Ganglion

Core tip: This paper is an original study that analyzes for the first time the many words and acronyms used in literature to describe lumbar extradural cysts, suggesting the term "ganglion cyst" in clinical practice. It also propose a morphological classification of these cysts, which could be useful for clinicians and surgeons. Finally, a description of microsurgical approaches to resect the cyst and avoid spinal instability is reported: As a guide to a common therapeutical strategy, we report a flow-chart, evaluating clinical conditions, mechanical stability and the most suitable treatment.

Domenicucci M, Ramieri A, Marruzzo D, Missori P, Miscusi M, Tarantino R, Delfini R. Lumbar ganglion cyst: Nosology, surgical management and proposal of a new classification based on 34 personal cases and literature review. *World J Orthop* 2017; 8(9): 697-704 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i9/697.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i9.697

INTRODUCTION

Ganglion cysts, more common in the hands and wrists[1,2], have been described for more than 2 millennia[3]. The Greek term "ganglion" indicates a knot of the tissues.

Ganglion cysts of the minor and major joints, especially at the level of the wrist and back of the hand, have been known since ancient times and were described by Hippocrates[3] more than two millennia ago. These cysts have an high incidence: Burke *et al*[1], reviewing the period 1990-2000, found between 44 and 55 new cases per 100000 inhabitants each year.

In the past century, similar cysts were also described as originated from lumbar zygapophyseal joints and occupying the spinal canal, most frequently in the lumbar spine and occasionally, in the cervical and thoracic spine[4-6]. To define these spinal neoformations, many terms have been adopted in the literature, according to the site of development or to the supposed origin: Ganglion[6], juxtafacet[7], flavum[8], cyfmos[9] and synovial[7,8,10-14].

The etiology of the cyst, not fully clear, could be strongly related to inflammatory phenomena secondary to facet hypermobility, which would produce modifications of the articular synovial membrane leading to cyst formation[13]. Microsurgical cystectomy is today the treatment of choice[15], with or without arthrodesis: Generally, microsurgical approach does not produce vertebral instability and arthrodesis is required only in case of a clear pre-operative instability, such as spondylolisthesis.

Evaluating all etiological factors and all treatment options, we propose an original morphological classification of lumbar ganglion cysts, based on their relation with the other anatomical structures. Lastly, in order to clarify the confusing terminology that describes these particular cysts, we suggest "spinal ganglion cyst" (SGC) as definitive term to be applied in clinical practice.

MATERIALS AND METHODS

Thirty-four cases of symptomatic lumbar SGCs surgically treated from 1995 to 2011 were enrolled ninths study. They include 18 previously published arthrodesis, with 3 hemorrhagic SGCs. All patients underwent preoperative magnetic resonance imaging (MRI) and computed tomography (CT) scan. To assess lumbar segmental instability, dynamic X-ray were also obtained in all patients but 4 cases, in which pain did not allow standing position.

Pain was evaluated by the Visual Analogic Scale (VAS score). Neurological examination was performed to assess signs of roots compression with any sensory and/or motor deficits.

All patients were operated through a microsurgical approach[15], to maintain articular congruence and not jeopardize vertebral stability. Cystectomy was achieved through laminotomy or hemilaminectomy. In presence of demonstrated pre-operative or iatrogenic intraoperative segmental instability (wide resection of the articular process), instrumented arthrodesis was also performed.

Histological examination of the cyst was performed in all cases to confirm the diagnosis.

Average follow-up was 28.5 mo (range 12-60). All patients underwent MRI, plain X-rays and were evaluated by VAS and modified Japanese Orthopaedic Association score (JOA score) for neurological improvement in the lower limbs.

The Wilcoxon signed rank test was used for statistical analysis, considering *P* value equal to or less than 0.05 as significant.

Based on our experience and literature review, we were able to construct a new and original classification of the ganglion cysts. By some drawings, performed by the first author (Maurizio D), we reported for the first time the main locations of these cysts, summarizing and comparing our radiological and surgical data with those from the pertinent literature.

RESULTS

The data regarding our 34 cases are summarized in Table 1. Average age was 63 (range 50-76 years): 13 (38%)

Table 1 Data regarding our 34 cases

Case	Age and sex	Location (side)	Instability		Treatment		Other data
			Verified	Supposed	Type 1	Type 2	
1	68 M	L5-S1 (left internal)		a	y		
2	75 M	L4-L5 (right medium)		a, b, c	y		Re
3	50 F	L4-L5 (right medium-internal)		a, b	y		
4	63 F	L5-S1 (right medium)		b, c	y		
5	76 F	L4-L5 (left medium-internal)		a	y		
6	75 M	L5-S1[1] (right medium-lateral)		a, b, d	y		
7	75 F	L4-L5 (right medium-lateral)	y	b, c		y	
8	62 M	L4-L5 (right medium-internal)	y	a, b		y	
9	60 M	L4-L5 (right lateral)		a, b, c	y		
10	73 F	L5-S1 (right lateral)		a, b, d	y		
11	55 M	L2-L3 (left medium-lateral)		a	y		
12	55 M	L4-L5 (left medium)	y	a, b		y	
13	74 F	L3-L4[1] (right medium-lateral)		b, c	y		
14	56 F	L3-L4 (left medium-lateral)	y	a		y	
15	67 F	L4-L5 (left medium-lateral)		b	y		
16	56 F	L4-L5 (right medium-lateral)		b, c	y		
17	66 F	L4-L5 (left medium-internal)		b	y		IF
18	68 M	L4-L5[1] (left medium-lateral)		a	y		
19	73 F	L5-S1[1] (left medium)		a, b	y		
20	53 F	L5-S1 (left medium-lateral)		a, b, c, d		y	
21	60 F	L4-L5 (right internal)		a, b, c, d		y	
22	52 M	L4-L5 (right medium-internal)	y	a		y	
23	64 F	L5-S1 (left internal)	y	a, b		y	
24	53 M	L5-S1 (left medium)	y	a, b		y	
25	73 F	L4-L5 (left medium-lateral)		a, b, c		y	IF
26	54 F	L3-L4 (right medium-internal)	y	a, b		y	
27	61 M	L4-L5 (left medium)		a, b, c		y	
28	65 M	L5-S1 (left medium)		a, d	y		
29	71 M	L5-S1 (right medium-internal)		a	y		
30	52 F	L4-L5 (left medium-lateral)		a, b	y		
31	63 F	L4-L5 (right medium)		a, b	y		
32	72 F	L4-L5 (right lateral)		a, b, d	y		
33	56 F	L4-L5 (right lateral)		a	y		
34	62 F	L4-L5 (left medium-lateral)		a	y		

[1]Hemorrhagic cyst; L: Left; R: Right; y: Yes; Type 1: Decompression; Type 2: Decompression with stabilization; Verified: Mobile olysthesis; a: Black disc; b: Interarticular liquid; c: Hyperintensity of the ligament on STIR MR images; d: Stable olisthesis; Re: Reoperated for postoperative instability with fusion; IF: Intraoperative fistula.

patients were males and 21 (62%) females. All patients had radicular pain, generally associated with lumbago. In 7 cases (21%), neurological deficits were also present. No cauda equina syndrome was detected. Duration of symptoms prior to surgical treatment varied from 1 to 3 years in 10 cases, whereas in the others average duration was 142 d (range 10-300 d). An acute onset, with a brief preoperative symptomatology, occurred in 4 hemorrhagic cysts.

Preoperative dynamic X-rays showed a mobile olisthesis in 8 cases (23%) and a stable one in 6 (18%). In all cases, preoperative CT and MRI showed signs of microinstability consisting of a reduced disc space and black disc (28 cases, 82%), increased interfacet synovial fluid (24 cases, 70%) and/or signal hyperintensity of the interspinous ligament on STIR sequences (10 cases, 29%).

All 14 pre-operative spondylolisthesis were submitted to arthrodesis. Instrumented fusion was achieved at the level of the cyst in 10 cases (Figure 1), while, in the remaining 4, it was extended to the level above (Figure 2).

During surgery, we observed 2 dural laceration that were successfully repaired. Histology confirmed the nature of the lesions as ganglion or synovial cysts.

Based on neuroradiological investigations and operative findings, the lumbar SGCs were classified according to the scheme illustrated in Figures 3 and 4. Using this classification, 3 cysts were internal, 7 medium, 8 medium-internal, 12 medium-lateral and 4 lateral.

In the immediate post-operative period, all patients presented remission of pain, gradual recovery from radicular deficits or improvement of claudication. At 12-mo follow-up, one patient developed an olisthesis at the level of cystectomy with low back pain. Instability was correlated with an excessive demolition of the articular process. Therefore, stabilization and fusion achieved remission of pain and good long-term outcome. No recurrences or new contralateral or adjacent SGCs were observed.

At long-term follow-up, VAS reduced from 7.4 ±

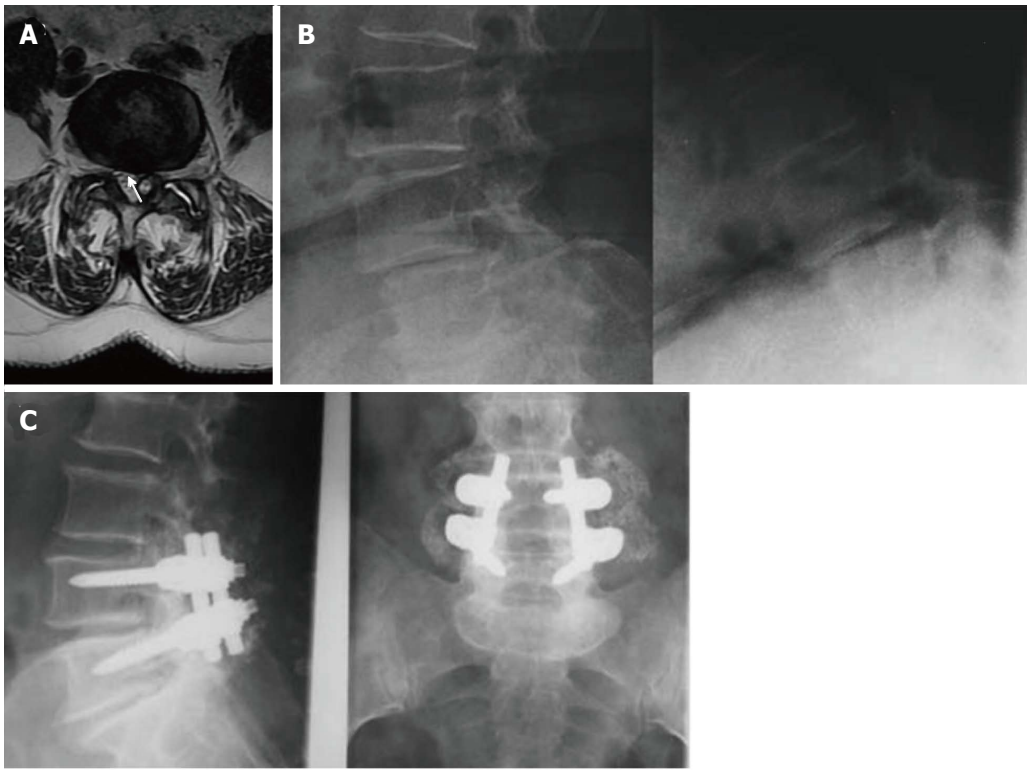

Figure 1 Case 2, Table 1. Preoperative axial T2-weighted MR image (A) showing a dehydrated and hypointense disk with a hyperintense cystic formation at right L4-L5 level (arrow). The cyst appeared to be of the internal or flavum type (see text for the classification). Sagittal dynamic images (B) 12 mo after the first surgical treatment showed an unstable olisthesis at L4-L5 level. Standard X-rays performed 1 year after surgical stabilization (C) showed the instrumentation to be well-positioned with an optimal profile and fusion at L4-L5.

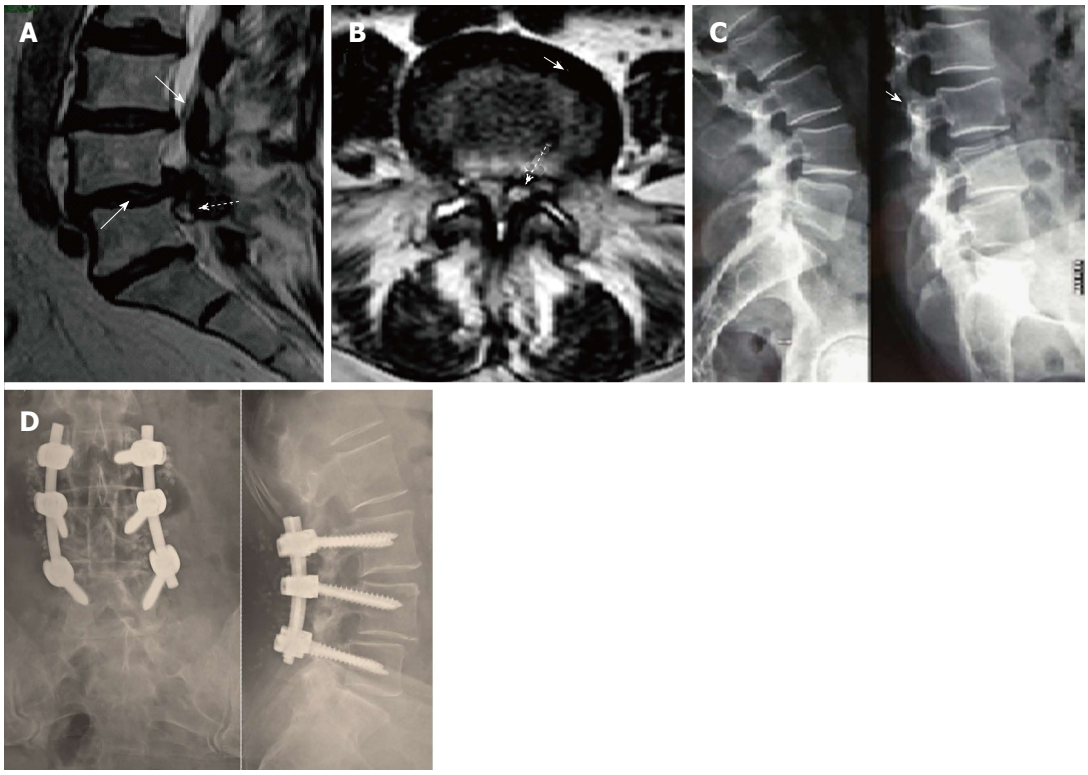

Figure 2 Case 12, Table 1. Preoperative sagittal T2-weighted MR image (A) showing a spinal ganglion cyst (dotted arrow) accompanied by olisthesis at L4/L5 with a dehydrated intervertebral disk (arrow), partially herniated into the spinal canal. On axial images (B) the cyst (dotted arrow) appeared to be of the medium or articular type (see text for classification). The interfacetal space contained an anomalous abundance of "sinovia" (commonly called synovial fluid), as the contralateral one did. Dynamic X-rays (C) showed an unstable olisthesis at L4/L5 and L3/L4. Postoperative outcome of the L3/L5 stabilization is documented by standard X-ray films (D) which confirmed good stability and fusion of the lumbar spine.

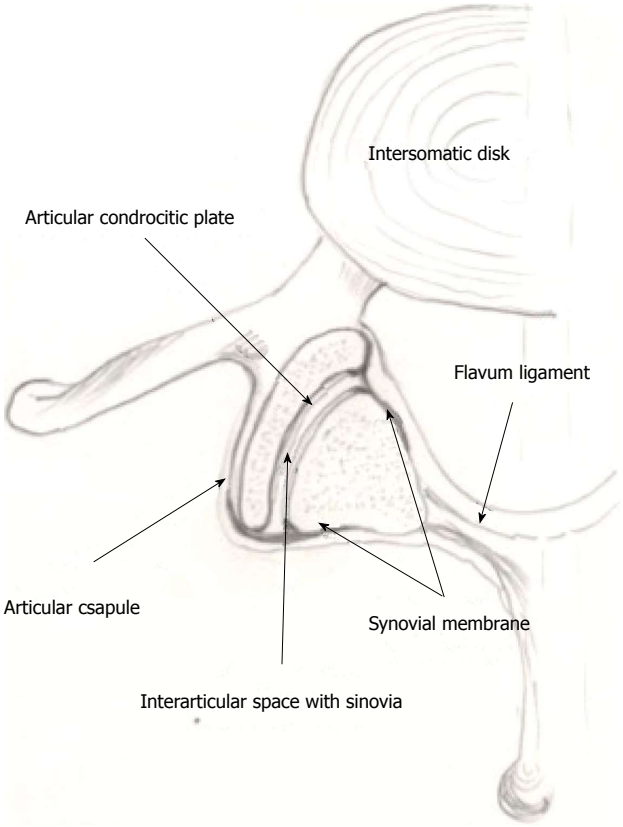

Figure 3 Schematic drawing of a lumbar facet joint showing the extension and distribution of the synovial membrane localized on the internal face of the articular capsule, extending to the external margins of the joint, up to the chondrocytic plates.

1.5 (6-10) to 1.3 ± 0.9 (0-2) (P = 0.037). JOA score improved from 7.6 ± 1.3 (7-9) to 2.5 ± 0.3 (0-3) (P = 0.041).

DISCUSSION

During the second half of the last century, articular cysts of the spine, prevalently lumbar, were likened to those of the wrist, hand, knee and hip and called, in the Greek language, *γαγγλιον* (ganglion). Hippocrate (460-377 a.C.), translated by Foesio *et al*[3] in 1596, in the chapter "De Articulis" describes some cutaneous periarticular cysts as "…quae ganglia dominant, quaecunque fluida sunt, et mucosam carnem continent…" (… these so-called ganglion, that contains a fluid or a mucous substance…). In 1930, Elmslie[16], during a knee surgery, observed a communication between the cyst and the synovial membrane, and used for the first time the term "synovial cyst". In 1968, Kao *et al*[6] described the first two cases of lumbar intraspinal extradural cyst, calling it "ganglion". In 1973, Sypert *et al*[10] referred the possible origin from the synovial cells of the lumbar zygapophyseal joints. In 1974, Kao *et al*[7], trying to establish terminology and nosology, published a review on spinal ganglion and synovial cysts, grouping them under a single definition: "Juxtafacet synovial cysts". This term was subsequently adopted by several authors[13,17-22], while others proposed other terms such as "flavum cyst"[8] or cyfmos[9], according respectively to the site of pathology or biomechanics of the mobile spine. They are all essentially correct, in relation to the tissue of origin[6,10], site[7-9] or etiology, but, in our hands, create some confusion. In order to identify this specific pathology in terms of pathogenesis, symptomatology and treatment, we reconsidered the ancient term of "ganglion": Spinal ganglion cyst (SGC) may be the term of choice if the cyst originates from the articular process: The distinction between ganglion and synovial cyst is in fact purely histological. Psaila and Mansel[23] defined that a ganglion cyst "…mainly consists of sheets of collagen fibers arranged in multidirectional strata" and "the ganglion tissue may be produced by the multifunctional mesenchymal cells". The main histological feature of the ganglion is the loss of continuity with the capsule of the facet joints, that makes it free inside and/or outside the spinal canal. On the contrary, the real and conserved synovial cyst is always in continuity with the capsule and recurrently presents synovial villi.

SGCs originate from the joint capsule, more precisely from the mesenchymal tissue[23] that constitutes the synovial membrane. This tissue covers the internal face of the capsule and also the external portion of the joint: This extension can explain the intra-articular or extra-articular development of SGCs. On the basis of these considerations, we propose an original classification that distinguishes the cysts between anterior or endocanalar and posterior or extra-canalar. The anterior variety can be subdivided into lateral or foraminal, medium or articular and internal or flavum.

To the best of the authors' knowledge, a comprehensive classification of SGCs has never been reported. Papers from the literature distinguished between synovial, posterior longitudinal ligament or flavum ligament cysts based on their location, origin or histopathological features. Our paper suggests for the first time the distinction between endo-canalar and extra-canalar SGC: The last one is posterior, generally asymptomatic and do not require treatment[24]. On the contrary, endo-canalar SGC is frequently symptomatic and neurological impairment is closely related to its position within the spinal canal, explaining different disorders ranging from single radiculopathy to cauda equina syndrome.

Factor responsible for proliferation of the synovial cells seems to be repeated articular micro-trauma that induces chronic inflammation, increase of synovial fluid and development of the cyst**.** Different grades of instability up to olisthesis can favor the weakening of the capsule and ultimately the cystic formation.

We observed lumbar degenerative olisthesis and SGC in more than 40% of our cases. These associated pathologies are frequently reported in the literature, in varying percentages from 30%[13] to 50%[25] of cases. Recently, Boviatsis *et al*[18], reviewing 499 SGCs, have found disc degeneration, osteoarthritis and spondylolisthesis. Many authors[9,13,18,24-27] underlined that SGCs originate in the most mobile spinal segments,

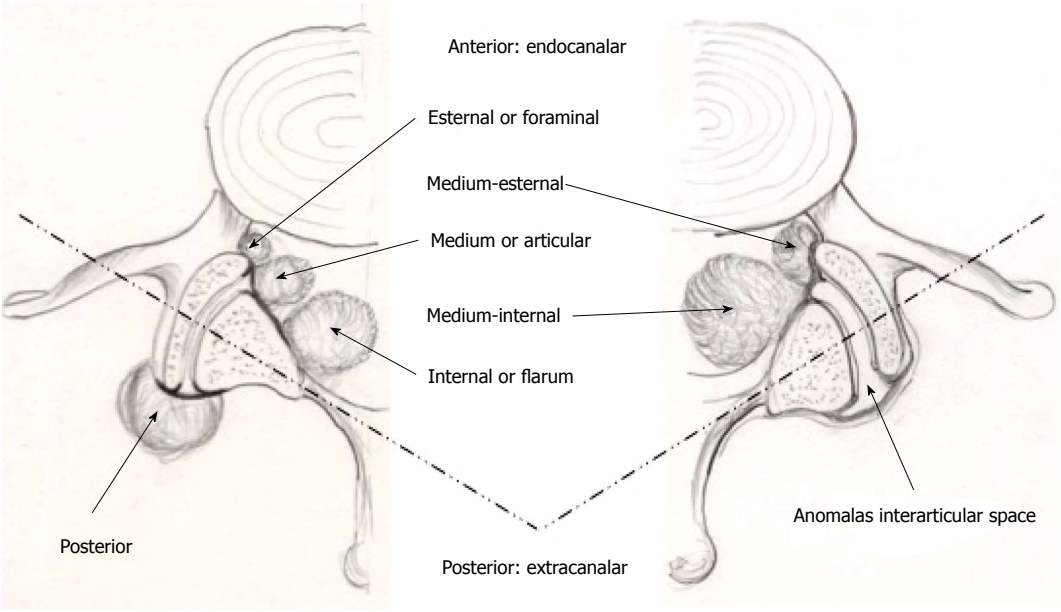

Figure 4 Localizations of lumbar spinal ganglion cysts (see text for the classification). The drawing on the right shows the joint with signs of instability (widened and misaligned interarticular space and increased amount of sinovia).

which are more susceptible to micro or macroinstability.

Cysts formation has been also presented in literature as consequence of an adjacent segment syndrome, due to the hypermobility of a segment just above or below other fixed vertebral segments; also in this case the mechanical stress would be the trigger necessary for mesenchimali tissue degeneration[28].

In our series and in the literature[9,13,18,24-26,29,30], SGCs were more frequent at L4-L5, which is notoriously the most mobile spinal level.

Clinical onset of SGCs is generally described as rapid and intense[14,18,19,21,31], characterized by radicular type disturbances, severe impairment of deambulation due to painful symptoms or, less frequently, motor deficits. Occasionally, onset may be extremely acute and intractable due to intracystic hemorrhage. In agreement with other authors[32-34], bleeding in such cysts is caused by neo-formed vessels following the repeated inflammations.

Radiological investigations mainly consist of MRI, which can visualize the SGC and relative degenerative phenomena, such as an increased quantity of "sinovia", more commonly described as interfacetal fluid, or inflammatory processes involving the interspinous ligament, which appears "shiny" mainly on T2 and STIR sequences[35]. In our series these phenomena were present in all cases, either singly or, more often, in combination.

Conventional radiography can play an important role. Standard load-bearing and flexion-extension X-rays may identify hypermobility or instability otherwise unrecognized: However, the severe painful symptoms sometimes make it impossible to perform this type of pre-operative investigation.

Once a diagnosis of SGC has been made, treatment depends on clinical conditions and neurological symptoms. In the literature[21], outcomes of different conservative treatments are reported. Surgery is indicated in case of severe pain resistant to medical therapy or when neurological deficits are present.

Operative approach has to totally remove the neoformation, taking into account the degree of instability of the spinal level involved by the cyst. Only when one part of the capsule appears tenaciously adherent to the dura mater it is advisable to perform a subtotal excision, to avoid risks of a CSF fistula. Microsurgical cystectomy seems to be able to maintain vertebral stability: Only one case developed vertebral slippage at follow-up. Fusion can be planned on the basis of preoperative investigations in presence of clear instability, as spondylolisthesis, or can be decided during surgery, evaluating the degree of joint demolition in order to achieve nerve roots decompression and radical cystectomy.

We limited posterior instrumented fusion to about a third of our cases, all suffering from spondylolisthesis: In the literature, fusion varies from over 50% of patients[29] to a percentage similar or lower than ours[9,12,13,17,25], whereas in other series surgery was performed without fusion[15,22,30,36,37]. This variability in surgical strategy illustrates how the indication for fusion do not follow common guidelines. As a guide to a common therapeutical strategy, we have laid out a flow-chart (Figure 5), evaluating clinical conditions, mechanical stability and the most suitable treatment.

The long-term outcomes in patients surgically treated are usually good, with complete remission from pre-operative disturbances, in our series as in others[9,11,12,13, 17,20,22,25,29,30,36,37]. Only one of our patients presented a symptomatic olisthesis about 1 year after treatment. This iatrogenic deformity, due to an excessive bone demolition, required posterior fusion to achieve resolution of symptoms. In the literature[11,13,19,20,25,30] a

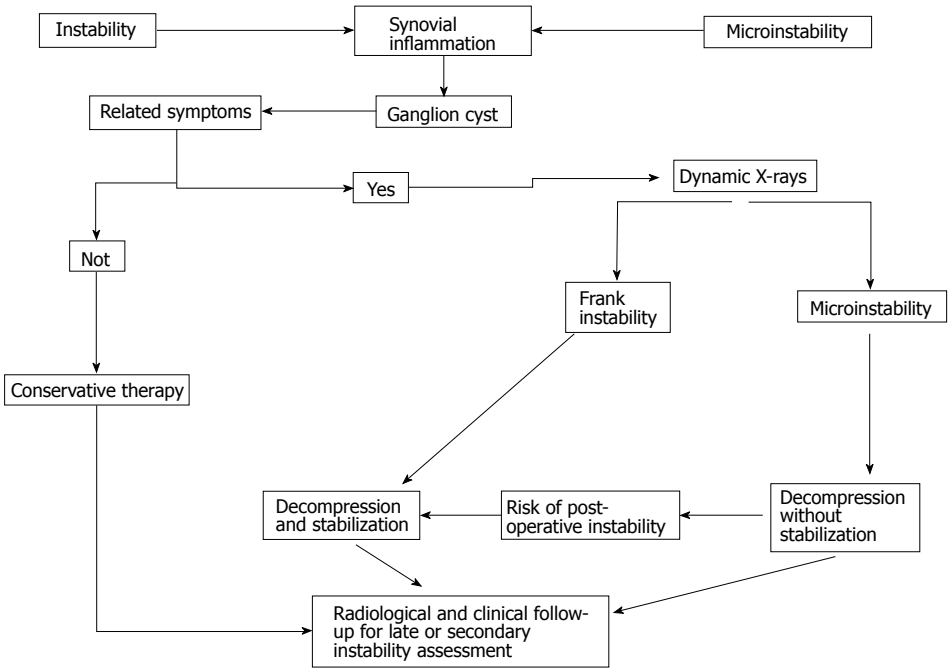

Figure 5 Flow-chart depicting options for the most appropriate approach to the lumbar spinal ganglion cysts.

similar complication was described with the same low incidence in the majority of the larger case series. A recurrence of an operated cyst is exceptional and only one case is described[13]. The appearance of a new SGC, contralateral, higher or lower, is more frequent and occurred in 15 cases[13,17,19,20,22,29,38]. No recurrences were observed in our case series.

In conclusion, spinal ganglion cysts are generally found in the lumbar spine. Over the past decades, a wide variety of terms used to describe them has generated confusion: For this reason, the authors decided to return to the ancient definition of "ganglion cyst". Their origin into the spine seems to be attributable to inflammatory phenomena, involving the synovial membrane and caused by repeated joint microtraumas, promoted by facet hypermobility or clear instability. The treatment of choice is microsurgical cystectomy, which generally does not require fusion. The need for fusion must be carefully evaluated: Pre-operative spondylolisthesis or a wide bone joint demolition are the main indications for fusion procedures. The proposal morphologic classification of SGCs is the first that clarifies different localizations of these cysts and may be clinically useful for radiologists and surgeons, together with the definition of ganglion, to speak the same scientific language.

COMMENTS

Background

Ganglion cysts of the minor and major joints, especially at the level of the wrist and back of the hand, have been known since ancient times. These cysts have a high incidence. In the past century, similar cysts were also described as originated from lumbar zygapophyseal joints and occupying the spinal canal, most frequently in the lumbar spine and occasionally, in the cervical and thoracic spine. To define these spinal neoformations, many terms have been adopted in the literature, according to the site of development or to the supposed origin: Ganglion, juxtafacet, flavum, cyfmos and synovial.

Research frontiers

The etiology of the cyst was related to inflammatory phenomena secondary to facet hypermobility, which would produce modifications of the articular synovial membrane leading to cyst formation. Microsurgical cystectomy is today the treatment of choice. Generally, microsurgical approach does not produce vertebral instability and arthrodesis is required only in case of a clear pre-operative instability.

Innovations and breakthroughs

Evaluating all etiological factors and all treatment options, the authors propose an original morphological classification of lumbar ganglion cysts, based on their relation with the other anatomical structures. Lastly, in order to clarify the confusing terminology that describes these particular cysts, the authors suggest "spinal ganglion cyst" (SGC) as definitive term to be applied in clinical practice.

Applications

The proposal morphologic classification of SGCs is the first that clarifies different localizations of these cysts and may be clinically useful for radiologists and surgeons, together with the definition of ganglion, to speak the same scientific language.

Peer-review

The authors present a case series and a proposed standardized language for lumbar ganglion cysts. The paper is generally well-written and easy to read.

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ORIGINAL ARTICLE

Retrospective Study

Acetabular components with or without screws in total hip arthroplasty

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Author contributions: Pepe M designed the research, planned the methods to generate hypothesis, conducted literature search and wrote the paper; Kocadal O designed the research and managed of the patients; Erener T designed the research, organized and reported data, contributed to the analysis; Ceritoglu K conducted literature search and explained the results; Aksahin E and Aktekin CN supervised the report.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Ankara Training and Research Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the retrospective anonymous clinical data were used that were obtained after each patient agreed to treatment by written consent. These consent forms are available in hospital archives patient's files. For full disclosure, the details are published on the home page of our hospital (http://www.ankarahastanesi.gov.tr/).

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Abstract

AIM

To compare the operation time, blood loss, and early outcomes of acetabular components with and without the screw.

METHODS

Thirty patients who underwent cementless acetabular component with or without screw and whose follow-up exceeded one year period in total hip arthroplasty were evaluated. A posterior approach was used in all surgical procedures by one experienced surgeon. Demographic data, operation time, intra- and postoperative blood loss volume, follow-up clinical score, cup migration, and osteolysis were recorded. The Kolmogorov-Smirnov test was performed for testing the normality of study data. Mann-Whitney *U* test was used to analyze the inter-group differences. A *P*-value of $\leqslant$ 0.05 was considered statistically significant.

RESULTS

Acetabular components were used in 16 (53.3%) patients with screw and 14 (46.7%) without screw. After one year of follow-up, an osteolytic lesion of 3 mm was found in only one patient in the screw group. No cup migration

was encountered. Intra-group mean Harris hip score significantly increased, but there was no significant inter-group difference. While the mean operation time of the screw group was 121.8 min (range; 95-140), it was 102.7 min (range; 80-120) in the no-screw group, and this difference was statistically significant (P = 0.002). The mean intraoperative/postoperative, and total blood loss were 556.6 mL (range: 350-800)/423.3 mL (range: 250-600), and 983.3 mL (range: 600-1350), respectively in the screw group; and 527 mL (range: 400-700)/456 mL (range: 230-600), and 983 mL (range: 630-1250), respectively in the no-screw group. The blood loss difference between the two groups was not significant. In the screw group, the operation time was 19.1 min longer than the no-screw group, and this difference was statistically significant.

CONCLUSION

Acetabular components with or without screw have similar results, but the use of screw increases the operation time significantly, while not changing the blood loss volume.

Key words: Hip arthroplasty; Acetabular fixation; With screw; Without screw; Operation time

Core tip: This is a retrospective study comparing the perioperative data and early outcomes of the screw and no-screw acetabular components in total hip arthroplasty. There is no study comparing the screw and no-screw components for perioperative data in the literature. Both components were characterized with similar clinical outcomes in the early term. But additional screws significantly increase the mean operative time.

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INTRODUCTION

Uncemented porous coated acetabular components have been preferred over cemented ones in primary total hip arthroplasty (THA) in the last 25 years[1]. Cementless acetabular cups can be implanted with or without screw[2]. While some studies have reported that the additional screw improves stability, others have mentioned that the press-fit implanted no-screw components have produced similar results with the screw fixation systems[3-6]. In addition, avoidance of screw reduces the risk of osteolysis of acetabular bone, neurovascular complications, and operational costs[7-9]. Screws could be responsible for an increased wear due to two phenomena. One is by contact with the insert, and the other one by corrosion between the screw and the cup. Screws can ensure stability in osteoporotic bones, acetabular defects, and when reliable implantation is not possible during surgery[10]. Studies comparing acetabular components with and without screws are of limited number, and the majority of them have focused on component migration, osteolysis, and clinical outcome[4,5,11]. According to our literature survey, no study has yet compared screw and no-screw fixation with respect to blood loss and operation time. In our study, we aimed to compare these two groups in terms of bleeding, surgery time, early clinical outcome, and cup migration.

MATERIALS AND METHODS

Patients who underwent THA with cementless porous coated acetabular component with or without screw for primary hip osteoarthritis and who had at least 12 mo of follow-up were included in this study. Patients with previous hip surgery, revision cases, cemented components, Crowe type 3 and 4 patients, less than 1 year follow-up, tumor or constrained prosthesis, and any bleeding diathesis were excluded from the study. The amount of intraoperative bleeding was determined by a resident by adding the total gauze weight to the difference between the irrigation and vacuum volumes[12,13]. The postoperative blood loss was calculated by the volume of drainage. No pharmacological agent was used to affect the bleeding; monopolar cauterization was applied for hemostasis during surgery. The time from the beginning of the surgical incision to the closure of the subcutaneous tissue was recorded as the operation time. Harris hip scores (HHP) were recorded by a resident at preoperative period and at postoperative 1st, 3rd, 6th, and 12th months. On the first day after surgery, articular suction drain was removed and walking and strengthening exercises without full loading were started. Patients began to walk with full weight bearing at 6th week after surgery. Radiolucent lines, osteolytic lesions more than 3 mm in diameter[14] and bone loss were recorded on radiographs of the patients at 3 acetabular regions described by Delee and Charnley[15]. This study was approved by the ethical committee of our hospital.

Surgical technique

All patients underwent unilateral THA. Preoperatively, pelvis and standing posteroanterior hip radiographs were obtained. Posterior approach was performed in all surgical procedures by one experienced surgeon. A cementless proximal 1/3 porous plasma spray coated Bi-Metric femoral component was used in all patients. A cementless Exceed ABT taper fit acetabular cup with C2A ceramic liner and head was used in patients under 65 years old. A cementless Exceed ABT Ringloc X acetabular cup and E1 10° polyethylene liner and M2A CoCrMo head was used in patients over 65 years old (Biomet, Warsaw,

Table 1 Preoperative and intraoperative data of groups *n* (%)

	Screw group	No-screw group
No. of patients	16 (53.3)	14 (46.7)
Age (yr)	56.5 (36-82)	54.0 (35-68)
Sex		
Male	4 (25)	6 (42.9)
Female	12 (75)	8 (57.1)
Diagnosis		
Osteoarthritis/posttraumatic	12	9
Inflammatory	2	3
Osteonecrosis	2	2
Head size		
28	1	0
32	15	14

IN). Acetabular socket preparation was similar in both groups and the region was reamed concentrically. When the maximum medial depth was reached, the acetabular cup was implanted. After the surgeon implanted the component, he attempted to move the cup bar antero-posteriorly and supero-inferiorly for the stability control, and two additional screws were used if the stabilization was suspicious. Otherwise it was implanted without screws.

Statistical analysis

SPSS Mac OS X 20.0 (SPSS, Chicago, IL) program was used for statistical analysis. The Kolmogorov–Smirnov test was used to test the normality of study data. Mann-Whitney *U* test was used for the analysis of operation time, bleeding volumes, and clinical scores between the groups. The Wilcoxon test was used to analyze the changes in intra-group clinical scores before and after the operation. A *P*-value below 0.05 was considered statistically significant.

RESULTS

Ten (33.3%) patients were male and 20 (66.7%) were female. Acetabular cups were used with screw in 16 (53.3%) patients and without screw in 14 (46.7%) patients. Table 1 shows the demographic data of the patients. While the mean operation time was 121.8 min (range; 95-140), in the screw group, it was 102.7 min (range; 80-120) in the no-screw group, and this difference was statistically significant ($P = 0.002$) (Figure 1). The mean intraoperative bleeding volume was 556.6 mL (range; 350-800)/527 mL (range; 400-700), the postoperative drainage volume was 423.3 mL (range; 250-600)/456 mL (range; 230-600), and the mean total bleeding volume was 983.3 mL (range; 600-1350)/983 mL (range; 630-1250) in the screw/no-screw group, respectively. The bleeding amount was not statistically significant between the groups ($P > 0.05$). Harris hip scores significantly increased within the groups, but no significant difference was found between the groups (Figure 2). Hip dislocation occurred in two patients. One of them occurred in the screw group 15 d after surgery and was relocated by sedation in the operating room; the other one was noticed in no-screw group at the early postoperative period and relocated on patient bed. No-screw group had a trochanteric fracture during femoral stem implantation. Plate fixation was performed and callus tissue formed at 6th month. None of the patients had acetabular component migration and revision surgery. One patient in screw group (6.2%) had osteolytic lesions around the screw (Table 1).

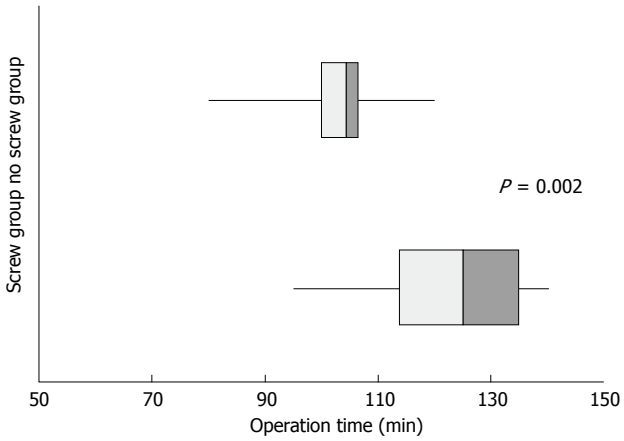

Figure 1 A bar diagram showing operation time and groups. Comparison of operation time between screw and no-screw groups with *P* values illustrated to show differences.

DISCUSSION

Transacetabular screw is used by surgeons to improve stability in total hip arthroplasty[10,16]. It has been shown to improve initial stability in cadaveric studies[10,17]. However, it is known that additional screws increase neurovascular complications[8], although there is no consensus whether they increase osteolytic lesions[11,18,19]. Some authors have attributed the increase in osteolytic lesions to a reaction to the debris escaping from the screw holes to the acetabular bone[6,20]. In contrast, Schmalzried *et al*[19] reported in their retrospective study that pelvic osteolysis is associated with significantly greater head size and longer follow-up than screw use. In our study, only one case of osteolysis was identified, which was in the screw group. We attributed the low number of osteolysis cases to a short follow-up period.

Cup migration can be evaluated not only by conventional radiography but also by radiostereometry[20]. Studies comparing middle- and long-term cup migration have yielded no significant differences between the screw and no-screw groups[11,20]. In our study, cup migration did not occur in either group at one-year follow up.

Thanner *et al*[4] reported a comparative study and found a mean HHP of 99 in the screw group and 98 in the no-screw group at the end of 2 years. In our study, at the end of one year, the mean HHP was 81.6 in the screw group and 84 in the no-screw group. Similar to the literature findings, our study did not reveal any significant differences between the two groups in terms of clinical outcomes and cup migration. Short-term follow-up and limited case series were the weak points

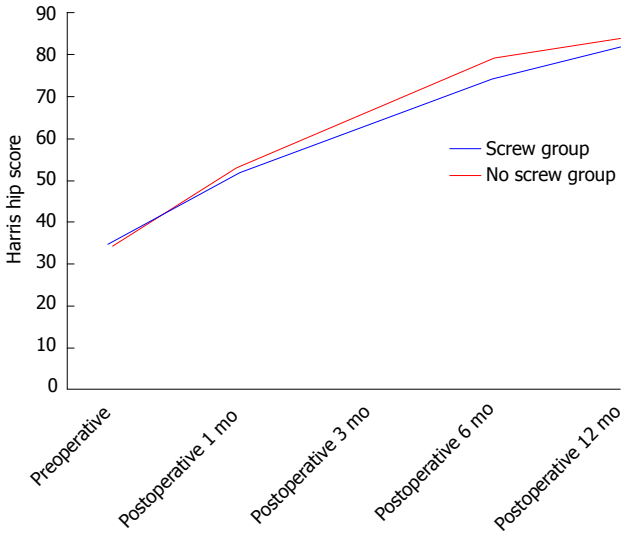

Figure 2 A line chart showing changes Harris hip score over time.

of our study.

The strength of our study is that it compared perioperative data. A review of the literature indicated that no study has yet compared the screw and no-screw groups with regard to volume of blood loss and operation time. Studies have reported that blood loss in THA ranges between 600 and 1800 mL[21,22]. The mean blood loss in our study was 983.3 mL in the screw group and 983 mL in the no-screw group, with the difference being statistically non-significant. The mean volume of intraoperative bleeding was greater by 29.6 mL in the screw group. We attributed this difference to a bleeding from screw holes, but it was not statistically significant. An analysis of the postoperative drain volumes revealed that the mean volume was greater by 32.7 mL in the no-screw group, which contributed to a slight difference of 0.3 mL between the two groups in the total amount of bleeding.

Duchman *et al*[23] reported that an operative time greater than 120 min was associated with increased short-term morbidity and risk of complications in THA. We found a mean operative time of 121.8 min in the screw group but no complication such as wound infection was encountered. We compared the screw and no-screw groups for the operation time and found that the mean time was 19.1 min greater in the screw group, and this difference was statistically significant. We attribute this difference to preparation of holes, sterile unpacking, and screwing.

Similar to the literature data, our study showed no difference between clinical outcome and cup migration between the screw and no-screw groups in the short term, whereas not using a screw provided a significant advantage in terms of operation time.

COMMENTS

Background

Cementless acetabular components in total hip arthroplasty can be implanted with or without screws. It is known that using screws increases neurovascular complications. However, its effects on osteolysis, component stability, and migration are still being debated. No study has compared the perioperative data of screw and no-screw components in the literature. In this study, the authors compared the acetabular components with and without screws in terms of bleeding, operation time, early clinical outcomes, and cup migration.

Research frontiers

The results of this study contribute to clarifying the effect of the screws used in the fixation of the acetabular component in total hip arthroplasty on the operation time, surgical bleeding, and early clinical outcomes.

Innovations and breakthroughs

Using screw did not affect clinical outcome and cup migration at the early postoperative period. Screw and no-screw groups showed similar results in respect to surgical bleeding. However, the use of the screw significantly increased the operation time.

Applications

This study showed that the implantation of the acetabular component without screw would have a significant advantage in the operation time.

Terminology

Osteolysis: Bone matrix resorption by osteoclast cells.

Peer-review

The sample size and the follow up is short of course but interesting.

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ORIGINAL ARTICLE

Retrospective Study

Single-stage anterior debridement and reconstruction with tantalum mesh cage for complicated infectious spondylitis

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Author contributions: All the authors contributed to the manuscript

Institutional review board statement: This retrospective study was undertaken using data from medical records. This study was approved by the ethical committee of the E-DA hospital (EMRP: 105-064).

Informed consent statement: Our retrospective study contained data from medical records only. The study was registered based on the data protection agency of our institute.

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Abstract

AIM

To evaluate the clinical and radiographic results of patients with complicated infectious spondylitis treated with single-stage anterior debridement and reconstruction using tantalum mesh cage (TaMC) followed by immediate instrumentation.

METHODS

Single-stage radical debridement and subsequent reconstruction with TaMC instead of autograft or allograft were performed to treat 20 patients with spinal deformity or instability due to complicated infectious spondylitis. Clinical outcomes were assessed by careful physical examination and regular serological tests to determine the infection control. In addition, the visual analog score (VAS), neurologic status, length of vertebral body reconstruction, and the correction of sagittal Cobb angle on radiography were recorded and compared before and after surgery. The conditions of the patients were evaluated based on the modified Brodsky's criteria.

RESULTS

The average VAS score significantly decreased after the surgery (from 7.4 ± 0.8 to 3.3 ± 0.8, $P < 0.001$). The average Cobb angle correction was 14.9 degrees. The neurologic status was significantly improved after the surgery ($P = 0.003$). One patient experienced refractory infection and underwent additional debridement. Eighteen patients achieved good outcome based on the modified Brodsky's criteria and significant improvement after the surgery ($P < 0.001$). No implant breakage or

TaMC dislodgement was found during at least 24 mo of follow-up.

CONCLUSION

Single-stage anterior debridement and reconstruction with TaMC followed by immediate instrumentation could be an alternative method to manage the patients with spinal deformity or instability due to complicated infectious spondylitis.

Key words: Anterior reconstruction; Complicated infectious spondylitis; Instrumentation; Spinal deformity; Tantalum mesh cage

Core tip: Complicated infectious spondylitis is a rare infection with vertebral pathological fracture and severe spinal destruction that require anterior reconstruction. The use of metallic implants for vertebral body stabilization and reconstruction following debridement at the lesion of infection remains controversial. In the present study a series of 20 patients with complicated infectious spondylitis were treated with single-stage anterior debridement and reconstruction using tantalum mesh cage (TaMC) followed by immediate instrumentation. The results demonstrated that good functional outcome and low complication rate could be achieved by a single-stage anterior debridement and reconstruction with TaMC.

Yang SC, Chen HS, Kao YH, Tu YK. Single-stage anterior debridement and reconstruction with tantalum mesh cage for complicated infectious spondylitis. *World J Orthop* 2017; 8(9): 710-718 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i9/710.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i9.710

INTRODUCTION

Spinal infections continue to be a challenge for clinical physicians and surgeons because of their initial vague symptoms with varied manifestations, and subsequent complex progression[1-6]. A delay or failure of diagnosis and treatment can lead to structural instability, spinal deformity, neurologic impairment, sepsis, and even death. Tuberculous spondylitis is common in almost all developing and underdeveloped regions of the world and is resurgent in developed nations. Neurologic involvement is usually gradual in onset and typically results from a kyphotic deformity with secondary spinal cord compression. Pyogenic spondylitis, either referred to as spondylodiscitis or vertebral osteomyelitis, generally results from arterial or venous hematogenous seeding, which can occur from infection in the urinary or respiratory tract, soft tissue, or elsewhere. The spine also can be seeded from infection related to the diagnostic and therapeutic procedures, or intravenous drug abuse[7-10]. Infectious spondylitis may be acute, subacute, or chronic. The virulence of the offending pathogens and the host condition are major determinants of clinical presentations.

Complicated infectious spondylitis indicated for anterior reconstruction is a spinal infection with vertebral pathologic fracture and severe spinal destruction. Various biological and mechanical spacers, including autograft, allograft, and titanium mesh cage (TiMC), are used to reconstruct the anterior column after corpectomy. Previously, the use of metallic implants for vertebral body stabilization and reconstruction following debridement at the lesion of infection is controversial. Recently, several reports of patients with vertebral osteomyelitis treated with cages for anterior reconstruction have been published. The results showed that TiMC did not increase the rate of recurrent or persistent infection[11-13]. Furthermore, a direct comparison between autograft and cages showed no difference in clinical and imaging outcomes[14]. Tantalum components are reported to be associated with an even lower incidence of subsequent infection when used in patients with periprosthetic joint infection[15]. However, no study has investigated the use of tantalum mesh cage (TaMC) for anterior reconstruction in the treatment of complicated infectious spondylitis. Therefore, this study aimed to evaluate the clinical and radiographic results of 20 patients with complicated infectious spondylitis treated with single-stage anterior debridement and reconstruction using TaMC followed by immediate instrumentation and followed-up at least 2 years.

MATERIALS AND METHODS

A total of 20 patients (7 women and 13 men) who underwent single-stage combined extensive debridement and anterior reconstruction using tantalum mesh cages at our university hospital between January 2012 and December 2014 were included in the study. This study was approved by the ethical committee in our institution. The patients' average age was 58.4 years (range, 39 to 73 years). Their medical records including outpatient and emergency room notes, admission notes, inpatient progress and nursing notes, discharge summaries, procedure notes, surgical reports, radiology reports, pathology reports, and microbiology laboratory results were reviewed. Infectious spondylitis was diagnosed based on clinical examinations including positive physical or neurological presentations, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values, and radiographic and magnetic resonance imaging findings. Complicated infectious spondylitis was defined as at least one-level vertebral osteomyelitis with pathological fracture or severe bony destruction and adjacent discitis, based on imaging studies. All 20 patients with complicated infectious spondylitis enrolled in this study met the surgical indications of failed conservative treatment or debridement procedure, neurological compromise, and

spinal instability or kyphotic deformity. These patients wore a rigid orthosis for protection at least 3 mo after surgery. Radiographic assessment was performed before and after surgery, and at the 3-, 6-, and 12-mo visit after discharge and every year thereafter. Systemic antibiotics or anti-tuberculous drugs were administered based on sensitivity studies for identified pathogens. A 6-wk full course of intravenous antibiotics was prescribed for pyogenic spondylitis, and a 12-mo full course of antimicrobial chemotherapy for tuberculous spondylitis. All 20 enrolled patients were followed-up for at least 24 mo after undergoing single-stage anterior debridement and reconstruction surgery.

Surgical technique

All patients underwent single-stage anterior debridement and reconstruction surgery carried out by our spinal surgery team. Three patients had cervical spine infection, and 17 patients had thoracolumbar spine infection. The patients were operated under general anesthesia with endotracheal intubation. During the operation, the vital signs of the patients, including heart rhythm, blood pressure, and pulse oxygenation levels, were continually monitored by anesthesiologists. A Smith-Robinson approach was used for patients with cervical spine lesions. An anterior transthoracic or retroperitoneal approach was performed for patients with thoracolumbar spine lesions. The infected lesion was debrided radically, and all destroyed tissues were removed. The spinal cord and neural elements were also decompressed completely. Smear, bacterial, and tuberculous cultures were all performed. The local area was irrigated thoroughly with diluted povidone-iodine and normal saline solution. The length of the defect after extensive debridement was determined, and a TaMC (Zimmer, NJ, United States) was then introduced into the space between the healthy vertebral bodies for anterior support and axial loading. The cervical locked plate was used for immediate stability after anterior reconstruction in patients with cervical spine lesions. Posterior transpedicular screw instrumentation was performed in patients with thoracolumbar spine lesion. The sequence of anterior or posterior surgery depended on the spinal stability and neurological status of the individual. The wound was closed with drain insertion.

Outcome assessment

The severity of the neurological status was evaluated using the Frankel scale before and after surgery, and regular follow-up visits. Radiographic examination images were used to compare the correction of the sagittal Cobb angle before and after surgery. The Cobb angle, defined as the angle between the superior endplate of the vertebrae above the implanted TaMC and the inferior endplate of the vertebrae below, was measured on plain lateral radiographs. Clinical outcomes were assessed by asking patients to qualify their pain on a visual analog scale (VAS) using a scale of 0-10 (0 = no pain and 10 = worst possible pain) and by careful physical examination and regular serological tests during admission and before discharge to determine the modified Brodsky criteria scores. Data of outcome assessment are presented as mean values with standard deviations or median values with interquartile ranges. The Frankel scale, sagittal Cobb angle, and VAS before and after surgery were compared and analyzed using the Wilcoxon signed-rank test. Nonparametric statistics were used because some variables did not have normally distributed data. SPSS 13.0 software (SPSS Inc., Chicago, United States) was used for data analysis. A value of $P < 0.05$ was considered statistically significant.

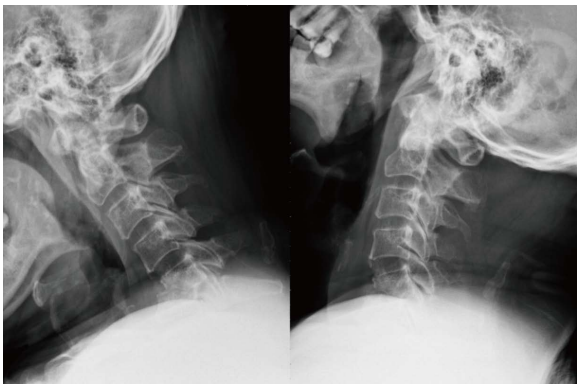

Figure 1 A 51-year-old man experienced intractable neck pain and neurologic deficit. Dynamic radiograph showed pathological fractures with kyphotic deformity of 5th and 6th cervical vertebrae.

RESULTS

Seventeen patients with thoracolumbar infection and 3 patients with cervical infection were enrolled in this study. Sixteen patients underwent anterior debridement with 1-level corpectomy and adjacent discectomies, 3 patients with 2 levels, and 1 patient with 3 levels. Sixteen patients underwent 2 levels above and 2 levels below instrumentation of anterior reconstruction using TaMCs after extensive debridement and corpectomy, 3 patients underwent 1 level above and 1 level below, and 1 patient underwent 3 levels above and 3 levels below (Figures 1-7). The average number of segments of resected vertebrae was 1.25 (4 in the cervical region, 6 in the thoracic region, and 15 in the lumbar region). The average length of the TaMC for anterior reconstruction was 36.9 mm. Kyphotic deformity reduced in all patients, with an average angle correction of 14.9° (Table 1).

Neurologic deficits were much improved, from the median of Frankel D before surgery to Frankel D before discharge ($P = 0.003$), and to Frankel E at the 1-year follow-up visit ($P = 0.001$). No patient experienced neurologic deterioration after the operation. Severe back pain related to infectious spondylitis significantly decreased from the average VAS of 7.4 ± 0.8 (range,

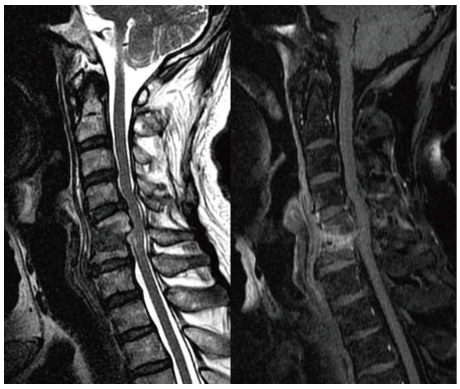

Figure 2 Sagittal T2-weighted and contrast-enhanced magnetic resonance imaging revealed C5-C6 infectious spondylitis with epidural abscess accumulation and spinal cord compression.

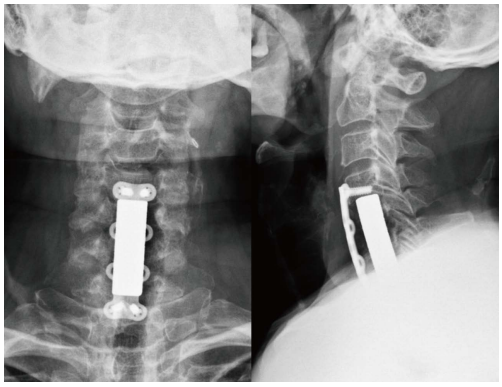

Figure 3 Single-stage anterior radical debridement and tantalum mesh cage implantation followed by supplemental anterior locked plate instrumentation were performed to treat infectious spondylitis and correct kyphotic deformity. Postoperative radiograph showed better alignment after single-stage anterior surgery for complicated infectious spondylitis.

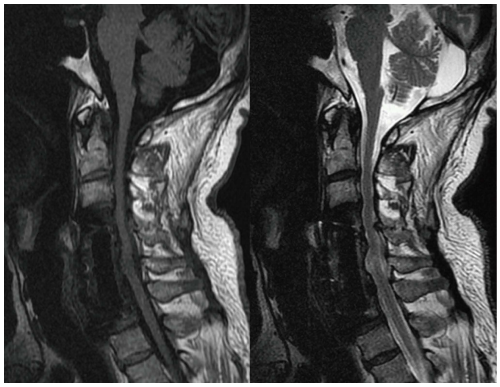

Figure 4 The follow-up sagittal T1- and T2-weighted magnetic resonance imaging demonstrated good implant position and no evidence of recurrent infection.

6 to 9) before surgery to VAS of 3.3 ± 0.8 (range, 2 to 5) after surgery ($P < 0.001$), and to VAS of 2.2 ± 0.9 (range, 1 to 4) at the 1-year follow-up visit ($P < 0.001$). Eight patients could achieve excellent outcomes. Ten patients have good outcomes based on the modified Brodsky's criteria, and the improvement showed

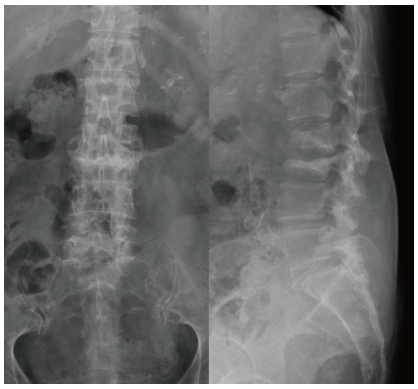

Figure 5 A 73-year-old woman with end-stage renal disease sustained severe back pain and intermittent high fever. Radiograph showed endplate erosion and destruction of the 2nd and 3rd lumbar vertebrae, and loss of lumbar lordotic alignment.

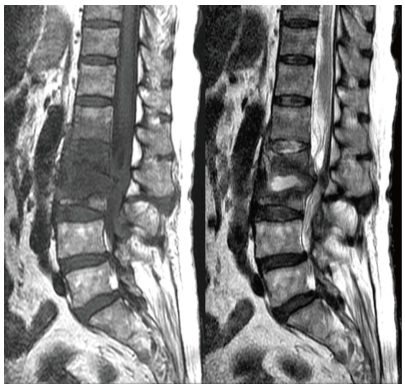

Figure 6 Sagittal T1- and T2-weighted magnetic resonance imaging revealed L2-L3 infectious spondylitis with epidural abscess accumulation.

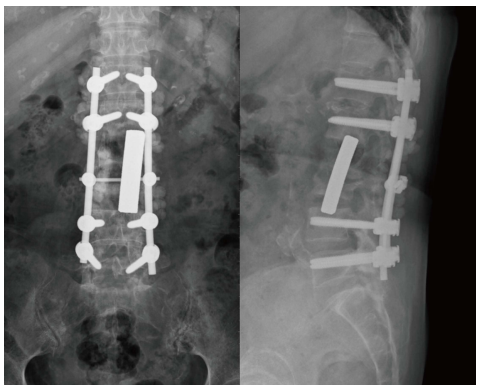

Figure 7 Single-stage anterior radical debridement and tantalum mesh cage implantation followed by supplemental posterior pedicle screw instrumentation were performed to treat infectious spondylitis and correct kyphotic deformity. The antibiotic beads were also deposited for infection control. Postoperative radiograph showed better lordotic alignment after single-stage combined anterior-posterior surgery for complicated infectious spondylitis.

significant differences 1 year after surgery ($P < 0.001$) (Table 2).

Causative bacteria were isolated in 19 (95%) of 20 biopsy cultures through either preoperative or

Table 1 Patient demographic data

Case no	Age (yr)	Gender	Infection level	Instrumented level	Length of mesh cage	Pathogen	Cobb angle correction
1	62	M	L2 and adjacent discs	T12L1 to L3L4	38 mm	OSSA	15°
2	50	M	L1 and adjacent discs	T11T12 to L2L3	35 mm	ORSA	18°
3	39	M	T11-L1 and adjacent discs	T8T9T10 to L2L3L4	56 mm	MT	25°
4	55	M	L2 and adjacent discs	T12L1 to L3L4	41 mm	SV	19°
5	48	F	L3 and adjacent discs	L1L2 to L4L5	35 mm	PA	6°
6	51	M	C5C6 and adjacent discs	C4 to C7	44 mm	ORSA	29°
7	70	F	L3 and adjacent discs	L1L2 to L4L5	33.5 mm	OSSA	12°
8	72	F	T8T9 and adjacent discs	T6T7 to T10T11	38 mm	MT	20°
9	69	F	C4 and adjacent discs	C3 to C5	24.5 mm	OSSA	22°
10	42	M	L1 and adjacent discs	T11T12 to L2L3	38 mm	OSSA	15°
11	52	M	L1 and adjacent discs	T11T12 to L2L3	38 mm	EF	9°
12	60	F	T12 and adjacent discs	T10T11 to L1L2	32 mm	No growth	8°
13	65	M	L1 and adjacent discs	T11T12 to L2L3	33.5 mm	ORSA	8°
14	59	M	L4 and adjacent discs	L2L3 to L5S1	41 mm	PA	10°
15	73	F	L2L3 and adjacent discs	T12L1 to L4L5	62 mm	EC	23°
16	58	M	T11 and adjacent discs	T9T10 to T12L1	29 mm	MT	15°
17	55	F	L1 and adjacent discs	T10T11 to L2L3	29 mm	OSSA	14°
18	64	M	C4 and adjacent discs	C3 to C5	23 mm	EC	12°
19	68	M	L1 and adjacent discs	T11T12 to L2L3	32 mm	ORSA	7°
20	56	M	L2 and adjacent discs	T12L1 to L3L4	35 mm	OSSA	11°

F: Female; M: Male; T: Thoracic spine; L: Lumbar spine; S: Sacrum; OSSA: Oxacillin-sensitive *staphylococcus aureus*; ORSA: Oxacillin-resistant *staphylococcus aureus*; MT: *Mycobacterium tuberculosis*; SV: *Streptococcus viridans*; PA: *Pseudomonas aeruginosa*; EF: *Enterococcus faecalis*; EC: *Escherichia coli*.

Table 2 Comparison of clinical outcomes and radiographic findings before surgery and after surgery

	Preop	Postop	1 yr later	P (a/b)
VAS	7.4 ± 0.8[1]	3.3 ± 0.8[1]	2.2 ± 0.9[1]	< 0.001/< 0.001
FS	D (C,E)[2]	D (D,E)[2]	E (E,E)[2]	= 0.003/= 0.001
MBC	F (P,F)[2]	G (G,G)[2]	G (G,E)[2]	< 0.001/< 0.001

[1]mean ± SD; [2]median (25th percentile, 75th percentile). Preop: Preoperative; Postop: Postoperative; a: Postop *vs* preop with Wilcoxon signed-rank test; b: Postop 1 year *vs* preop with Wilcoxon signed-rank test. VAS: Visual analog scale: 0 means no pain and 10 means the most pain possible. MBC: Modified Brodsky criteria: P = poor, F = fair, G = good, E = excellent; FS: Frankel scale: A = complete paralysis; B = sensory function only below the injury level; C = incomplete motor function below injury level; D = fair to good motor function below injury level; E = normal function.

intraoperative procedure. Ten of the 20 patients were infected with *Staphylococcus aureus*, including 6 with the oxacillin-sensitive strain and 4 with the oxacillin-resistant strain. Three patients had *Mycobacterium tuberculosis* infection, 2 had *Pseudomonas aeruginosa* infection, 2 had *Escherichia coli* infection, and 2 had *Streptococcus viridans* and *Enterococcus faecalis* infections. Intravenous antibiotic therapy was continuously administered for a minimum of 6 wk postoperatively based on the specific microbial sensitivities and the identified pathogenic organism. Oral antibiotics were not routinely used after discharge. At outpatient clinics, anti-tuberculous chemotherapy was given for 12 mo or longer. A full course of broad-spectrum antibiotics was administered for the patient with negative culture results. Both elevated CRP and ESR values returned to normal limits at the 1-year follow-up visit (Figure 8).

No implant breakage or tantalum mesh cage dislodgement was found. One patient who was receiving regular hemodialysis experienced refractory infection and underwent additional debridement with antibiotic bead deposition. No recurrent infections were found among the patients during the postoperative follow-up.

DISCUSSION

Infectious spondylitis has generally been regarded as medical disease. Effective antibiotic therapy is the mainstay of successful nonsurgical treatment. Surgery has historically been recommended in several circumstances: Cases refractory to appropriate conservative management, spinal cord compression resulting in neurologic deficit, progressive instability due to significant destruction, severe scoliosis or kyphosis caused by chronic infection[16,17]. All patients in the present study sustained complicated infectious spondylitis with pathological fracture and adjacent discitis. Extensive destruction of the vertebral body resulted in a large amount of epidural abscess accumulation, progressive scoliotic or/and kyphotic deformity, severe back pain, spinal instability, and neurological impairment. A single-stage anterior or combined anterior-posterior procedure, including an anterior surgery for initially radical debridement and subsequent TaMC reconstruction, was performed to treat these patients An additional posterior surgery was used for immediate pedicle screw instrumentation to keep physiologic alignment and secure spinal stability in patients with thoracolumbar spine infection. Anterior instrumentation using locked plate/screw one above and one below was used for

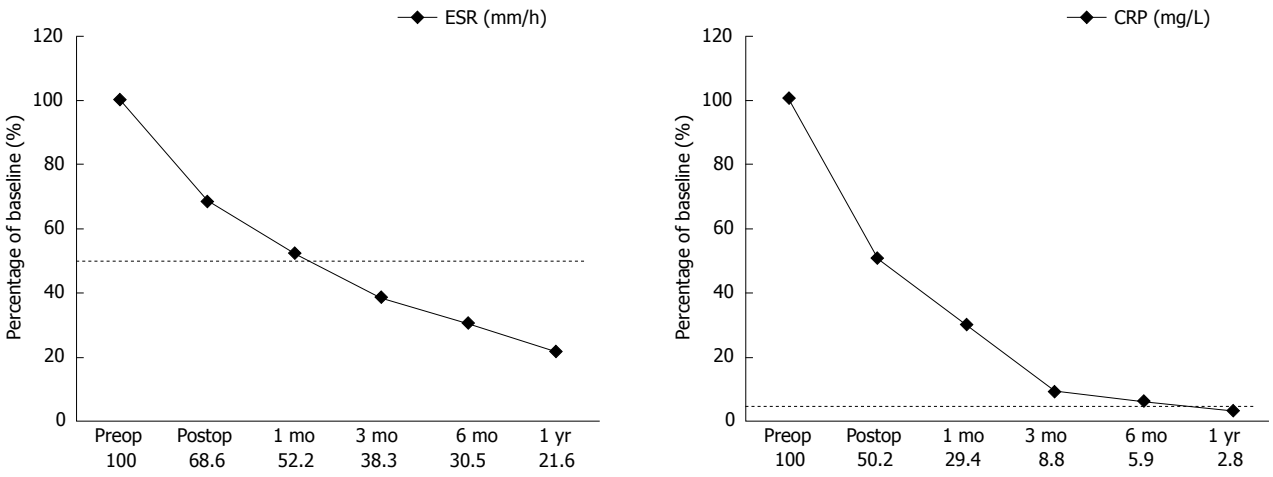

Figure 8 Percentage changes in serological values before and after single-stage anterior and/or posterior surgery in patients with complicated infectious spondylitis.

patients with cervical spine infection.

Various biological and mechanical spacers, including fibular autograft, fibular allograft, and even antibiotic-impregnated methylmethacrylate, are used to reconstruct the anterior column after corpectomy[18-21]. Antibiotic-impregnated methylmethacrylate is sometimes formed into antibiotic beads to salvage deep wound infection in our clinical practice. The defect after corpectomy is usually repaired by an autologous bone graft from the fibula or the iliac crest, which may cause a 25% increase in permanent morbidity of the donor site[22-25]. The advantages of allograft bone include the elimination of the harvesting surgical site, the related postoperative pain, and the added expense of a second operative procedure. However, there is still a slight chance of disease transmission using allograft. The other concern is that the sources or sufficient allograft is usually unavailable in most hospitals. The use of metallic implants for vertebral body reconstruction and stabilization following extensive debridement at the site of infection is controversial. Only few retrospective cohort studies including few cases have been previously published. Recent studies have focused on the usefulness, stability, and safety with minimal recurrence of internal fixation of metallic implants in eradicating an active spinal infection[26-29]. In an observational cohort study at 5 tertiary care hospitals in South Korea, 153 patients with spinal infection requiring surgical management were enrolled. Among these patients, 94 (61.4%) underwent non-instrumented surgery and 59 (38.6%) underwent instrumented surgery[30]. Clinical outcomes were evaluated using the following measures: Infection-related death, primary failure, recurrence, and sequelae. The results showed that placement of spinal instrumentation did not adversely affect the clinical outcomes. The authors concluded that concerns about infection recurrence and complications should not prevent the use of instrumentation in the management of vertebral osteomyelitis where spinal stability is necessary.

Despite the fact that there is evidence for bacterial adhesion to metal implants, the strong immunity of the highly vascularized cancellous vertebral body bone is unique, even in the presence of infection. In an in vitro cell culture experimental study, *S. aureus* and *Staphylococcus epidermidis* were used to evaluate qualitatively and quantitatively bacterial adherence to metallic implants including tantalum, tantalum-coated stainless steel, titanium, titanium alloy, and grit-blasted and polished stainless steel. The results showed that pure tantalum presents with a lower or similar bacterial adhesion when compared with commonly used materials in orthopedic implants[31]. Schildhauer *et al*[32] compared the functions and cytokine response of human leukocytes and equally sized solid orthopedic metal implant materials (pure titanium, titanium alloy, stainless steel, pure tantalum, and tantalum-coated stainless steel) toward porous tantalum foam biomaterial. The results indicated that leukocyte activation at the surface of tantalum material induces a microenvironment, which promotes local host defense mechanism with increased phagocytosis, chemotaxis, and whole blood *S. aureus* killing rate. In a clinical study, Tokarski *et al* compared the use of tantalum and titanium acetabular components in revision total hip arthroplasty[15]. They concluded that tantalum components are associated with a lower incidence of subsequent infection when used in patients with periprosthetic joint infection.

TaMC derived from trabecular metal (TM) Technology has an advanced fixation surface designed for orthopedic implants. With a high coefficient of friction (0.98), it provides excellent initial scratch fit. In contrast to coatings and other surfaces, TM material has up to 80% porosity, which enhances the potential for bone ingrowth and soft tissue vascularization[33]. Sinclair *et al*[34] reported an *in vivo* assessment of polyetheretherketone (PEEK) and porous tantalum cervical interbody fusion devices in a goat model. The result showed that bone growth into and around the TM implant margins was better than the PEEK devices. Ordway *et al*[35] examined the

implant-endplate interface using a cyclic fatigue loading protocol to model the subsidence observed *in vivo*. The TM construct demonstrated comparable axial stability and subsidence to a fibular allograft. Given the above-mentioned reasons, it could be an alternative material for anterior reconstruction in spine surgery.

A single-stage combined anterior-posterior approach, as opposed to 2-stage surgery, has advantages of a shorter anesthesia time, less anxiety for the patient and family, less blood loss, and earlier mobilization. In the current study, nineteen out of twenty (95%) patients achieved excellent outcome without complication, which was better than the previous reports. Additional anterior debridement and antibiotic bead deposition successfully treated the residual patient with refractory infection and anterior wound dehiscence. All 20 patients who received this combined surgery for their complicated infectious spondylitis recovered from the illness uneventfully. Tantalum with adequate length was used for anterior column reconstruction after radical debridement. All patients had significant improvement of neurologic function and back pain. Good recovery of the sagittal alignment was achieved with an average 14.9° correction of the Cobb angle. No complications related to the single-stage combined surgery were noted. Tokarski *et al*[15] analyzed 10 clinical series involving 106 patients undergoing a single-stage procedure for their spinal infection. Deep wound infections were reported in 6.6% of patients, with most treated by debridement and secondary granulation. Superficial wound infections were found in 2.8% of patients. Patients undergoing spinal instrumentation for spinal disorders other than infection treatment had a similar incidence of postoperative infection. An incidence as high as 20% in instrumented spinal surgery was even reported in previous studies[36,37]. Therefore, if a cooperative surgical team and care unit are available, a single-stage combined anterior-posterior surgery may be a good alternative in consideration of complications of staged surgeries.

This study has several limitations. First, only 20 cases were examined. Second, this retrospective study did not include patients receiving variant treatment strategies for comparison, and lacked randomization. A large patient population with prospectively controlled comparison groups may be required to evaluate the benefit and feasibility of this single-stage combined anterior-posterior procedure using tantalum reconstruction for complicated infectious spondylitis. Third, most of the patients in this study had received different types of treatment, either open surgery or conservative antibiotics, and then were admitted to our institute due to progressive infection at their original hospital and/or previous failed treatment. After careful examination and evaluation, a primary or revision surgery was performed in these eligible patients, which might cause selective and therapeutic bias. However, uncontrolled infection and difficulty in bony incorporation did not occur in the patients with either single-stage surgery or anterior reconstruction using tantalum, based on the clinical results of this small patient population.

In conclusion, single-stage anterior debridement and reconstruction combined with anterior instrumentation for cervical spine and posterior instrumentation for thoracolumbar spine can be recommended to treat patients with complicated infectious spondylitis. Anterior radical debridement and TaMC implantation and associated supplemental instrument fixation provide immediate secure stability, successful infection management, neurologic impairment recovery, better physiological alignment, satisfactory pain relief, and significant improvement of daily activities. TaMC can be considered an alternative for anterior column reconstruction, which can provide biomechanical support, avoid donor site morbidity, proceed to bony incorporation, and appear to be protective against infection. However, an administration of a full course of offending pathogens specific intravenous antibiotics or chemotherapy is mandatory to maintain good long-term outcomes and eliminate the risk of recurrent infection.

COMMENTS

Background

Spinal infections challenge clinical physicians because of their varied presentation and complicated course. The use of metallic implants for vertebral body stabilization and reconstruction following debridement at the lesion of infection is controversial. Previously, no study has investigated the use of tantalum mesh cage (TaMC) for anterior reconstruction in the treatment of complicated infectious spondylitis. The primary aim of this study was to evaluate the efficacy of TaMC in patients with Complicated infectious spondylitis.

Research frontiers

The authors demonstrated that TaMC could be a good alternative for anterior reconstruction.

Innovations and breakthroughs

Single-stage anterior debridement and TaMC implantation followed by immediate instrumentation provided immediate stability, successful infection control, neurologic deficit recovery, more satisfactory alignment, adequate pain relief, and better improvement of daily activities.

Applications

Single-stage anterior debridement and TaMC implantation followed by immediate instrumentation was useful for patients with complicated infectious spondylitis. This method could avoid the complications derived from various biological spacers such as autograft and allograft.

Terminology

TaMC derived from Trabecular Metal (TM) Technology has an advanced fixation surface designed for orthopedic implants. TM material has up to 80% porosity, which enhances the potential for bone ingrowth and soft tissue vascularization.

Peer-review

This is a good study, which evaluates clinical and radiological results of patients with complicated infectious spondylitis treated with single-stage anterior debridement and reconstruction using tantalum mesh cage followed by immediate instrumentation.

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ORIGINAL ARTICLE

Prospective Study

Association of adiponectin gene polymorphisms with knee osteoarthritis

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Abstract

AIM

To investigate the possible relationship of adiponectin (*ADIPOQ*) gene polymorphisms, plasma adiponectin, and the risk of knee osteoarthritis (OA).

METHODS

A total of 398 subjects, 202 knee OA patients and 196 healthy individuals, were enrolled in the case-control study. Genotyping at +45T/G (rs2241766) and +276G/T (rs1501299) loci was performed using polymerase chain reaction-restriction fragment length polymorphism. Plasma adiponectin levels were assessed using enzyme-linked immunosorbent assay. OA severity was determined using the Kellgren-Lawrence (KL) grading system.

RESULTS

No significant associations were observed in the genotype distributions and allele frequencies at two loci of +45T/G and +276G/T polymorphisms in the ADIPOQ between

knee OA patients and control subjects. There was a significant association between genotype distribution of +276G/T polymorphism and KL grade 2, 3 or 4 (P = 0.037, P = 0.046, P = 0.016, respectively). At +45T/G locus, the percentage of GG genotype was notably greater in control subjects (13.40%) compared with OA subjects (1.70%) (P = 0.023). Plasma adiponectin was markedly decreased in OA subjects compared with control subjects (P = 0.03). Likewise, circulating adiponectin in OA subjects was notably lesser than that in control subjects in GG genotype of +45T/G (P = 0.029) and +276G/T polymorphisms (P = 0.012).

CONCLUSION

Polymorphisms +45T/G and +276G/T of the *ADIPOQ* gene might not be responsible for OA susceptibility among Thais.

Key words: Adiponectin; *ADIPOQ*; Polymorphism; Knee osteoarthritis; Plasma

Core tip: Plasma adiponectin levels were significantly lower in knee osteoarthritis (OA) than controls. No significant associations were observed in the genotype distributions and allele frequencies of *ADIPOQ* +45T/G and +276G/T polymorphisms between knee OA subjects and controls. There was a significant association between genotype distribution of +276G/T polymorphism and OA severity. In addition, plasma adiponectin in OA subjects was seemingly lower than that in control subjects in GG genotype of +45T/G and +276G/T polymorphisms. Polymorphisms +45T/G and +276G/T of the *ADIPOQ* gene might not be responsible for the susceptibility to knee OA in the Thai population.

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INTRODUCTION

Osteoarthritis (OA), also known as degenerative joint disorder, is characterized by progressive cartilagenous damage, chronic synovial inflammation, development of bone spurs, subchondral cyst formation, and osteosclerosis, leading to joint disability. OA of the knee remains a main cause of mobility impairment, particularly in the elderly population and has been recognized as a major global health problem. A wide variety of potential factors including environments, biomechanics, biochemical processes and/or genetics have been demonstrated to play substantial parts in the progression of OA. Nonetheless, the cause of OA is still a mystery. Numerous single-nucleotide polymorphisms (SNPs) related to OA have been previously investigated.

Besides storing-energy, adipogenous tissue is also recognized as a metabolic and endocrine organ with significance, complication and high activity. Hormones secreted from adipose tissue are named after adipokines that associate with metabolic processes and inflammatory reaction as well as performance cytokine-like function including anti- and pro-inflammatory effects[1-3]. In human chromosome 3q27, *ADIPOQ* gene encodes one essential adipokine - adiponectin which contains 244 amino acid residues. It is synthesized in differentiated adipocytes and maintains high levels in blood circulation. The function and effect of adiponectin have been clearly elaborated in anti-diabetic and anti-atherogenic properties. It is still controversial whether adiponectin may have a contributing role in the development of OA. Recently, adiponectin was identified in cartilage, osteophytes, meniscus, synovial membrane and infrapatellar fat pad taken from the knees of OA patients, with the highest concentrations found in the last two[4]. Previous investigations demonstrated that circulating and synovial adiponectin concentrations were negatively correlated with the radiographic severity in OA subjects[5,6]. In chondrocytes, adiponectin could modulate cartilage destruction through increasing tissue inhibitor of metalloproteinase-2 and decreasing interleukin-1β (IL-1β)[7]. Accumulating documentation proposes that adiponectin might act as a protective cytokine in OA.

As an essential component of the etiology of OA, candidate genes encoding proteins about metabolism of the articular cartilage and inflammation of synovial membrane have been proved with the pathogenesis of OA. It is ascertained that a number of SNPs involving in OA surrounding genes of estrogen receptor alpha[8], interleukin-6[9] and matrix metalloproteinase-3 (MMP-3)[10]. However, until recently, the study of adiponectin gene polymorphisms in OA patients has received little attention. There are many genetic variations of the human adiponectin gene reported, including several non-synonymous mutations. Some metabolic disorders have been recognized to be related with the two most commonly investigated polymorphisms of *ADIPOQ*, +45T/G and +276G/T SNPs[11,12]. Additionally, Qi *et al*[13] found that greater circulating adiponectin concentration in control subjects carried more T allele at +276G/T locus. We hypothesized that the adiponectin gene would play a part in the development of OA. Thus, the objective of the present investigation is to determine the association between +45T/G or +276G/T *ADIPOQ* polymorphisms and OA susceptibility and plasma adiponectin in knee OA subjects.

MATERIALS AND METHODS

This study was approved by the Institutional Review

Board on Human Research of the Faculty of Medicine, Chulalongkorn University. The present study was conducted in compliance with the guidelines of the Declaration of Helsinki. All subjects gave written informed consent prior to their participation in the study.

Study population

The current study recruited 202 primary knee OA patients (average age 68.80 ± 7.80 years, range from 50-84 years), including 136 female and 66 male subjects. Diagnostic criteria of the American College of Rheumatology were used to identify knee OA subjects. We precluded individuals who had other chronic inflammatory diseases or immunological abnormalities, or preceding knee trauma or surgery. Kellgren-Lawrence (KL) classification system was assigned to determine the severity of knee OA into KL grade 1, 2, 3, or 4 corresponding to radiographic examination[14]. Furthermore, 196 healthy individuals (average age 65.20 ± 6.20 years, 128 female and 68 male) without any symptoms and signs and previous history of OA were used as control subjects.

DNA isolation and ADIPOQ gene polymorphisms

Peripheral venous blood specimens of 3 mL were collected from each participant by standard venipuncture. Genomic DNA was extracted from buffy coats by using the commercially available Illustra Blood Genomic Prep Midi Flow Kit (GE Healthcare, Buckinghamshire, United Kingdom) and was maintained at -20 ℃ until analysed. +45T/G and +276G/T polymorphisms of adiponectin gene were detected by polymerase chain reaction (PCR) restriction fragment length polymorphism (PCR-RFLP). PCR amplifications were conducted for the +45T/G (rs2241766) SNP by using the published primer set[15]: forward, 5′-TCCTTTGTAGGTCCCAACT-3′ and reverse, 5′ GCAGCAAAGCCAAAGTCTTC-3′. The PCR for +45T/G SNP was performed with the following protocols: 95 ℃ for 15 min, repeated by 35 amplification cycles at 95 ℃ for 30 s, 56 ℃ for 30 s, and 72 ℃ for 1 min, and a last extension at 72 ℃ for 7 min. After digestion with the restriction enzyme *BspH1* (New England Biolabs, Beverly, MA) in 37 ℃ water bath for 16 h, the PCR amplified 503 base pair length sequence was cleaved into 375 and 128 base pair segments (T allele of +45T/G). PCR amplifications were conducted for the +276G/T (rs1501299) SNP by using the published primers set[15]: Forward primer 5′-ACACTGATATAAACGCCATGAA-3′ and reverse primer 5′-GCAGCAAAGCCAAAGTCTTC-3′. The PCR for +276G/T (rs1501299) SNP was performed with the following protocols: 95 ℃ for 10 min, repeated by 40 amplification cycles at 95 ℃ for 30 s, 48 ℃ for 1 min and 72 ℃ for 1 min, and a last extension at 72 ℃ for 7 min. After digestion with the restriction enzyme *Bgl1* (New England Biolabs, Beverly, MA) in 37 ℃ water bath for 16 h, the PCR amplified 168 base pair length sequence was cleaved into 147 and 21 base pair segments (G allele of +276G/T). The digested sequences were resolved by electrophoresis in 2.5% agarose gel or 12% polyacrylamide gel. The gels were stained with ethidium bromide and analysed by exposure to ultraviolet light on a transilluminator.

Assessment of plasma adiponectin

Following blood sample collection, the plasma were centrifuged and kept promptly at -20 ℃ till analysis. Plasma adiponectin concentrations were assessed by a commercially available sandwich enzyme-linked immunosorbent assay kit (DuoSet ELISA Development kit for human adiponectin, R and D Systems, Minneapolis, MN). Based on the guidelines of manufacturer, 100 μL of samples or standards in reagent diluent were added into a 96-well plate which was precoated with capture antibody overnight at room temperature (RT). After incubating for 2 h at RT and washing three times with washing buffer, 100 μL of the specific detection antibody was pipetted and kept for 2 h at RT. After thoroughly four washes with washing buffer, 100 μL of streptavidin-HRP (1:200) was pipetted to each well and kept for 20 min at RT to avoid in direct light. One hundred slightly of substrate solution was pipetted and kept for another 20 min. Finally, 50 μL of stop solution was pipetted to terminate reactions. The optical density (OD) of each well was determined immediately using a micro-plate reader. The readings at 450 nm were subtracted at 570 nm to correct for optical imperfections in the plate. Adiponectin value was assessed using a linear standard calibration curve constructed from a series of adiponectin standard.

Statistical analysis

All data were analysed were with SPSS version 22.0 software (SPSS Inc., Chicago, IL) and GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). The Hardy-Weinberg equilibrium analyses of two SNPs were determined by the χ^2 test to examine the differences in allele frequency and genotype distribution between OA group and control group. Odds ratios (ORs) and 95% confidence intervals (CIs) of genotypes and alleles were assessed by using the Medcalc® (Medcalc® Software, Mariakerke, Belgium) statistical software program. Their haplotypes and linkage disequilibrium (LD), D′ and r2 were conducted with Haploview software version 4.1 (Broad Institute Cambridge, MA). Unpaired Student's *t*-test and one-way analysis of variance were utilised to analyse quantitative data of two and more than two independent groups. Genotype distribution and allele frequency of *ADIPOQ* in OA patients and control subjects was calculated by the χ^2 test. The statistical review of the study was performed by a biomedical statistician. *P* values < 0.05 were considered as statistical difference.

RESULTS

The distributions of the genotypes in the control and OA groups conformed to the Hardy-Weinberg equilibrium. The genotype and allele frequency of +45T/G *ADIPOQ* polymorphisms were present in Table 1. No statistically significant differences were observed in the

Table 1 Genotype distributions and allele frequencies of adiponectin gene +45T/G (rs2241766) single-nucleotide polymorphism in control and osteoarthritis groups

+45T/G SNP (rs2241766)		Control *n* (%)	OA *n* (%)	OR (95%CI)	*P*
Genotype	TT	96 (48.98)	84 (41.6)	1	-
	TG	75 (38.27)	93 (46)	1.417 (0.929-2.162)	0.106
	GG	25 (12.75)	25 (12.4)	1.143 (0.611-2.139)	0.676
Allele	T	267 (68.11)	261 (64.6)	1	
	G	125 (31.89)	143 (35.4)	1.170 (0.872-1.571)	0.295

OA: Osteoarthritis; SNP: Single-nucleotide polymorphism.

Table 2 Genotype distributions and allele frequencies of the adiponectin gene +276G/T (rs1501299) single-nucleotide polymorphism in control and osteoarthritis groups

+276G/T SNP (rs1501299)		Control *n* (%)	OA *n* (%)	OR (95%CI)	*P*
Genotype	GG	102 (52)	106 (52.5)	1	-
	GT	77 (39.3)	76 (37.6)	0.950 (0.626-1.442)	0.809
	TT	17 (8.7)	20 (9.9)	1.132 (0.561-2.283)	0.729
Allele	G	281 (71.68)	288 (71.29)	1	
	T	111 (28.32)	116 (28.71)	1.020 (0.750-1.387)	0.901

OA: Osteoarthritis; SNP: Single-nucleotide polymorphism.

Table 3 Based on radiographic severity of osteoarthritis, genotype distribution of adiponectin gene +45T/G polymorphism in osteoarthritis patients

OA severity	Genotype			*P*	[a]*P*
KL system	TT	TG	GG		
Grade 2	27	30	8		
Grade 3	29	29	8	NS	
Grade 4	28	34	9	NS	NS

P value for difference in distribution of genotype between grade 2 and grade 3 or grade 4. [a]*P* value for genotype distribution between grade 3 and grade 4. OA: Osteoarthritis; KL: Kellgren-Lawrence; NS: Not significant.

Table 4 Based on radiographic severity of osteoarthritis, genotype distribution of adiponectin gene +276G/T polymorphism in osteoarthritis patients

OA severity	Genotype			*P*	[a]*P*
KL system	GG	GT	TT		
Grade 2	20	29	5		
Grade 3	41	22	8	0.037	
Grade 4	45	25	7	0.046	NS

P value for difference in distribution of genotype between grade 2 and grade 3 or grade 4. [a]*P* value for genotype distribution between grade 3 and grade 4. OA: Osteoarthritis; KL: Kellgren-Lawrence; NS: Not significant.

genotype and allele frequencies between knee OA and control groups. The T allele frequency was 68.11% in control group and 64.60% in OA group, and the G allele frequency was 31.89% in control subjects and 35.40% in OA group (P = 0.295). For the +276G/T polymorphism, there was no difference in the genotypic distribution and allelic frequency between knee OA participants and control subjects (Table 2). The G allele frequency was 71.68% in control group and 71.29% in OA group, and the T allele frequency was 28.32% in control group and 28.71% in OA group. There were no remarkable differences in the +45T/G and +276G/T loci haplotype distributions. The correlation coefficient of the frequencies r^2 is 0.033 in Linkage disequilibrium (LD) in these two polymorphisms.

The association between genotypes of the +45T/G *ADIPOQ* gene polymorphism and radiographic severity of OA patients was shown in Table 3. The genotypic distribution and allelic frequency of the +45T/G SNP was not significantly different among various groups of OA severity. Corresponding to the genotypes of the +276G/T *ADIPOQ* SNP, however, there were significantly different between KL grade 2 and KL grade 3 at +276G/T genotypes (P = 0.037), as well as between KL grade 2 and KL grade 4 (P = 0.046) (Table 4). The allele frequency of +276G/T polymorphism was not significantly different.

Circulating adiponectin concentrations of control group and knee OA group were shown in Figure 1. Circulating adiponectin values in OA group were notably lesser than those of the control group (2.58 ± 0.60 μg/mL *vs* 2.78 ± 0.68 μg/mL, P = 0.033). Further analysis of plasma adiponectin based on gender was shown in Figure 2. Plasma adiponectin of female subjects was seemingly greater than that of male subjects in both controls and OA patients (P < 0.001).

Figure 3 demonstrates plasma adiponectin concentrations of various genotypes of +45T/G and +276G/T loci. Plasma adiponectin levels of GG genotype were statistically higher than those of the TT genotype at

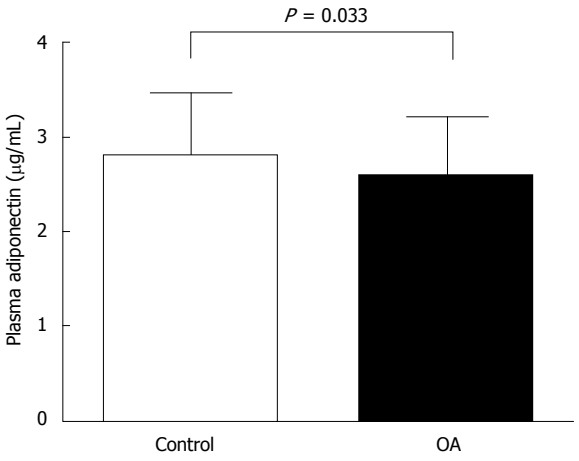

Figure 1 Adiponectin levels in plasma between control and osteoarthritis groups. OA: Osteoarthritis.

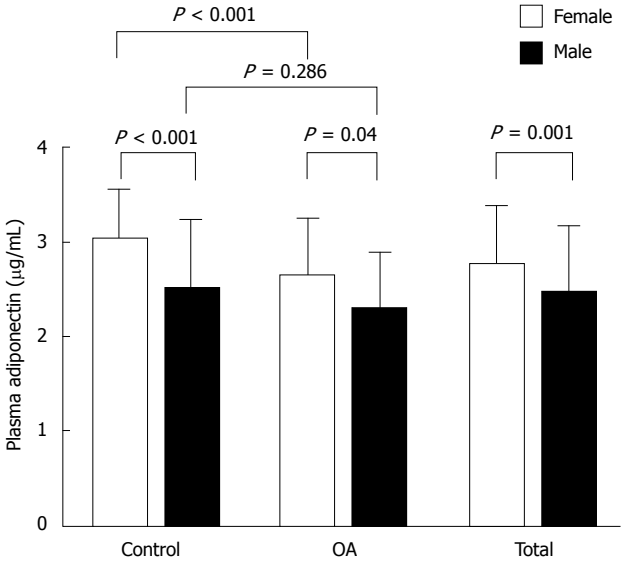

Figure 2 Comparison of plasma adiponectin levels between female and male in control group osteoarthritis group and total subjects. OA: Osteoarthritis.

the +45T/G polymorphism of control group (3.16 ± 0.63 μg/mL *vs* 2.66 ± 0.66 μg/mL, $P = 0.019$). In the GG genotype of the +45T/G locus, the circulating adiponectin levels of control group were significantly greater than those of OA group ($P = 0.029$). In control group, the mean value of plasma adiponectin in TT of +276 G/T was lowest among three genotypes (2.34 ± 0.88, 2.81 ± 0.66, 2.84 ± 0.63 μg/mL, respectively). In the +276G/T polymorphism, plasma adiponectin levels were more elevated in GG genotype when compared with those in TT genotype of healthy individuals ($P = 0.046$). In GG genotype of +276 G/T locus, the plasma adiponectin of control group was significantly greater than that of OA group ($P = 0.012$) (Figure 4).

DISCUSSION

Adiponectin is a novel adipocyte-derived hormone with various biological functions. Most previous studies have

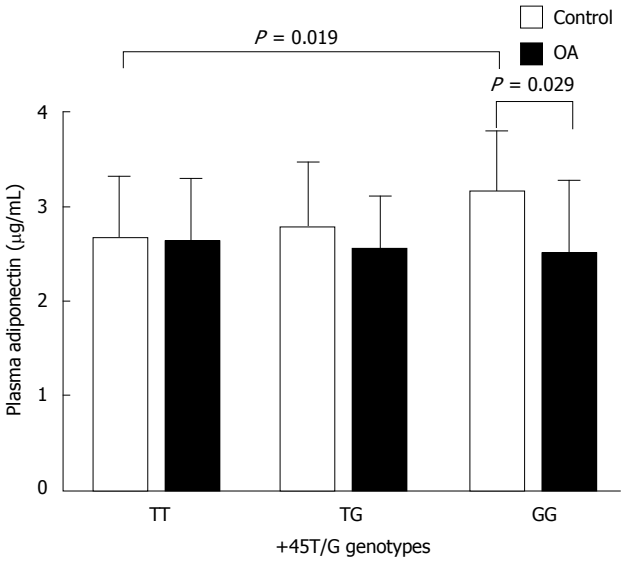

Figure 3 Genotypes of +45T/G locus and their plasma adiponectin levels in control group and osteoarthritis group. OA: Osteoarthritis.

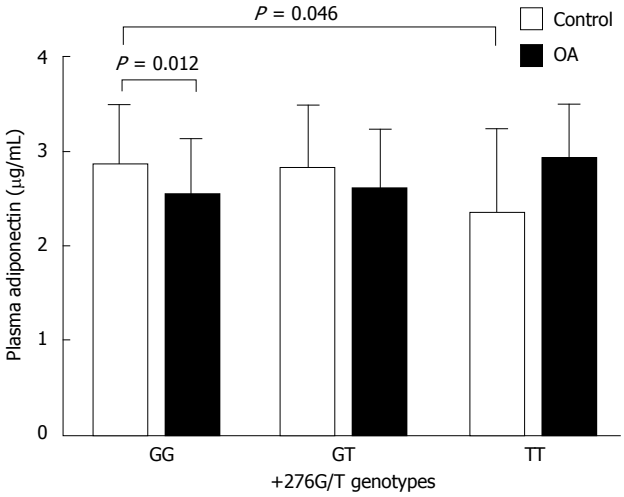

Figure 4 Genotypes of +276G/T locus and their plasma adiponectin levels in control group and osteoarthritis group. OA: Osteoarthritis.

suggested that circulating adiponectin levels have been found to be decreased in patients with OA. The genetic mechanism of low adiponectin level and its significance in the pathogenesis of OA needed to be determined. The purpose of the current investigation was to investigate the relationship between 2 single nucleotide polymorphisms, +45T/G (rs2241766) and +276G/T (rs1501299), in *ADIPOQ* gene with the risk of OA in Thai population. Moreover, we empasized on the impact of the 2 SNPs on plasma adiponectin values. We postulated that the *ADIPOQ* SNPs could serve as genetic parameters that affected the risk of OA.

This study is the first to explore the possible relationship between +45T/G and +276G/T polymorphisms of the *ADIPOQ* with the susceptibility of knee OA. The population of this study was ethnically homogeneous

according to the Hardy-Weinberg equilibrium, which makes the possibility of confounding ethnic heterogeneity less possible. Compared with other diseases, OA is a polygenic disease on the basis of the epidemiologic and genetic studies.

Adiponectin is derived from adipocytes, has anti-inflammatory and anti-atherogeneic effects as well as multiple beneficial effects on metabolism[16]. Studies indicate that adiponectin modulates the function and phenotypes of macrophages in chronic inflammation[3], suppressed the production of TNF-alpha[2]. Moreover, it was shown that adiponectin up-regulated tissue inhibitor of metalloproteinases-2 (TIMP-2)[17] and down-regulated IL-1β-induced MMP-13[7]. Until now, there are two-loci polymorphisms in adiponectin gene have been researched extensively, +45T/G SNP located in exon 2 and +276G/T SNP located in intron 2. The two loci polymorphisms have been identified to associate with amount of diseases related with metabolism and inflammation. Our findings indicated that the percentage of alleles and the genotypic distributions were not statistically different between knee OA participants and control subjects. Interestingly, based on knee OA severity, *ADIPOQ* genotype at +276G/T was significant difference between KL grade 2 and grade 3 or 4, suggesting that OA patients with GG genotype are more likely to develop, or be more severe OA than those with GT and TT genotype. The association of *ADIPOQ* polymorphisms with circulating adiponectin concentration is in line with the previous finding that +276G/T polymorphism was significantly associated with serum adiponectin in Chingford study by Kyriakou *et al*[18].

It has been widely studied that the relationship between plasma adiponectin levels and the +45T/G and +276 G/T polymorphisms. Our study revealed that plasma adiponectin level in OA group was significantly lower than control group. Additionally, the GG genotype at +45T/G and +276 G/T polymorphisms in knee OA patients was associated with lower circulating adiponectin concentration. Different body fat distribution may have a contributory role on adiponectin expression and response in obesity individuals with low-grade inflammatory reaction[19]. Therefore, genetic variation in the *ADIPOQ* could regulate adiponectin level in the circulation.

How the +276G/T polymorphism affects the *ADIPOQ* gene function and expression remains questionable. The changed genotype at a specific polymorphism locus could not alter amino acid sequence or structure of the protein. In other words, no obviously biological function might not be precluded. As a matter of fact, it has been demostrated by Yang *et al*[20] in ADIPOQ gene. On the other hand, linkage disequilibrium could exist at this SNP to influence its gene with other mutation sites. A recent study reported that the single nucleotide mutation at +276G/T locus arised linkage disequilibrium with inserted "A" nucleotide at +2019 SNP of adiponectin gene three prime untranslated region (3' UTR) which was known as an important part to affect synthesis and degradation of adiponectin mRNA[21]. Furthermore, it has been demonstrated that mRNA stability would be affected by 3'UTR polymorphisms of other reseached genes[22]. The discrepancy persists in several studies regarding to the association of the SNPs with OA. The susceptibility of candidate genes for OA has previously been demonstrated by some studies, but variants will be controversial by other researchers. This study included a relatively small number of participants in this single-center trial study. It is necessary to conduct additional observations under administration of multiple centers with a larger increased sample size. Multiple risk factors contribute to OA including mechanical stress, inflammation, obesity, aging, and genetic alteration. The susceptibility of OA could vary in different populations. Environmental factors may influence the genetic contributions to the susceptibility of OA.

Taken together, our study suggested that the +45T/G and +276G/T polymorphisms were not related with the risk of knee OA in our Thai population. The knee OA patients with the GG genotype at the +276G/T locus seemed to have a higher potential risk in the severity of OA than those having the GT and TT genotypes. The GG genotypes at SNP +45T/G and +276G/T loci were associated with plasma adiponectin concentration in healthy controls and knee OA patients. Further studies will be needed to clarify the relationship of two single nucleotide polymorphisms in larger sample size and different ethnic cohort on knee joint or other joints to yield a better understanding of these polymorphisms in the development of OA.

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COMMENTS

Background

The understanding of genetic factors in the pathogenesis of osteoarthritis (OA) is still incomplete. There is growing awareness of the role of adiponectin in knee OA. Understanding the polymorphisms of adiponectin might help explain why these polymorphisms play roles in the development of knee OA.

Research frontiers

Adiponectin +45T/G and +276G/T polymorphisms and plasma adiponectin levels have been studied in patients with knee OA, including healthy controls.

Innovations and breakthroughs

This is a novel study in that it addresses the polymorphisms and plasma of adiponectin in patients with knee OA, including healthy controls. The authors

found that Plasma adiponectin levels were significantly lower in knee OA than controls. There were no significant differences in the genotype distributions and allele frequencies of *ADIPOQ* +45T/G and +276G/T polymorphisms between patients with knee OA and controls.

Applications

Understanding the role of adiponectin +45T/G and +276G/T polymorphisms in OA could help find possible biomarkers of susceptibility of OA. It could also serve as predictive parameter for disease severity of knee OA.

Peer-review

The study is interesting.

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SYSTEMATIC REVIEWS

Osteoarthritis action alliance consensus opinion - best practice features of anterior cruciate ligament and lower limb injury prevention programs

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Abstract

AIM

To identify best practice features of an anterior cruciate ligament (ACL) and lower limb injury prevention programs (IPPs) to reduce osteoarthritis (OA).

METHODS

This consensus statement started with us performing a systematic literature search for all relevant articles from 1960 through January 2017 in PubMed, Web of Science and CINAHL. The search strategy combined the Medical Subject Heading (MeSH) and keywords for terms: (1) ACL OR "knee injury" OR "anterior cruciate ligament"; (2) "prevention and control" OR "risk reduction" OR "injury prevention" OR "neuromuscular training"; and (3) meta-analysis OR "systematic review" OR "cohort study" OR randomized. We found 166 different titles. The abstracts were reviewed for pertinent papers. The papers were reviewed by at least two authors and consensus of best practice for IPP to prevent OA was obtained by conference calls and e-mail discussions. All authors participated in the discussion.

RESULTS

The best practice features of an IPP have the following six components: (1) lower extremity and core strengthening; (2) plyometrics; (3) continual feedback to athletes regarding proper technique; (4) sufficient dosage; (5) minimal-to-no additional equipment; and (6) balance training to help prevent injuries. Exercises focused on preventing ankle sprains, hamstring injuries and lateral trunk movements are important. Plyometric exercises should focus on correcting knee valgus movement.

Exercises should focus on optimizing the hamstring to quadriceps strength ratio. In order for IPP to be successful, there should be increased education and verbal feedback along with increased athletic compliance. Additional equipment is not necessary. Balance training alone does not significantly reduce injuries, but is beneficial with other exercises. Not enough evidence to recommend stretching and agility exercises, with no ill effects identified. Therefore, we suggest making these optional features.

CONCLUSION

Best practice features for ACL and lower limb IPPs to help prevent OA contain six key components along with two optional.

Key words: Anterior cruciate ligament; Lower limb; Injury prevention program; Knee injury

Core tip: Sports participation can provide health benefits, but also increase the injury risk to the lower limbs especially the anterior cruciate ligament. Many different types of injury prevention programs (IPPs) exist to train athletes to reduce inherent risk factors. The aim of this review is to provide a comprehensive analysis of both systematic and meta-analyses studies to identify the best practice features (lower extremity and core strengthening, plyometrics, continual feedback to athletes regarding proper technique, sufficient doses, minimal-to-no additional equipment, and balance training along with optional components of stretching and agility exercises) of an IPP to help protect the athlete.

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INTRODUCTION

The osteoarthritis action alliance (OAAA) is a broad coalition of public health leaders and stakeholders committed to elevating osteoarthritis (OA) as a national health priority and promoting effective policy solutions that aim to address the individual and national toll of OA. The authors of the paper are members of the OAAA prevention working group. Our goal is to prevent the onset of OA through effective injury prevention and weight management strategies. One of our strategies is to promote widespread implementation of activity-specific rules and policies for organized sports, recreation and school athletics to prevent joint injuries that can lead to OA. We believe that implementing anterior cruciate ligament (ACL) and lower limb injury prevention programs (IPPs) will prevent OA of the knee.

Sports participation can generally enhance one's health benefits *via* regular physical activity. However, there is an increased risk for injuries that occurs in athletics. Lower limbs injuries are very common.

ACL injuries are common in a high-risk sport occurring in 2.1% of college female soccer players per season[1] and 12.3% of female college soccer players report a previous ACL tear[1]. The annual ACL injury incidence does vary with reported rates for amateur athletes (ranging from 0.03% to 1.62% in studies of at least moderate sample size), which are lower than professional sports but higher than national surveys[2].

An injury to the ACL has both significant short-term (time away from sport) and long-term implications. In particular, injury to the ACL of the knee significantly increases a person's risk for (OA) in the injured knee[3,4]. In particular, an ACL injury significantly increases a person's risk for OA in the injured knee with around 20% of ACL-injured knees having moderate or severe radiologic changes (Kellgren and Lawrence grade Ⅲ or Ⅳ)[3]. OA is a chronic, painful, and disabling disease, and it is prevalent in 1 in 3 people around 10-15 years after an ACL injury regardless of treatment (operative or non-operative)[3,5]. Therefore we believe the best practice is to prevent knee injuries and ACL injuries.

Studies suggest that a beneficial effect exists when utilizing both lower limb and ACL IPPs[6,7]. Prevention programs that incorporate a variety of strategies to target modifiable risk factors can be crucial in reducing the number of ACL injuries sustained. The number of athletes needed to treat to prevent one ACL tear varies with estimates at 89-128[7-9] depending on age of participants and inclusion of all ACL tears or non-contact ACL tears only. It is estimated that an ACL reconstruction lifetime cost to society is US $38121[10]. IPP for high risk sports for those 12-25 years of age (IPP for HR 12-25) is estimated to prevent 842 lifetime cases of OA per 100000 individuals and 584 total knee replacements per 100000 are subsequently averted[11]. IPP for HR 12-25 would avert US$ 693 of direct healthcare costs per person per lifetime. As well, other studies have found cost-savings from IPP from prevention of ACL surgeries not just the savings from OA prevented[12-15].

The purpose of this consensus statement is to provide a comprehensive evaluation of the literature to identify the best practice features of an ACL and lower limb IPP and determine essential components that are required to help protect the athlete from sustaining such traumatic injuries, thereby reducing OA. Multiple systematic reviews and meta-analyses have attempted to identify the essential components required for an effective ACL IPP[9,16-31]. Based on a comprehensive review of this literature, OA Action Alliance injury prevention experts recommend that the following six core components: (1) lower extremity and core strengthening; (2) plyometrics; (3) continual feedback to athletes regarding proper

technique; (4) sufficient doses; (5) minimal-to-no additional equipment; and (6) balance training along with optional components of stretching and agility exercises be included in a structured warm-up to maximize effectiveness of ACL and lower extremity IPP's for youth athletes.

MATERIALS AND METHODS

We performed a systematic literature search for all relevant articles from 1960 through January 2017 in PubMed, Web of Science and CINAHL. The search strategy combined the Medical Subject Heading (MeSH) and keywords for terms: (1) ACL OR "Knee injury" OR "anterior cruciate ligament"; (2) "prevention and control" OR "risk reduction" OR "injury prevention" OR "neuromuscular training"; and (3) meta-analysis OR "systematic review" OR "cohort study" OR randomized.

We found 166 different titles. The abstracts were reviewed for pertinent papers. In addition, we performed a manual search of references from reports of randomized controlled trials (RCTs), prior meta-analyses and review articles to identify additional relevant studies. Articles published by the authors of this paper were reviewed for relevant citations. The authors reviewed the search and suggested other papers. All were found in the search criteria.

To be included the paper needed to be a randomized control trial, systematic review or meta-analysis on the effectiveness of IPP for the prevention primarily ACL injury or secondary lower limb injury prevention.

The papers were reviewed by at least two authors and consensus of best practice for IPP to prevent OA was obtained by conference calls and e-mail discussions. All authors participated in the discussion.

RESULTS

Based on a comprehensive review of this literature, OA Action Alliance injury prevention experts recommend that the following six core components: (1) lower extremity and core strengthening; (2) plyometrics; (3) continual feedback to athletes regarding proper technique; (4) sufficient doses; (5) minimal-to-no additional equipment; and (6) balance training along with optional components of stretching and agility exercises be included in a structured warm-up to maximize effectiveness of an ACL and lower extremity IPP's for youth athletes.

Lower extremity and core muscle strength training

We note that hamstring/quadriceps ratio is a noted risk factor for ACL injuries[32]. Hence, these muscle group are considered to be an important risk factors for an ACL injury[16,21,25,32-34]. Eccentric hamstring exercises such as Russian/Nordic exercises should be incorporated as it has been proven to increase hamstring/quadriceps strength ratio and improve eccentric hamstring torque and isometric strength[18,25]. Core strengthening, such as planks, aid in preventing injuries[16,19,23,25,35-40]. It is key to have continual feedback to ensure proper technique with the use of body-weight exercises that focus on the trunk and hamstring strength[26,41].

Plyometrics

Plyometrics is an essential component in an IPP. Studies have shown that oth balance and plyometric training reduces peak valgus knee moments[25], this improves in an athlete's motor control during side-stepping and/or single leg landing tasks. Sports specific Neuromuscular Training (NMT) that focuses on jumping and landing tasks improves ground reaction force and stance time as well as unanticipated cutting maneuvers are important[26,27]. Since excessive medial knee displacement is considered to be a risk factor for an ACL injury, it is important for NMT to include exercises that involve the entire kinetic chain of the lower limb which can be individualized for the team and practice facility[12,26]. Plyometric exercises in programs have included jumping forwards and backwards, jumping side to side, tuck and scissor jumps, and single leg squats[18].

Continual feedback

Prevention programs applying both proprioception and technique modification are effective in reducing ACL injuries[26,31,42,43]. Education and verbal feedback from athletic trainers regarding proper technique has shown to decrease peak vertical ground forces from landing (soft landing with bent knee, knee in alignment with the second toe, and proper deceleration techniques) and is a large contributor to the success of IPP's[8,27,34,44]. An external focus (EF) for the acquisition and control of complex motor skills required for sport with positive over negative feedback is recommended[45].

Sufficient doses

IPP need time to take effect therefore at least 6 wk (10 to 15 min at least 3 d per week) should be given for lead time (ideally during a preseason) and then continued during the season with less frequency (1-2 times a week)[8,26]. NMT programs performed for longer times per day and more frequently demonstrated greater NMT prophylactic effects[46] but lower compliance. Combining pre-season and during season is the most effective process to reduce ACL injuries rather than either NMT programs alone[46].

Besides the frequency of IPP's, compliance rates play a major role. Coaches are more likely to perform a 10 min IPP than 20 min or longer[47]. High compliance rates showed 35% lower risks and 39% risk reduction rate compared to intermediate compliance rate[46,48]. Moderate to strong evidence exists to support the importance of compliance especially consistent attendance by involved athletes and commitment to the completion of sessions throughout the intervention period contributed to the effectiveness of the IPP[48,49]. There are fewer ACL, acute knee, and lower extremity

injuries when there is higher compliance rates with the IPP[27,48,50]. We recommend a shorter 10 min program started in the pre-season and continued through the season every week as part of the standard warm-up.

Minimal-to-no additional equipment

A number of neuromuscular warm-up strategies do not require the acquisition of additional equipment, such as a balance board, to produce an effective IPP[35]. Drawbacks of some IPP's is the need for additional equipment, most notably many teams lack this equipment and resources may preclude compliance among participants of IPP[16,35]. Utilizing additional equipment has not shown significant reduction in lower limb injuries[35]. Therefore, we recommend that the best practice IPP have no additional equipment needs.

Balance exercises

Some studies have found prevention programs that only apply balance training did not significantly reduce the overall lower limb injury rate reduce or to modify risk factors for ACL injuries despite good athletic adherence to the intervention[25,42,51]. However, there have been randomized control trials that have shown that balance exercises might be efficacious in preventing other lower extremity, such as ankle ligamentous injuries[25,35]. Balance exercises demonstrated a 41% reduction in ACL injury rate compared to a 66% reduction by preventive NMT without balance exercises[18]. The effectiveness of balance exercises can be enhanced when utilized in conjunction with proprioceptive exercises[17]. We recommend that balance training be done in conjunction but not alone to prevent ACL injuries.

Stretching exercises

Current evidence suggests that stretching alone may confer no injury prevention benefit[35]. A review found that greater durations during an IPP that static stretching was performed was associated with a lower risk for non-contact ACL injuries[30]. We note that one study greatly affected their analysis[30]. There is not enough evidence to support static stretching in ACL injury prevention, although dynamic stretching may be beneficial for other reasons, including perceptions about flexibility[30,35,42]. In conclusion, additional research is needed to understand how stretching influences risk for ACL injury. We recommend stretching as an optional exercise, with dynamic stretching being emphasized over static stretching.

Agility exercises

There is not enough evidence to support agility exercises in ACL injury prevention. However, there is evidence to suggest that the addition of this component provides beneficial effects of reducing non-contact ACL injury rates in sport-specific training by increasing the emphasis and duration of agility training[26,30]. In order to improve lower extremity neuromuscular control/balance, specific drills targeted at improving running technique and coordination could be targeted[25].

DISCUSSION

Unfortunately, ACL injuries are commonly encountered in various sporting activities. The mechanism of ACL injury can be categorized as contact and non-contact[17]. Contact ACL injuries are non-preventable, but utilizing lower limb and ACL IPP's can prevent non-contact ones. Prevention of such injuries is essential given the long-term effects and high economic costs for the patient and health care system[42]. Much of literature focuses on female athletes as equivocal data exists for male athletes[42]. This is because there is a paucity of literature available and controversial data on the effectiveness of IPP's modifying risk factors for ACL injuries and injury reduction rates[42]. However, it is firmly established that IPP's successfully reduce noncontact ACL injury incidence rates in female adolescent athletes[27].

Current evidence supports that the implementation of NMT and decrease in ACL tear incidence is age-related[20]. The change in biomechanics and the onset of ACL injuries indicate that there is a potential optimal time to start these programs. This would be before the onset of changes in biomechanics and increase in ACL injuries[20]. Therefore, initiation of IPP should be during early adolescence prior to these changes[20].

Regardless, it is imperative that IPP's incorporate a wide variety and combination of strategies to help target ACL injury prevention. The comprehensive review of both systematic and meta-analyses studies are discussed in order to identify the best practice features of an ACL and lower limb IPP and determine the six essential components: (1) lower extremity and core strengthening; (2) plyometrics; (3) continual feedback to athletes regarding proper technique; (4) sufficient doses; (5) minimal-to-no additional equipment; and (6) balance training along with optional components of stretching and agility exercises that are required to help protect the athlete from sustaining such traumatic injuries.

Lower extremity and core muscle strength training

Of the lower extremity components, hamstring injuries are fairly commonly. The hamstrings are noted to be an antagonist of the quadriceps and provide a protective posterior force on the tibia[18]. The ACL's anteromedial bundle is under the most tension during the last 30° of knee extension, therefore this posterior force could be protective by decreasing anterior translation[18]. The quadriceps muscle contraction *via* the patella tendon-tibia shaft angle determines the anterior shear force that is generated during knee extension as well as during the contact phase of landing[18]. Inherently, there exists an aberrant ratio of hamstrings to quadriceps neuromuscular activation[18,26,27,35]. In order to reduce such forces, programs should incorporate exercises

such as isometric warm-up exercises, hamstring flexibility, and eccentric strength training (Russian/Nordic hamstring exercises), walking lunge, and single toe raise (gastrocnemius/soleus exercises) increase the muscle power to stabilize the knee to reduce injuries[17,18,25,35].

Core strength is another important factor in reducing the risk of other injuries[35]. Evidence supports that core muscle weakness may raise the risk of groin strain and knee joint injuries[18,35]. Athletes who injured their ACLs were noted to have increased lateral trunk flexion and knee abduction angles[18]. Exercises incorporating planks (front and side), sit-ups and abdominal curl are important[18,35].

Another risk factor that should be targeted is excessive knee valgus motion. Certain movements in a sport adds stress to the medial passive and active stabilizing knee structures that predisposes one to an ACL injury[26]. Specific NMT of the entire kinetic chain of the lower limb that are targeted for individual sports and their specific conditions of play are particularly required[26]. For example, female basketball players exhibit increased medical knee displacement than female soccer players due to increased internal ACL loading[26]. Therefore, it is important to have sport specific NMT focusing on jumping and landing tasks as well as the stop phase of a sidestep cutting maneuver for basketball that are based on ground reaction force and stance time data[26].

Furthermore, the importance of ankle injuries can not be ignored. There is sufficient evidence that balance exercises might be effective in preventing ankle ligament injuries[52]. Exercises that focus on the dynamic balance and strengthening such as single leg balance exercises. This can be performed by standing on one leg while throwing a ball with a partner, resisting a push from a partner while balancing on one leg, hopping across a line on the field or court, and one legged squat exercises should also be added[35]. A program involving a combination of balance, eccentric hamstring, plyometrics and strength exercises could be efficacious in preventing lower limb injuries[25]. Therefore, there is consensus that a multifaceted exercise program that is aimed at reducing general lower limb injuries is efficacious especially when combining strengthen and proximal control training[18,25].

Plyometrics

NMT programs utilizing plyometric exercises and a preseason component were noted to be most beneficial[10,26]. Plyometric exercises often incorporate sidestepping and/or single leg squats, jumping forwards and backwards, jumping side to side, and tuck and scissor jumps[18,25]. This is to target the elevated knee abduction moment as well as to increase the knee flexion range by focusing on increasing power, muscle strength, and speed and improving motor control to reduce the peak knee valgus moments[8,12,17,18,25]. Evidence shows that there is a 17%-26% reduction in ground reaction force on landing after 6-9 wk of training along with asymmetrical landing patterns reducing the side to side asymmetry landing force[18]. This is especially important considering that high ground reaction forces are identified as one of the risk factors for future non-contact ACL injuries in female athletes[18]. Overall, individual components of NMT programs such as plyometrics, strengthening, and proximal control training have been estimated to lead to ACL injury risk reduction of 61%, 68%, and 67% respectively[18].

Continual feedback

Continual feedback on proper technique by the certified athletic trainer or sports physical therapist has been shown to be efficacious in reducing ACL injuries. The benefit may best be seen in sports with emphasis on landing and cutting maneuvers by altering landing patterns in frontal plan[18,26], with the use of plyometric exercises to teach proper landing technique. Vocal cues during plyometric exercises such as "land light like a feather" can emphasize soft landing with the proper positioning of knees bent, patellar alignment with the second toe, and proper deceleration[8,18,27]. Emphasis on biomechanical technique correction and individualized feedback that athletes receive appears to be a central element among the most successful programs that reduce ACL injury rate[34].

Sufficient doses

For a NMT program to be successful, frequency and duration as well as adherence to the program is vital in reducing ACL injuries. The actual number of completed training sessions is likely more valuable than the prescribed number of sessions when considering the effectiveness of programs[53,54]. Evidence supports prevention program should be performed two (2) or more times a week for a minimum of six weeks[26]. Duration longer than 6 wk does not necessarily improve the effectiveness of the programs[34]. Current analyses suggest performing preventive NMT interventions less than 20 min per session once a week during in-season can reduce 38%-39% of ACL injury risk[46]. Fewer than two NMT session per week during the in-season without previous 6 wk pre-season NMT workouts of more than one session per week is less likely to demonstrate the prophylactic effects on ACL injury reduction than two or more sessions for 6 or more weeks[46]. In addition, the IPP studies with statistically significant reductions in ACL injury rates had athletes performing preseason neuromuscular training[53,54]. Therefore, it is recommended that a NMT program be performed for 10 to 20 min (higher compliance is seen with the shorter 10 min) at least two days per week in the preseason and at least 1 session per week during the season.

Additionally, better compliance is needed for sufficient training effects to reduce injuries[35]. Compliance is a major issue and one should monitor the compliance for

the training program to ensure the desired protective transformations in reaction times, fatigue resistance and the correct movement patterns is obtained[26,55]. Adjustment to the program may be needed if compliance diminishes to fit the individual team needs. There is an inverse dose-response relationship seen between NMT compliance and incidence rates of ACL injury[12,49,50]. More specifically, it was noted that athletes with a low or moderate compliance rate had a risk of injuring their ACLs 4.9 and 3.1 times greater, respectively, than their counterparts who had high compliance rates[49]. It is also speculated that the decrease in player compliance as the season progresses may be due to reduction of player attendance at training sessions over the season[55]. In order for an ACL IPP to be effective, the overall compliance rate needs to be more than 66%[49].

The importance of player level compliance in addition to team compliance is sometimes underestimated[55]. It is possible that that motivational barriers and facilitators among coaches over the entire season may need to be further investigated in order to maintain a high compliance rate for the NMT program[55]. Consistent attendance by involved athletes and commitment to the completion of NMT throughout the season contributes to the effectiveness of the IPP[49]. We recommend addressing issues of compliance with coaches and administration to determine reasons for reduced compliance and in order to correct these barriers.

Minimal-to-no additional equipment

A number of neuromuscular warm-up strategies do not require the acquisition of additional equipment[35]. Balance work (using balance boards) and neuromuscular exercises (without balance boards) revealed that ankle sprains were reduced by 36% and 50%, respectively[35]. However, neuromuscular strategies alone can reduce injuries without requiring the need to purchase additional equipment which would require resources many teams do not have available to them[35]. Since a NMT programs can be performed with similar outcomes with and without additional equipment, we recommend no additional equipment.

Balance exercises

We recognize that in one review balance was associated with worse outcomes from IPP but this association was only with total hours of balance training and this was skewed by the inclusion of one study with an excessive amount of balance training[30]. Balance exercises are considered effective when used in conjunction with other types of exercises for IPP[18,26,35,42,51,56]. There is strong evidence for the prevention of ankle ligament injuries for the use of neuromuscular control and balance exercise, in addition a multifaceted program for the prevention of lower limb injuries[25]. Balance programs may reduce ankle injuries, but the effects could be enhanced by utilizing proprioceptive exercises[17,25,30].

Additionally, balance training may be required to build proximal segment stability in order to further enhance trunk control[18]. An asymmetrical landing pattern and landing favoring one foot is a risk factor for ACL injury which can be altered by incorporating balance training along with plyometrics[18]. Balance training demonstrated improvement in the center of pressure measurements and a reduction in GRF during a single leg landing[18]. Balance and plyometric training improve an athlete's motor control during tasks like sidestepping and/or single leg landing, reducing peak valgus knee moments (a risk factor of non-contact ACL injuries)[25]. Therefore, NMT programs that incorporate plyometrics, and strengthening exercises have demonstrated effectiveness in reducing ACL injury risk factors[16,17].

Stretching exercises

Stretching during warm-up routine before exercise has been historically advocated to prevent injury[35]. However, current evidence time and again does not support static stretching alone for injury prevention benefit[35]. Although studies have shown that static and dynamic stretching may have a positive impact on reducing injury rates when performed in an ACL prevention program[30]. Previous studies have found that static stretching has no overall impact on preventing general musculoskeletal athletic injuries, but may have some relationship with reducing ligamentous injuries[30]. Perhaps a beneficial effect in ACL injury reduction could be due to static stretching modifying the structural properties of ligamentous tissues[30]. One downside of eliminating stretching from an IPP is athletes believe stretching is an essential part of an IPP and removal might decrease compliance[57].

Agility exercises

Agility exercises are activities that improve the ability to move and change direction under control both quickly and effectively[30]. Increasing the emphasis and duration of agility training in an IPP is beneficial in reducing non-contact ACL injury rates[30,35,43]. Lower extremity mechanics during landing and cutting tasks are affected by a fatigue-producing agility training programs[30]. Therefore, timing of the agility training intervention may be important. Specific agility exercises like shuttle run, diagonal run, bounding run or zigzag running with pressure technique should be supplemented by landing technique with feedback so that the players learn to avoid the high-risk landing and cutting positions[26,35,43].

Limitations

A comprehensive review of literature containing both systematic and meta-analysis studies contain different limitations. The combination of mixed design studies can lead to difficult interpretations and incorrect results[17]. Furthermore, the heterogeneous treatment protocols with exercise programs having varying intensity levels is another concern[17]. Most of the studies can be

generalized to only the young female population as there is a dearth of studies on the males[18]. Additionally, the limitations of systematic review include those inherent in determining the results of studies of varying design (*e.g.*, frequency, duration, and start of training); how the training was performed; who supervised; the components of the training program; and how exposure data was determined[7,27,46,49]. To identify the exact essential exercise for IPP that are responsible for the reduction of injury incidence is not possible because of these inconsistencies. Furthermore, different types of neuromuscular training were applied to different sports, ages and study designs which makes the analysis challenging to identify imperative aspects of neuromuscular training[7,46].

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COMMENTS

Background

Sports participation can increase the risk for injuries to the lower limbs especially the anterior cruciate ligament (ACL). When utilizing injury prevention program (IPP)'s, a variety of strategies to help target risk factors can be crucial in reducing the number of knee and ACL injuries, and therefore future knee osteoarthritis (OA). A comprehensive review of multiple systematic reviews and meta-analyses have identified the essential components to be lower extremity and core strengthening, plyometrics, continual feedback to athletes regarding proper technique, sufficient doses, minimal-to-no additional equipment, and balance training along with optional components of stretching and agility exercises to be included in a structured warm-up to maximize effectiveness of an ACL and lower extremity IPP's for youth athletics. The authors believe that participating in 10 min of IPP most days of the week that contain these features will diminish knee OA and reduce health care costs.

Research frontiers

The authors recommend future studies looking at compact 10-15 min programs in multiple groups and ages followed out for many years to determine the reduction of knee OA and health care costs.

Innovations and breakthroughs

IPP's have been important in modifying inherent risk factors in athletes to help reduce the number of ACL injuries and subsequent OA. Retrieved literature has provided an in depth overview of the various techniques that are pertinent in the various strategies utilized in IPP's.

Applications

This review suggests that IPP's should contain the six strategies in order to be effective in preventing athletes from sustaining ACL and lower limb injuries and subsequent OA. These should become incorporated into every high-risk sports training program.

Terminology

IPP's that incorporate a variety of strategies in NMTs to help target risk factors can be crucial in reducing the number of ACL and lower limb injuries sustained and subsequent OA.

Peer-review

The authors provide comprehensive study on lower limb injury prevention.

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CASE REPORT

Using humeral nail for surgical reconstruction of femur in adolescents with osteogenesis imperfecta

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Author contributions: Sa-ngasoongsong P and Mulpruek P performed all operations together; Sa-ngasoongsong P drafted manuscript; Saisongcroh T collected the patients' clinical data and drafted the manuscript; Angsanuntsukh C and Woratanarat P provided material and technical support; Mulpruek P designed the study and revised manuscript for important intellectual content; all authors have read and approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Ethical Clearance Committee on Human Rights to Research Including Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (Protocol ID 02-58-67).

Informed consent statement: According to the ethical approval, there was no need for informed consent from individual patients in retrospective study (all data were retrieved from medical records).

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Abstract

Osteogenesis imperfecta (OI) is a rare inherited connective tissue disorder caused by mutation of collagen which results in a wide spectrum of clinical manifestations including long bone fragility fractures and deformities. While the treatment for these fractures was recommended as using intramedullary fixation for minimizing stress concentration, the selection of the best implant in the adolescent OI patients for the surgical reconstruction of femur was still problematic, due to anatomy distortion and implant availability. We are reporting the surgical modification by using a humeral nail for femoral fixation in three adolescent OI patients with favorable outcomes.

Key words: Osteogenesis imperfecta; Adolescent; Humeral nail; Femoral fracture; Femoral bowing deformity

Core tip: This case report presented the satisfactory clinical outcome of the adolescent osteogenesis imperfecta patients suffering from femoral fracture or bowing deformity which had been treated with the modification of humeral nail as intramedullary implant.

P, Mulpruek P. Using humeral nail for surgical reconstruction of femur in adolescents with osteogenesis imperfecta. *World J Orthop* 2017; 8(9): 735-740 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i9/735.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i9.735

INTRODUCTION

Osteogenesis imperfecta (OI) is a rare hereditary connective tissue disorders with the common clinical presentation of excessive bone fragility caused by mutations in collagen[1]. Clinical manifestations of OI are wide spectrum and could be vary from lethal forms in the perinatal period to the subtle forms, which could be hardly identified and comparable to a normal person. However, the common orthopaedic problems in the OI patients, that is related to the excessive fragility, are frequent fractures, progressive deformity of long bones and impaired ambulation. The treatment of OI requires a multidisciplinary approach including both medical treatment, such as using bisphosphonates therapy to increase bone mineral density and reduce long bone fractures rate[2-4], and surgical treatment for fracture fixation or deformity correction[4].

Regarding surgical management of OI, the treatment goals are to minimize the incidence of fracture, restore bone axis and avoid bone bowing[4]. The recommended surgical implant in OI was a load-sharing intramedullary (IM) device, with the largest diameter as possible, due to the better biomechanical property in fragile bone over plate construct[1] and avoid plate-related complications, such as bony resorption from stress shielding, implant failure, and subsequent fracture at the plate ending[5,6]. However, the surgical fixation in OI, especially in adolescent OI patients with femoral fracture or nonunion, are still problematic due to particular abnormal femoral anatomy (such as short limb, non-anatomical alignment secondary to previous injury, and narrow and non-linear medullary canal with superphysiologic bowing)[1] resulting in implant selection difficulty which was suitable for medullary canal size and bone length. Although there is an advanced surgical system, like a telescopic rod, which is specifically designed for OI patients with many different sizes that allow fixation in all age groups, this implant is not available everywhere, including our country. Moreover, the traditional implant standard pediatric IM devices such as single Rush pin might not be appropriate in these adolescent OI patients due to its small size and inability to provide rotational stability[6-8]. Recently, there has been a few studies which reported that the small IM interlocking nail, such as humeral nail, could be used in femoral fixation in normal adolescent patients due to the advantages of the entry point lateral to tip of greater trochanter resulting in avoiding iatrogenic vascular injury and being the IM locking device with smaller diameter and shorter length than conventional femoral nail which was appropriate for small-sized adolescent femoral anatomy[9,10]. Therefore, this humeral nail should be also suitable for femoral fixation in adolescent OI patients. This study aimed to demonstrate the outcome of adolescent OI patients with femoral fracture or deformity and treated with humeral nail fixation.

CASE REPORT

Case 1

A 12-year-old girl with type Ⅰ OI presented with progressive left femur deformity (August, 2013). Her height and weight were 138 cm and 51 kg. Initially, she had been diagnosed as type Ⅰ b (Silence classification)/Tarda B (Shapiro classification) and received treatment since age of 7 years. Three years ago (2010), she had been treated with corrective osteotomy and Ender nail fixation for left femur bowing deformity and the fracture was united uneventfully. However, she had experienced the progressive deformity on her left thigh without pain on weight bearing. The radiographs showed anterolateral femoral bowing due to femoral varus and flexion deformity with 8.5-mm medullary canal diameter (Figure 1A).

Preoperative planning for progressive left femoral deformity was discussed. The goal of treatment was rigid fixation with load-sharing intramedullary (IM) device[1]. The IM instrument options were K-wire, Rush pin, and telescoping IM device. K-wire and Rush was suitable only for small children with small IM canal due to the size of implant. Telescoping IM device was suitable for older children with larger IM canal, although this device was not available in our country. Therefore, we decided to use humeral IM nail for femoral osteotomy stabilization in this case due to two reasons. Firstly, the humeral nail was the interlocking nail that was available in smaller size and shorter length than conventional femoral nail. Thus, the humeral nail would be better in biomechanical property than single Rush pin. Secondly, the humeral nail geometry was rather straight than femoral nail resulting in the more lateral entry point for humeral nail insertion at the lateral to the tip of greater trochanter, and so avoiding the iatrogenic vascular injury on piriformis fossa.

Surgical technique: The patient was placed in lateral decubitus position under general anesthesia (GA). Multi-level corrective osteotomy was performed with drill and osteotome. Then the femur was reduced to acceptable alignment. The entry point was made at the tip of greater trochanter (GT), and the medullary canal was gently prepared by hand reaming using 6-mm and 7-mm T-reamer. Then a 7-mm diameter Expert humeral nail (Synthes®, Inc.) with 290-mm length was inserted following by proximal blade and distal locking screw insertion under fluoroscopic guidance. One additional wiring was performed due to iatrogenic cortical crack on the osteotomized fragment (Figure 1B). The operative time was 4 h, and the total length of hospital stay was 6

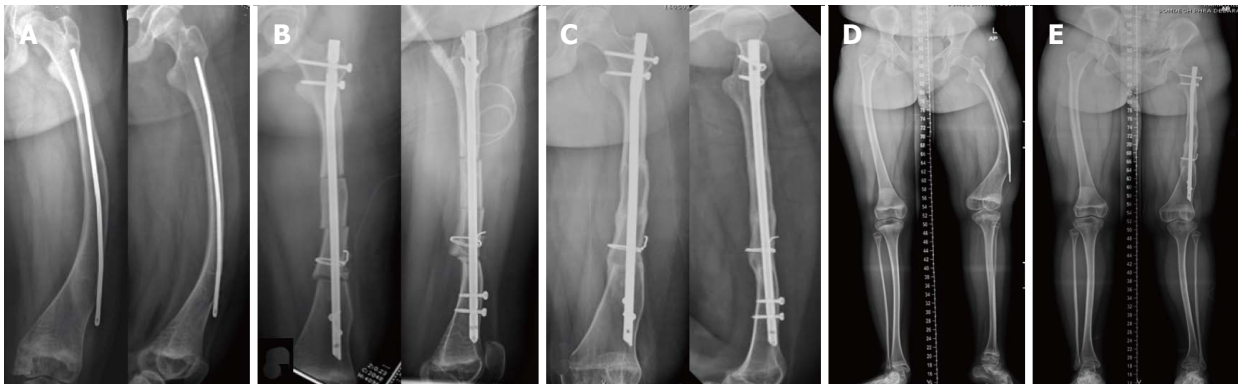

Figure 1 Clinical presentation of case 1. A 12-year-old girl with type Ⅰ osteogenesis imperfecta presented with progressive bowing of left shaft femur after ender nail fixation for 3 years. Plain radiographs of left femur in anteroposterior and lateral views on preoperative period (A), immediately after multi-level osteotomy and internal fixation with humeral nail (B), 9-mo after humeral nail fixation (C), preoperative scanogram (D) compared with 1-year postoperative scanogram (E).

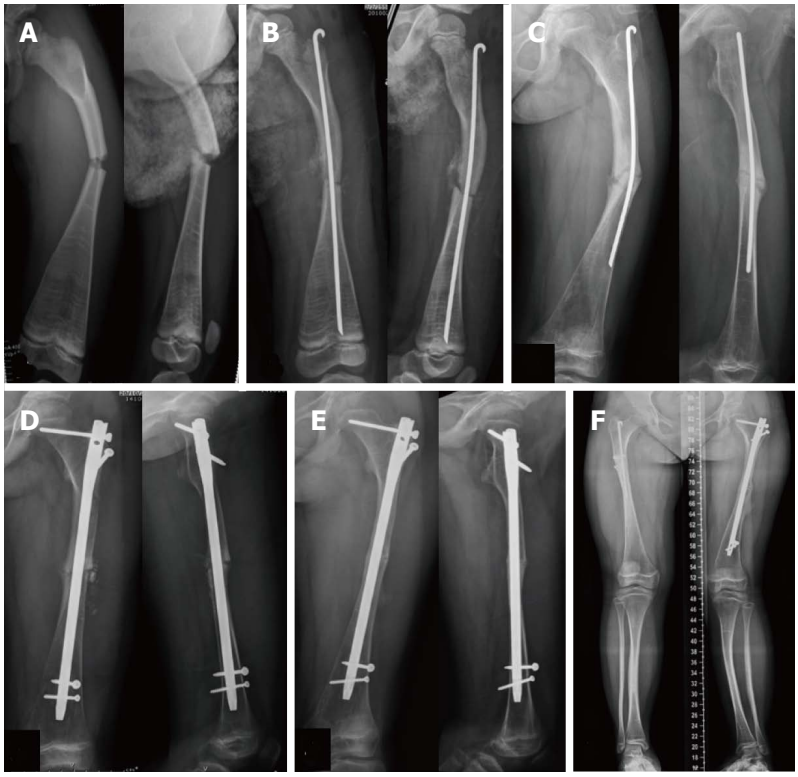

Figure 2 Clinical presentation of case 2. A 12-year-old girl with type III osteogenesis imperfecta presented with limping and pain on full weight bearing after Rush pin fixation for 4 years. Plain radiographs in anteroposterior and lateral views after injury (A), immediately after Rush pin fixation (B), 4 years after Rush pin fixation (C), immediately after humeral nail fixation (D), 9 mo after humeral nail fixation (E), and 1-year postoperative scanogram after humeral nail fixation (F).

d. Estimated blood loss was 350 mL.

Postoperative care and rehabilitation: The postoperative protocol was initially 6-wk toe touch weight bearing with gait aids following by progressive weight bearing as tolerated. The patient reported clinical union (pain-free full weight bearing without tenderness on osteotomy site) at 6 mo postoperatively, and the radiographic union was completed at 9 mo postoperatively (Figure 1C). On 3-year postoperative follow-up period, the patient had normal hip range of motion and function. The radiographs showed no evidence of avascular necrosis of femoral head (Figure 1D and E).

Case 2

A 12-year-old girl with type Ⅲ OI presented with left femoral shaft oligotrophic nonunion with failed Rush pin fixation (2014). Her height and weight were 122 cm and 25 kg. She had been diagnosed as type Ⅲ (Silence classification)/Tarda A (Shapiro classification) after birth and treated with intravenous bisphosphate therapy since the age of 3 mo. On 2010, at the age of 7 years, she sustained left femoral shaft fracture and had been treated with single Rush pin fixation (Figure 2A and B). After surgery, she was lost to follow-up for 3 years

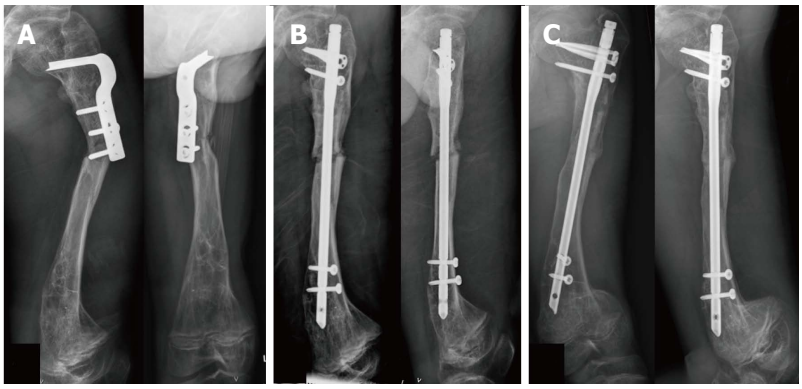

Figure 3 Clinical presentation of case 3 during the first operation. A 16-year-old male with type III osteogenesis imperfecta presented with subtrochanteric peri-implant fracture of left femur after corrective osteotomy and fixation with osteotomy plate for 10 mo. Plain radiographs in anteroposterior and lateral views after injury (A), immediately after humeral nail fixation (B), and 8 mo after humeral nail fixation (C).

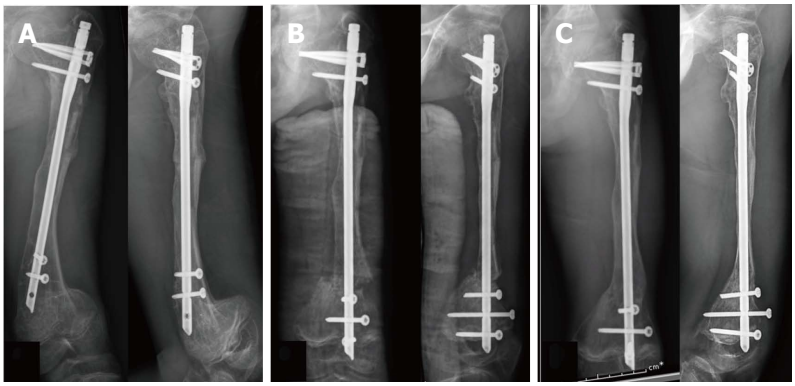

Figure 4 Clinical presentation of case 3 during the second operation. A 16-year-old male with type III osteogenesis imperfecta presented with progressive deformity of left distal femur after first humeral nail fixation for 10 mo. Plain radiographs in anteroposterior and lateral views on preoperative period (A), immediately after corrective osteotomy with humeral nail fixation (B), and 9 mo after humeral nail fixation (C).

(2011-2014) and then came back to our clinic 4-year postoperatively with limping and mild pain on full weight bearing. The radiographs showed that the fracture was still non-united with progressive bending of Rush pin (Figure 2C), and the medullary canal diameter was 9.2 mm. Therefore, the revision operation was planned as Rush pin removal with nonunion resection and humeral nail insertion with local bone graft.

Surgical technique: The patient was placed on lateral decubitus position under general anesthesia. The Rush pain was removed from old surgical scar. The nonunion site was opened directly with subvastus approach. Nonunion fibrous tissue was resected and previous bony callus was harvested for local bone graft. The humeral nail insertion was performed, with the same technique as above, using previous Rush pin entry point at the tip of GT. A 8-mm diameter M/DN Humeral Intramedullary nail (Zimmer, Warsaw, IN) with 255-mm length was applied and locked proximally and distally. Then local bone graft was inserted around the fracture site (Figure 2D). The operative time was 3.5 h, and the total length of hospital stay was 5 d. Estimated blood loss was 300 mL.

Postoperative care and rehabilitation: The patient was allowed 6-wk toe touch weight bearing followed by progressive weight bearing as tolerated. The clinical union was achieved within 6 mo and the radiographic union was completed within 9 mo postoperatively (Figure 2E). On 2-year postoperative follow-up period, the patient had normal function without pain on FWB. The radiographs showed no evidence of avascular necrosis of femoral head (Figure 2F).

Case 3

A 16-year-old male with type Ⅲ OI presented with left subtrochanteric peri-implant fracture after falling on the ground (September, 2014). His height and weight were 130 cm and 27 kg. He was diagnosed as type Ⅲ (Silence classification)/Congenita A (Shapiro classification) during antenatal care period, and treated with intravenous bisphosphate therapy since the age of 19 mo. He had previous bilateral leg deformity and had been treated with bilateral femoral and tibial corrective osteotomy. The radiographs showed displaced left subtrochanteric fracture below osteotomy plate with varus angulation, and bilateral distal femur extension deformity (Figures 3A, 4A, and 5A). The left and right medullary canal

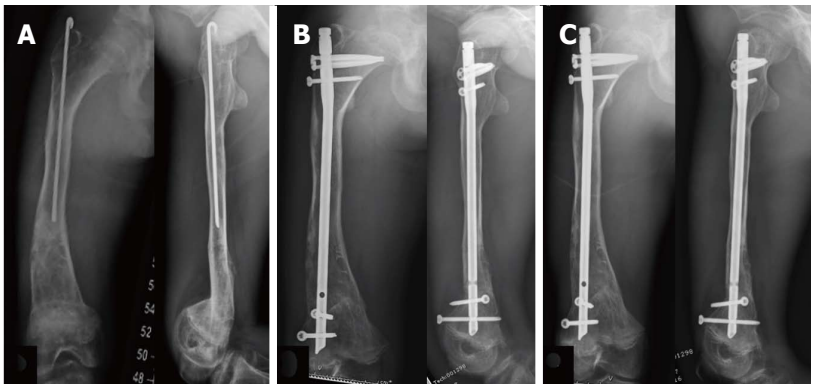

Figure 5 Clinical presentation of case 3 during the third operation. A 17-year-old male with type III osteogenesis imperfecta presented with progressive deformity after Rush pin fixation right shaft femur at early childhood. Plain radiographs in anteroposterior and lateral views on preoperative period (A), immediately after corrective osteotomy with humeral nail fixation (B), and 6 mo after humeral nail fixation (C).

diameters were 8.6 and 9.0 mm respectively.

Surgical technique: After preoperative planning was discussed, bilateral staged femoral reconstructions were planned as: (1) osteotomy plate removal and humeral nail insertion (August, 2014) (Figure 3B); (2) corrective hinged osteotomy left distal femur with humeral nail (June 2015) (Figure 4B); and (3) corrective osteotomy right distal femur with humeral nail (March, 2016) (Figure 5B). All operations were performed using the same technique as mentioned above with Expert humeral nail (Synthes®, Inc.). The operative times were 2.5, 3.5, and 3 h respectively. The lengths of hospital stay were 4, 4, and 3 d. Estimated blood loss were 200, 500, and 350 mL, respectively.

Postoperative care and rehabilitation: After the first and second operation on left femur, due to bilateral deformity, the patient was allowed for 8-wk wheel chair mobilization, and followed by weight bearing as tolerated with full weight bearing after 3 mo postoperatively. The subtrochanteric fracture and osteotomy site both showed clinical union and radiographic union at 3-mo and 8-mo postoperatively (Figures 3C and 4C). After the third operation on his right femur, the postoperative protocol was the same as case no.1 and no.2 due to complete fracture healing with good alignment on left femur. The clinical and radiographic union were shown at 3-mo and 5-mo postoperatively, respectively (Figure 5C). At the most recent follow-up (postoperative 10 mo after the third operation), the patient showed normal hip range of motion with pain-free weight bearing. No avascular necrosis of femoral head was found.

DISCUSSION

OI is a heritable disorder of collagen synthesis that commonly presents as bone fragility with multiple long bone fractures and deformities. These boney problems usually require surgical management for fracture fixation or reconstruction by the load-sharing IM device. However, the surgical fixation in OI patients, especially in the older children with femoral fracture or deformity, is very difficult due to the abnormal femoral anatomy resulting in implant selection problems such as a mismatch with conventional femoral IM nail, the poor fixation stability of standard pediatric IM device (Rush pin), and the high cost of advanced telescopic rod. This study aimed to present the usefulness of humeral nail fixation as a surgical tool for femoral reconstruction in adolescent OI patients.

The humeral nail application for femoral fixation in adolescent OI patients has many advantages. Firstly, humeral nail implant, which is available in smaller diameter and shorter length than conventional femoral IM nail, is more suitable with these patients' femoral anatomy with narrow medullary canal and short limb. Secondly, humeral nail geometry has narrow width and is easier to insert into the lateral transtrochanter area[9] which can avoid the risk of iatrogenic injury to greater trochanter physis[11] or medial femoral circumflex artery[12]. Thirdly, due to the interlocking nail property, the humeral nail would offer superior biomechanical benefits than the standard Rush pin fixation as better in rotational stability and leg length control, especially for the patients with multilevel corrective osteotomy.

However, there were also some limitations for using humeral nail for femoral reconstruction in adolescent OI patients. First, most of the humeral nail designs had only 90-100 degree of the cephalomedullary angle for proximal locking blade/screw, which was more varus than the neck-shaft angle of the femur and resulting in suboptimal fixation for proximal femur. Therefore, we recommended carefully adjustment of the proximal blade/screw position to achieve the best position and longest length as possible for the stable femoral head and neck fixation (Figures 2-5). Second, the required length for distal locking screw was usually longer than normal due to the wider width of distal femur than distal humerus, thus it was necessary to prepare the extra-length distal locking screw or using the other types of screw, such as 3.5 mm or 4.5 mm cortical screw, instead. Lastly, due to the abnormal femoral anatomy and using humeral nail design, we recommended

performing the rotational alignment examination by intraoperative checking hip rotation in every cases.

The results of this study showed that using humeral nail implant in femoral fixation was possible and could be used in proximal, middle or distal location. Moreover, this option could be indicated for fixation of fracture and nonunion, or corrective osteotomy. Our study also demonstrated the favorable outcome with 100% fracture healing [the mean clinical union time of 4.2 mo (range 3-6 mo) and the mean radiographic union time of 7.8 mo (range 5-9 mo)] and without the implant-related complications such as infection, nonunion, or AVN. Therefore, we concluded that the humeral nail application for femoral fixation in adolescent OI patients would be one of the possible options with satisfactory outcomes.

COMMENTS

Case characteristics

Three adolescent patients with underlying osteogenesis imperfecta presented with progressive femoral deformity (case 1) or nonunion (case 2) or peri-implant fracture and bilateral distal femur deformity (case 3).

Clinical diagnosis

Case 1: Varus and flexion deformity on left femur without local tenderness. Case 2: Antalgic gait with pain on weight bearing, and local tenderness on the fracture site. Case 3: Moderate swelling, local tenderness on left thigh, and limited movement by pain with bilateral distal thigh deformity.

Differential diagnosis

Progressive deformity associated with osteogenesis imperfecta (OI), fracture or osteotomy nonunion, infection, implant irritation.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Case 1: Radiographs showed anterolateral femoral bowing deformity. Case 2: Radiographs showed persistent radiolucent line on fracture site and progressive Rush pin bending. Case 3: Radiographs showed displaced subtrochanteric fracture below osteotomy plate with bilateral distal femur deformity.

Treatment

Case 1: Ender nails removal and multi-level corrective osteotomy with humeral nail. Case 2: Rush pin removal, and open reduction and internal fixation with humeral nail and local bone graft. Case 3: Bilateral staged femoral reconstructions; (1) osteotomy plate removal and humeral nail insertion; (2) corrective hinged osteotomy left distal femur with humeral nail; and (3) corrective osteotomy right distal femur with humeral nail.

Related reports

The recommended surgical treatment of long bone fracture in OI patients is load-sharing intramedullary fixation to avoid plate-related complications (implant failure, peri-implant fracture, *etc.*). However, the femoral reconstruction in these adolescent OI patients was difficult due to the abnormal femoral anatomy (short limb, abnormal alignment from previous fracture or bowing, and narrow medullary canal), and the unavailability of the specific IM implant.

Term explanation

OI is a rare genetic disorder of the synthesis of collagen that mainly affects the bone, and commonly presents as recurrent fracture and deformity.

Experiences and lessons

The humeral nail application for femoral fixation in adolescent OI patients should be performed with careful preoperative planning, gentle fracture manipulation, and strict postoperative rehabilitation protocol.

Peer-review

The authors demonstrated excellent results for treatment of femur deformity in OI adolescents with humeral nail. The paper is well written and instructive.

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CASE REPORT

Hernia mesh prevent dislocation after wide excision and reconstruction of giant cell tumor distal radius

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Author contributions: Wiratnaya IGE, Budiartha IGBAM, Setiawan IGNY and Sindhughosa DA designed the report; Wiratnaya IGE and Budiartha IGBAM perform the surgery; Budiartha IGBAM, Setiawan IGNY, Kawiyana IKS and Astawa P collected the patient's clinical data; Wiratnaya IGE and Sindhughosa DA wrote the paper.

Institutional review board statement: This case report was approved by the ethics committee of Sanglah General Hospital (Bali, Indonesia).

Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest regarding this work.

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Abstract

Giant cell tumor (GCT) remains as major health problem. GCT which located at the lower end of the radius tends to be more aggressive. Wide excision and reconstruction of the wrist in stage 3 of distal radius GCT lesion is an optimal modality to prevent tumor recurrence. However, dislocation often occurs as its complication. We are reporting patient with GCT of distal radius treated with wide excision and reconstruction using nonvascularized fibular graft and the addition of hernia mesh. Circumferential non-absorbable polypropylene hernia mesh was applied, covered radioulnar joint and volar aspect of radius, and served as additional support to prevent dislocation. During five years and two months of follow-up, we found no dislocation in our patient. Furthermore, good functional outcome was obtained. Our finding suggests that the addition of hernia mesh after wide excision and reconstruction with nonvascularized fibular graft may benefit to prevent dislocation and provides an excellent functional outcome.

Key words: Giant cell tumor; Wide excision; Fibular graft; Hernia mesh; Dislocation

Core tip: Dislocation after wide excision and reconstruction

with nonvascularized fibular graft on giant cell tumor (GCT) distal radius often occur and becomes a problem for the patient. This case report presented the outcome of a patient with GCT of distal radius and treated with wide excision and nonvascularized fibular graft with the addition of non-absorbable polypropylene hernia mesh. Circumferential non-absorbable polypropylene hernia mesh may prevent the occurrence of dislocation and provides an excellent functional outcome.

Wiratnaya IGE, Budiartha IGBAM, Setiawan IGNY, Sindhughosa DA, Kawiyana IKS, Astawa P. Hernia mesh prevent dislocation after wide excision and reconstruction of giant cell tumor distal radius. *World J Orthop* 2017; 8(9): 741-746 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i9/741.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i9.741

INTRODUCTION

Giant cell tumor (GCT) is an aggressive lesion with a high rate of recurrence[1]. Most GCTs are located in the epiphyseal regions of long bones, however studies reported that GCT in the lower end of the radius more aggressive and possess higher tendency for local recurrence[2,3]. Treatments for GCT of distal radius include curettage followed by bone graft or cementing, en-bloc excision and reconstruction either with nonvascular or vascular fibular autograft, ulnar translocation, endoprosthesis, or amputation[4-6].

Wide excision is the optimal surgical treatment modality to prevent tumor recurrence in stage 3 of distal radius GCT lesion. However, reconstruction of wrist after wide excision of distal radius remains a challenging task. Most patients are active young adults who demand cosmetically acceptable and functionally adequate wrist. Nonvascularized proximal fibular graft without arthrodesis still used for reconstruction with excellence function, but dislocation of radiocarpal joint often occur as its complication after surgery[7]. Here we try to prevent dislocation of radiocarpal joint by using hernia mesh.

CASE REPORT

A 28-year-old female presented with lump and pain on the left wrist since one year. The lump was getting bigger, and the pain was felt while flexing the wrist. On examination, the lump was observed on the distal end of the radius with tissue exposure on the dorsal side (Figure 1). The skin was shiny, tense, tenderness with ill-defined margins. The wrist's range of movements was restricted with intact neurovascular status. Left wrist anteroposterior and lateral radiograph revealed extensive local bony destruction along with significant soft-tissue expansion (campanaci grade 3) (Figure 2). She was suspected with GCT of the left distal radius. However, she refused open biopsy and went to bone setter. She came back to the outpatient clinic and then an open biopsy was performed. Histopathology examination revealed GCT of bone (Figure 3).

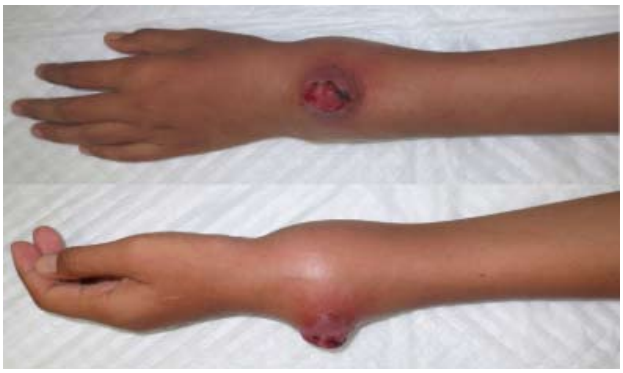

Figure 1 Clinical photograph of the patient.

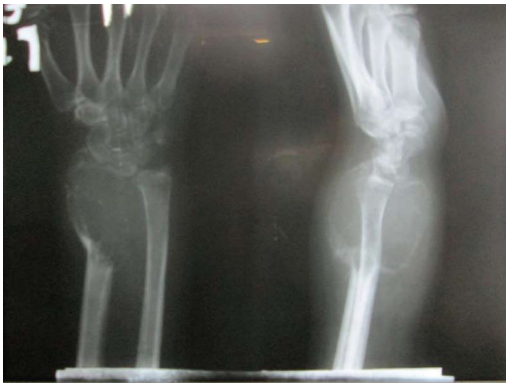

Figure 2 Preoperative X-ray of the patient.

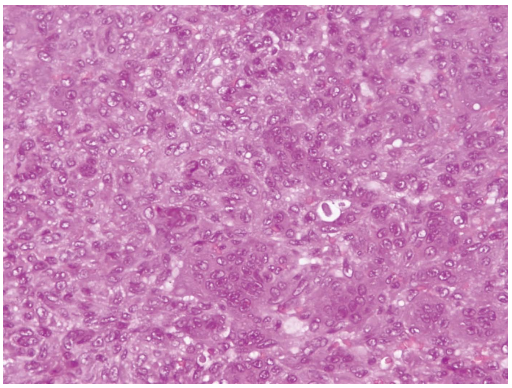

Figure 3 Histopathology examination of the tumor. Multinucleated giant cells were observed from the examination with background of mononuclear cells.

We did wide excision (Figure 4) with a posterior approach along with intracapsular resection (Figure 5) and osteotomy 9 cm proximal from styloid of radius (Figure 6). Flexor, extensor tendon, radial, ulnar artery, median and ulnar nerve were able to preserve. Subsequently, the lateral approach was used for harvesting entire proximal fibula including the head of fibula and bicep tendon with a length of 4 cm. The

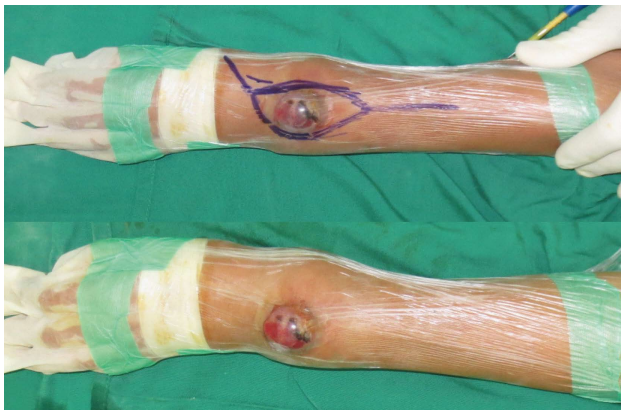

Figure 4 Intra-operative photograph of wide excision with posterior approach.

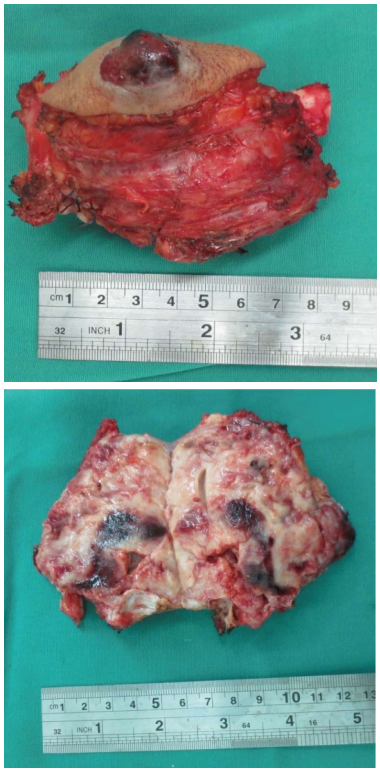

Figure 5 Excision of tumor.

common peroneal nerve was identified and osteotomy 10 cm from the head of fibula was done (Figure 7).

The harvested fibula was fixed to the radius with 3.5 locking plate. The tip of fibula should lie for the radial styloid and its articular surface articulated with scaphoid. The dorsal radiocarpal capsule was sutured with bicep tendon, and the transplanted fibula stabilized to ulnar with 1.6 K wire. To prevent dislocation of the radioulnar and radiocarpal joint, circumferential non-absorbable polypropylene hernia mesh was applied circularly. At the distal part, the mesh was sutured to the remain of the capsule and the ligament of os carpalia at the volar, while at the proximal part the mesh was sutured to the periosteum and the surrounding soft tissue, attached

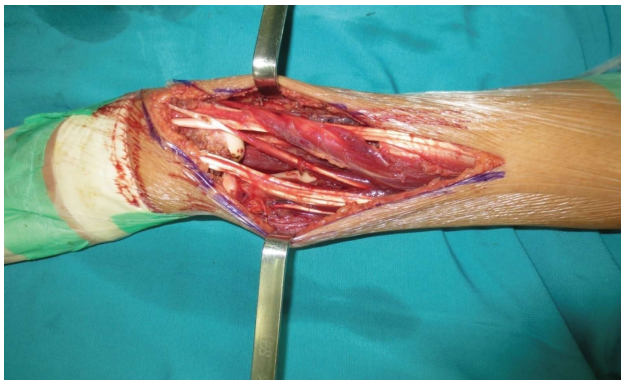

Figure 6 Intra-operative photograph showing large defect due to wide excision.

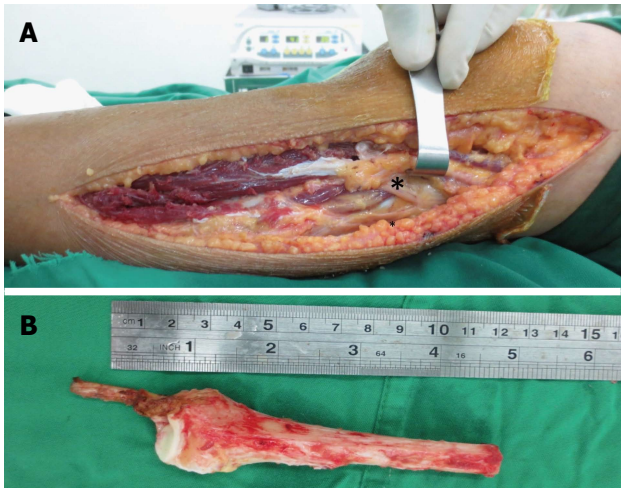

Figure 7 Proximal fibula harvested *via* lateral approach. The asterisk showing the intact of peroneal nerve (A) including head of fibula and bicep tendon (B).

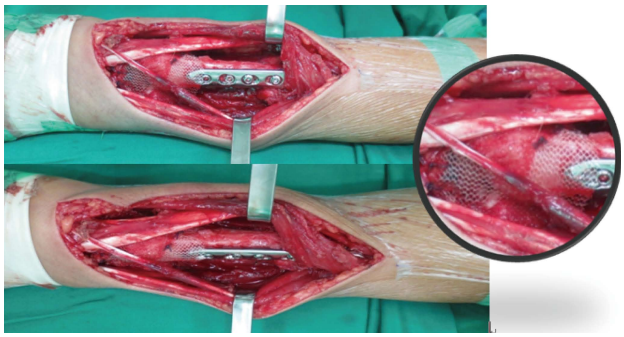

Figure 8 Fibular graft implantation fixed with 3.5 locking plate and covered with hernia mesh on radioulnar joint and volar aspect of radius. The inset showing the hernia mesh.

to fibular graft. The mesh covered the radioulnar joint (Figure 8). This hernia mesh is used to provide additional support to weakened or damaged tissue in this area. Afterward, X-ray examination was performed (Figure 9). A short arm splint in 30° wrist extension was applied. Splint and pins were removed six weeks post

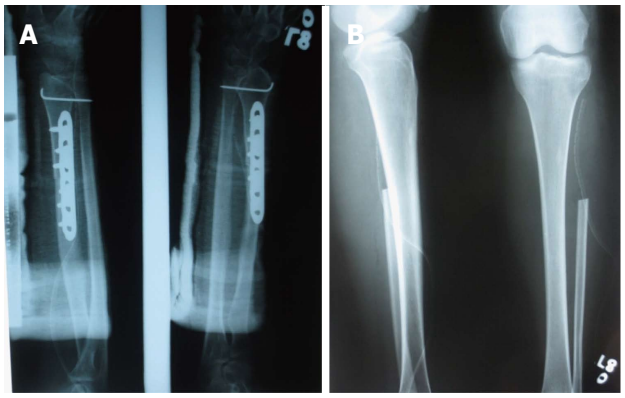

Figure 9 The post operative X-ray after wide excision of giant cell tumor of distal radius (A) and defect in fibula (B).

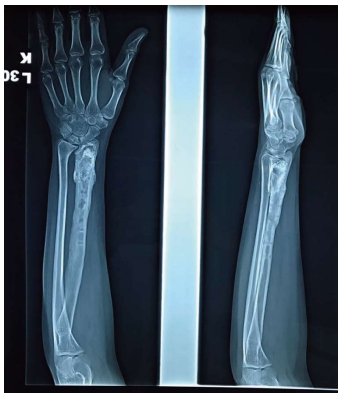

Figure 10 The follow-up X-ray 5 years after the wide excision of giant cell tumor distal radius and fibular autograft and after removal of plate and screw.

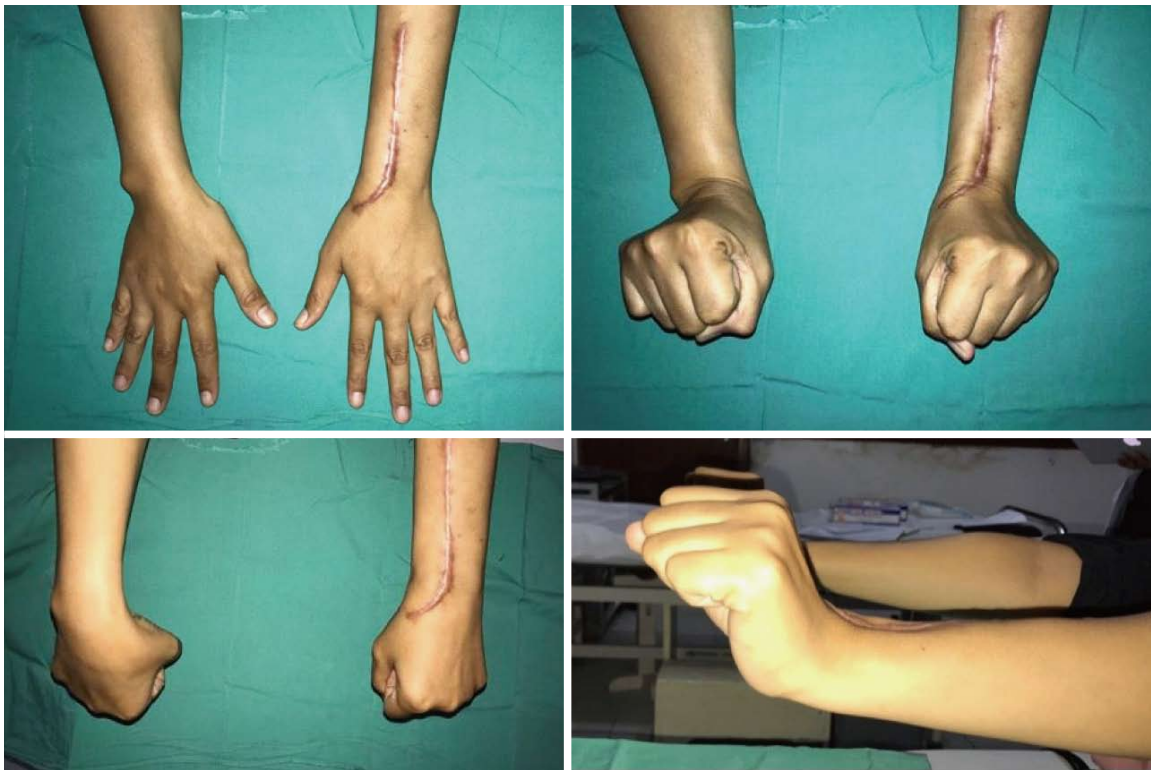

Figure 11 The clinical picture of functional outcome after five years of follow-up. The pictures showing a range of motion of 75%-99% of normal side, and grip strength of 100% compared with normal hand.

operation and gentle range of motion was advised.

Four months post operation we evaluate her functional outcome by using Mayo Wrist Score and obtained a good result. Evaluation with quick dash score also obtained a good result. The total disabilities involving the arm, shoulder and hand (DASH) score was 9.2. During five years and two months of follow-up, no subluxation was observed in our patient (Figure 10). The total Mayo Wrist Score was 90. The patient did not feel any pain, returned to regular employment, range of motion of 75%-99% of normal side, and grip strength of 100% compared with normal hand (Figure 11).

DISCUSSION

En bloc excision method leaving a large defect in excision area, thus reconstruction on this site is necessary. Various techniques have been described for reconstruction, including iliac crest graft, centralization of ulna, distal radial allograft, vascularized or non-vascularized fibular graft, and prosthesis. Non-vascularized fibular autograft is one reconstruction technique to fill the defect caused by the wide excision. It was first used in 1945 for congenital absence of radius. The fibula was chosen since its size and shape are similar with distal radius[8]. Later,

fibular transplant was used by various authors for tumors of the lower end of radius.

Nonvascularized fibular autograft possesses more advantages compared with other procedures. It has low morbidity of the donor site, satisfactory functional result, and free of major complications although some minor complications exist[7,9,10]. A study by Saini *et al*[11] in twelve patients with GCT of distal radius treated with wide excision of tumor and ipsilateral nonvascularized fibular autograft obtained the average of grip strength was 70% (24%-86%) compared with normal contralateral side and well preserved of forearm supination and pronation movement. However, a complication in term of subluxation occurs in 3 cases.

Subluxation is a commonly-occurring complication in defect reconstruction with nonvascularized fibular autograft method. With the addition of hernia mesh, the patient in our case did not develop any dislocation or subluxation, but the incidences reported in the literature are quite high. A study by Saikia *et al*[7] (2010) obtained 10 cases of subluxation from the total of 24 GCT of distal radius cases treated with en bloc resection and arthroplasty reconstruction of autogenous non-vascularized ipsilateral fibular graft. Seven of them occur 3-12 mo after surgery. A study by Dhammi *et al*[12] in 16 patient with GCT of lower end radius treated with similar method reported 10 cases suffered from wrist subluxation out of 16 patients, with follow-up duration ranges from two to five years. Saraf *et al*[13] reported subluxation on 2 patients from 15 patients which caused significant pain, deformity, and loss of function.

Fibular graft with appropriate length is a method to prevent subluxation of wrist joint after the reconstruction was performed. Saikia *et al*[7] ensure the appropriate length obtained with the addition of 2-3 mm longer than the required length, which is the resection tumor and safe margin, so that the compression at the host-graft junction during fixation with DCP was achieved and subluxation could be prevented. K-wire fixation used to stabilized wrist joint. However, this method did not ensure the prevention of subluxation.

We perform modification with a different approach than previous technique that is the addition of hernia mesh to prevent subluxation or dislocation. Circumferential hernia mesh which covered radioulnar joint and volar aspect of the radius was applied to stabilize the graft. Furthermore, the tensile strength of the mesh may withstand the local pressure forces, hence prevent the occurrence of dislocation or subluxation. During five years and two months of follow-up, no subluxation was observed in our patient. The total Mayo Wrist Score was 90. The patient did not feel any pain, returned to regular employment, the range of motion of 75%-99% of normal side, and grip strength of 100% compared with normal hand.

In conclusion, the complication in the form of subluxation did not occur in our case. Reconstruction method with the addition of hernia mesh to prevent subluxation provides an excellent functional outcome.

COMMENTS

Case characteristics

A 28-year-old female with lump which getting bigger in the last one year and pain on left wrist, aggravated by flexion of the wrist.

Clinical diagnosis

Swelling on the distal end of radius, the skin condition was shiny, tense, tenderness with ill-defined margins, and tissue exposure on the dorsal side.

Differential diagnosis

Aneurysmal bone cyst and tuberculosis of bone.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Anteroposterior and lateral radiograph of the left wrist showed extensive local bony destruction along with significant soft-tissue expansion (campanaci grade 3).

Pathological diagnosis

Multinucleated giant cells with a background of mononuclear cells, appropriate for giant cell tumor (GCT).

Treatment

Wide excision and reconstruction using non vascularized fibular graft with the addition of hernia mesh.

Related reports

GCT located in the lower end of the radius tend to be more aggressive and has a higher tendency for local recurrence. The optimal surgical treatment to prevent tumor recurrence in stage 3 of GCT distal radius is wide excision along with non-vascularized fibular autograft to repair the large defect in excision area. Subluxation is a commonly-occurring complication in defect reconstruction with nonvascularized fibular autograft method. The addition of hernia mesh may advantageous to prevent the subluxation, affecting the functional outcome of the patient.

Term explanation

GCTs are benign tumors which have a tendency for aggressive characteristics and ability to metastasize. The disabilities of the arm, shoulder and hand (DASH) score is an outcome instrument for measuring upper-extremity disability and symptoms.

Experiences and lessons

The addition of hernia mesh after wide excision and reconstruction using nonvascularized fibular graft of GCT of distal radius prevent the complication in term of subluxation and offer excellent functional outcome.

Peer-review

The authors present a very interesting paper on the reconstruction of the wrist after radius bone excision for a GCT.

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