Histological changes in articular cartilage by exercise

Review Article

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Histological changes in articular cartilage by exercise

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KEY WORDS
disuse atrophy, articular cartilage, exercise

Introduction

Physiotherapists often consider joint disease and its complications as part of their clinical work. Articular cartilage, a major mobile joint tissue, is important for ensuring shock absorption and smooth mobility under loading or exercise. However, few basic or clinical studies have examined articular cartilage, making it difficult for physical therapists to update their knowledge. We have conducted basic research on articular cartilage in rats. The focus of this review is to summarize new and existing articular cartilage research findings.

Histology of Articular Cartilage

There are three types of cartilage: hyaline, elastic, and fibrotic. Articular cartilage, which appears as a translucent milky-white tissue, is classified as hyaline, and composed of chondrocytes and cartilage matrix (Figure 1). In humans, articular cartilage is ~0.8-5.0 mm thick, depending on the region. Multiple chondrocytes form the cartilage's lumen, which produces a cartilage matrix such as proteoglycans. The cartilage matrix is composed of water (~70%), type II collagen (~15%), and proteoglycans (~10%). Cellular components comprise <5% of the cartilage's structure[1)]. One of the characteristics of its surface is its low friction coefficient (0.002–0.006, 1/10 that of ice skates), impossible to produce by artificial means[1)].

Structure of Articular Cartilage

Underneath the surface layer of articular cartilage are tangential, transitional, radial, and calcified layers (Figure 2). These layers gradually transition into subchondral bone and bone tissues. Each layer of articular cartilage is characterized by differences in collagen arrangement, chondrocyte density, and proteoglycan content[2)]. Superficially, collagen fibers are arranged parallel to the articular surface; meanwhile, fibers within deeper layers are perpendicular to the surface[2-4)]. While superficial layers contain relatively few chondrocytes and proteoglycan, they are increasingly abundant in deeper layers[2-4)]. Layer-specific differences in cartilage composition mirror differences in each layer's function and role[2-4)]. For example, collagen fibers respond to friction and shear forces by aligning parallel to the articular surface[2-4)]. However, the middle and deeper layers—which contain more proteoglycans—are specialized to absorb shock by repeated compression and restoration in response to loading[2-4)].

Nutrition and Repair Capability of Articular Cartilage

Since articular cartilage contains no blood vessels, nerves, membrane, or lymphatic channels, its nutritional support depends on synovial fluid diffusion. Even in the knee joint—the largest joint cavity in the human body—there is very little (~2 ml) synovial fluid.

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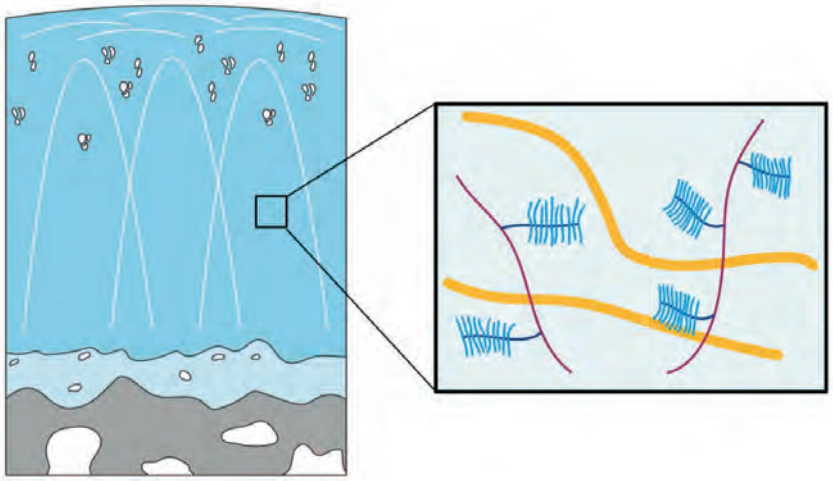

Figure 1　Articular cartilage matrix
The enlarged image (right) depicts articular cartilage water (light blue), type II collagen (yellow), and proteoglycan aggregate composition. The proteoglycan aggregates are composed of hyaluronic acid (purple), core proteins (dark blue), and mucopolysaccharides like chondroitin sulfate and keratan sulfate (bright blue).

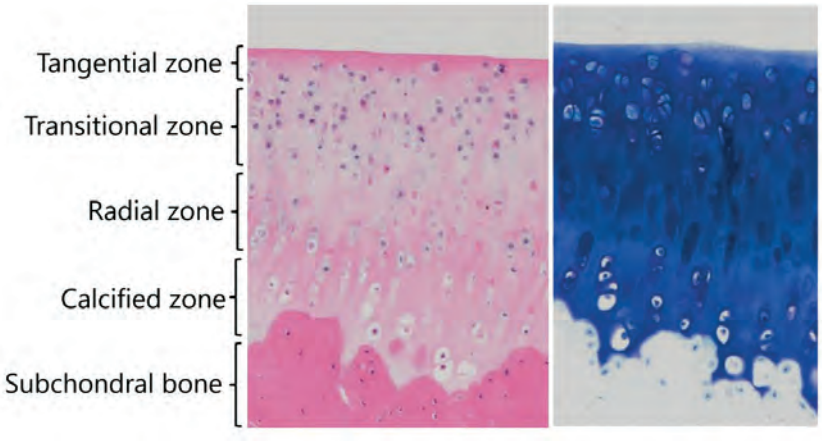

Figure 2　Articular cartilage histology
These photographs depict histological images of articular cartilage in rats. In the hematoxylin-eosin stain (left), articular cartilage is stained light pink, and chondrocyte nuclei are stained dark blue to purple. In the toluidine blue staining (right), the mucopolysaccharides in the articular cartilage matrix are stained blue.

Normally, tissue damage results in hemorrhage and inflammation[1,5]. Eventually, the damaged tissue is replaced by granulation tissue, and the repair process of articular cartilage is markedly different from that of other tissues[1,5]. The avascular nature of articular cartilage prevents hemorrhage, and its low cell density limits cellular repair capacity[1,5]. For example, only a small amount of matrix is produced in response to partial-thickness defects that do not reach the subchondral bone; the defect is rarely filled[1,5,6]. On the other hand, full-thickness defects that reach the subchondral bone and cause hemorrhage are repaired by fibrocartilage, a specialized and less-durable form of articular cartilage, potentially resulting in pain and progressively diminished mobility[1,5,6].

Because of this low repair capacity, articular cartilage has traditionally been considered a low-metabolism tissue. Indeed, per unit volume, it contains very few cells, as mentioned above. However, articular cartilage's per-cell metabolism is reportedly similar to other tissues[1].

The Uniqueness of Articular Cartilage

First, articular cartilage comprises a cartilage matrix, which accounts for >90% of its volume, and has very few cells compared to other tissues[1]. Second, articular cartilage lacks blood vessels, nerves, and lymphatic

vessels; the only other tissue in the human body with these features is the eye[1]. Third, articular cartilage is reportedly isolated from the immune system[7], making it similar to the blood-brain and blood-cerebrospinal barriers and placenta during pregnancy[7]. Forth, whereas most cartilages feature a vascularized chondrocyte membrane, this feature is absent from articular cartilage, further increasing the uniqueness of this bodily tissue.

Age-related Changes in Articular Cartilage

With age, articular cartilages yellows and the chondrocyte metabolism slows. Although age-related histological changes in articular cartilage are largely unknown, it likely thins and hardens while the tissue's cell density further decreases[8,9].

Response to Exercise

The response of articular cartilage to exercise is similar to that of skeletal muscle. In other words, articular cartilage can be maintained or hypertrophied by moderate loading or increased exercise, destroyed by excessive exercise, and atrophied by decreased exercise or lack of loading.

1. Given moderate loading, articular cartilage hypertrophies

When exercised at a moderate intensity, normal articular cartilage thickens, chondrocyte density increases, and cartilage composition is altered. These changes occur in humans and other animals[10-12]. For example, Ni et al. observed increased cartilage thickness and chondrocyte density in rats subjected to treadmill running at low and moderate intensities[13]. Hamann found similar increases in matrix staining with exercise[14]. A systematic review in normal animals also found a relationship between daily physical activity and cartilage composition[12]. Thus, moderate mechanical stress may have a protective effect on normal articular cartilage by stimulating articular cartilage's metabolism.

Also, Protection afforded by moderate exercise has been observed with OA cartilages[12]. Galois et al. used rats with surgically induced OA and set up three different running protocols based on total running distance[15]. On day 14 and 28 of the experiment, the Mankin score, which indicates the severity of cartilage degeneration according to the structure, cellularity, toluidine blue staining, thickness of hypertrophic chondrocyte layer, bone remodeling, and osteolysis, was significantly lower in rats in the short- and medium-distance groups than in the OA group[15]. Furthermore, on day 28 of the experiment, rats in the medium-distance group had significantly less caspase, which is associated with cell death, than rats in the OA group[15]. Iijima et al. used rats with surgically induced OA and set up two speed-based running protocols. In addition to articular cartilage degeneration, both protocols suppressed osteophyte formation and subchondral bone damage[16,17].

Thus, moderate loading exerted positive effects on normal and OA cartilages. However, it is not clear what loading level is truly "moderate" or appropriate given each cartilage's unique characteristics; further research is needed.

2. Excessive stress causes OA

When a load exceeds normal articular cartilage's mechanical loading threshold, chondrocytes produce matrix-degrading enzymes, which gradually destroy the cartilage matrix[18,19]. Alternatively, excessive mechanical stress can cause OA in normal articular cartilage[18,19]. Research using animal models found that high-load running results produced OA-like histological changes and reduced cartilage thickness and cell density[13]. Excess mechanical stress can cause adverse effects like structural failure of cartilage and cartilage cell death[18-20].

3. Insufficiency causes disuse atrophy

Immobility causes skeletal muscle atrophy. Similarly, unloading causes histological changes in articular cartilage that resemble disuse[21-24]. Vincent et al. proposed that these histological changes caused by reduced mechanical stress—specifically cartilage thinning and reduced matrix staining—comprise "articular cartilage atrophy." Of note, this atrophy is *not* accompanied by changes in chondrocyte density and surface irregularities[25]. We observed cartilage atrophy in rats, specifically thinning and decreased matrix staining in the tibial cartilage, after 4 weeks of unloading (Figure 3)[26-27]. The main mechanism of atrophy is assumed to decrease the synthesis of proteoglycans and other matrix components by chondrocytes[25]. However, the mechanical strength and metabolic characteristics of atrophied articular cartilage remain unclear. The next section discusses our articular cartilage disuse atrophy findings.

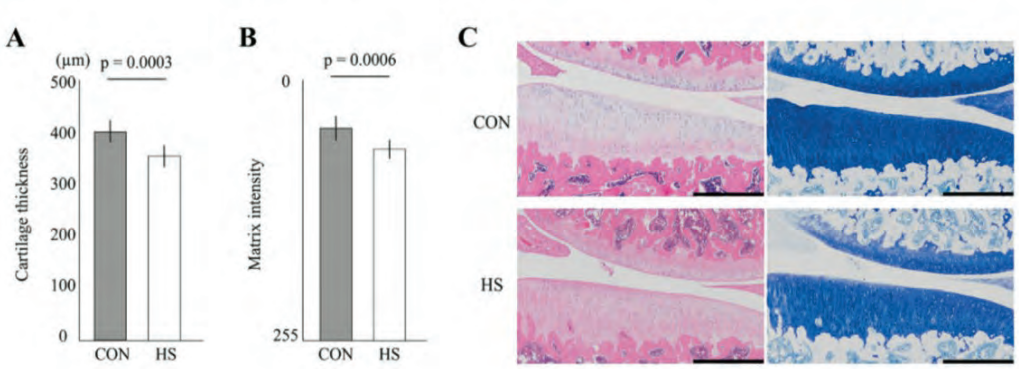

Figure 3　Histological findings associated with articular cartilage atrophy secondary to unloading
Four weeks of unloading caused articular cartilage disuse atrophy. CON, control group; HS, experimental group (kept in an unloaded environment for 4 weeks). Articular cartilage thickness is significantly thinner in experimental, compared to control, group rates (A and C). Matrix staining is significantly reduced (B and C) in experimental group rats. Scale bar = 500 μm. Figure credit: Takahashi et al.[19]

1) Associations between Atrophy and OA

We hypothesized that atrophied cartilage would be thinner and have reduced matrix staining, reducing its endurance to mechanical stress, and making it more prone to OA or more severe OA. To examine this hypothesis, we subjected rats to a combination of surgically induced OA and disuse atrophy of articular cartilage induced by tail suspension[24]. Our histological findings indicated that, compared to normal cartilage, atrophied cartilage was associated with more severe and wider OA and subchondral bone damage (Figure 4). Thus, OA progresses faster and is more severe in atrophied articular cartilage. Our results suggested that articular cartilage disuse atrophy may precede, and potentially lead to, OA.

2) Can Atrophied Articular Cartilage Recover?

As noted in "Nutrition and Repair Potential of Articular Cartilage," the ability of articular cartilage to repair damage or defects is poor. However, atrophy and damage are very different pathologies. Given the adaptive increases in articular cartilage thickness due to the exercise described above, and our previous studies' results, we hypothesized that disuse atrophy of articular cartilage would be restored by reloading.

To achieve our experimental objective, we created a novel tail-suspension model to induce disuse atrophy of articular cartilage in rats and histologically examine the effects of reloading[27]. We found that atrophied cartilage could be restored by reloading the hindlimb for 2-4 weeks (Figure 5). Specifically, the results confirmed that keeping the hindlimbs unloaded for 4 weeks caused thinning and decreased matrix staining of the tibial cartilage[24,27]. Subsequently, 2 weeks of reloaded recovered cartilage thickness and matrix staining to a level comparable to that of the control group. In addition to cartilage thickness and matrix staining, the following changes were observed in many parameters. There was no significant change in cell density with unloading, but cell density increased significantly after reloading. The proportion of noncalcified layers decreased with unloading and recovered after 4 weeks of reloading. Immunohistochemical analysis showed that the staining intensity of type II collagen showed no significant change with unloading and reloading, whereas that of aggrecan increased significantly with unloading and reloading. The positive cell density of degradative enzymes, matrix metalloprotease 13 (MMP13) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5), significantly increased by unloading, but not during reloading. Although additional aspects related to the mechanism of this recovery need to be investigated, disuse atrophy of articular cartilage differs from damage caused by injury or defect and could be recovered by reloading. Considering that atrophied cartilage is more likely to develop OA, physiotherapy could help restore atrophied articular cartilage. In other words, disuse atrophy of articular cartilage, like disuse muscular atrophy, may become a new indication for physical therapy.

3) Can Articular Cartilage Atrophy be Prevented?

Based on these results of our study, we speculated

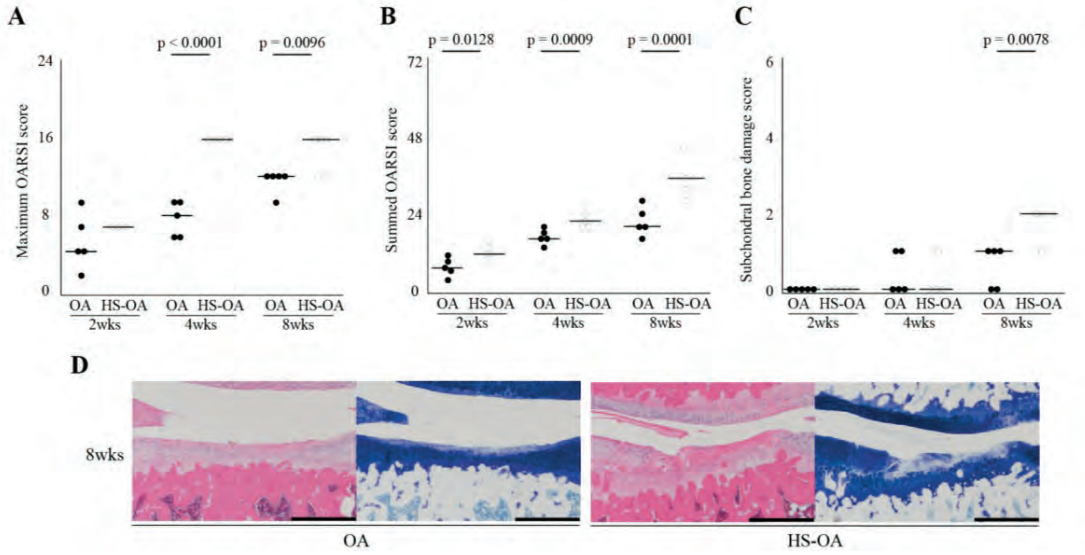

Figure 4 Histological findings associated with OA and articular cartilage disuse atrophy
OA is more severe in atrophied, compared to normal, cartilage. Further, atrophied articular cartilage features wider OA degeneration and more-severe damage to subchondral bone. The OARSI score comprises six grades and four stages on a scale from 0 (normal) to 24 (severe cartilage lesion). The maximum OARSI score measures lesion severity, and the summed OARSI score measures lesion extent. OA group rats were maintained normally for 4 weeks, then OA was surgically induced. HS-OA rats were kept in hindlimb suspension for 4 weeks, then OA was surgically induced. Scale bar = 500 μm. Figure credit: Takahashi et al.[19]

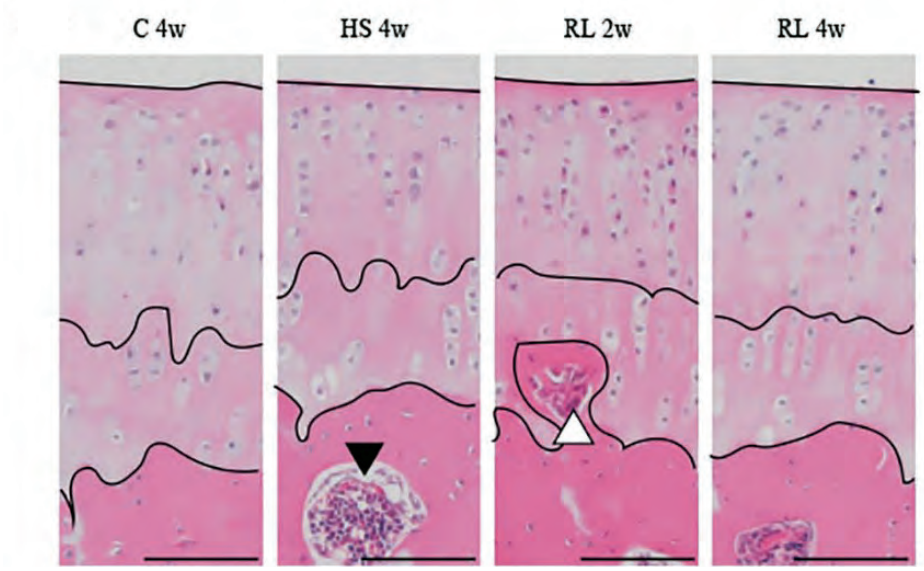

Figure 5 Histological findings associated with atrophied cartilage recovery secondary to reloading
Articular cartilage thinned by unloading was recovered by reloading. The control group (Group C) was maintained in normal conditions for 4 weeks; the HS group was kept in an unloaded environment for 4 weeks. Black triangles indicate marrow invasion, and white triangles indicate vascular invasion. Scale bar = 100 μm. Figure credit: Takahashi et al.[21]

that temporary loading and walking during the unloading period could prevent articular cartilage disuse atrophy progression. We conducted an experiment to determine the effect of temporary loading and walking during a period of unloading on preventing articular cartilage atrophy in the rat knee[28]. Rats were divided into four experimental groups, including control (CON), hindlimb suspension (HS), physiological loading (PL), and treadmill walking (TW) groups. Rats in the CON group were kept in a cage with physiological environment. Rats in the HS, PL, and TW groups were subjected to hindlimb suspension for four weeks. The

rats in the PL group were allowed to walk freely for four weeks in a physiological environment using all the limbs for 1 hour per day and 5 days per week. The rats in the TW group were subjected to treadmill walking for four weeks at the rate of 12 m/min for 20 minutes per day and 5 days per week. As a result, in the TW group, cartilage thinning, decreased matrix staining, and decreased noncalcified layers were significantly suppressed (Figure 6). The PL group exhibited no significant suppression of cartilage thinning or decreased noncalcified layers. Therefore, disuse atrophy of the articular cartilage could be prevented by treadmill walking in rat knee joints. However, mechanical stress is difficult to quantify. Although the histological results suggested that the mechanical stress applied to the TW group was greater than that of the PL group, we explored previous studies and found that it difficult to quantify and compare the mechanical stress applied to both the groups. Thus, in clinical case, avoidance of unnecessary bed rest and early discontinuation of bed rest may favorably affect articular cartilage.

4) Future Directions

The results of our basic research on articular cartilage disuse atrophy suggest that it can be treated using physiotherapy. However, there are still many unknowns, such as the mechanism by which disuse atrophy of articular cartilage progresses, the mechanisms by which it recovers, and if exercise can hasten the recovery of atrophied articular cartilage. Clarification of these points will improve our understanding of articular cartilage disuse

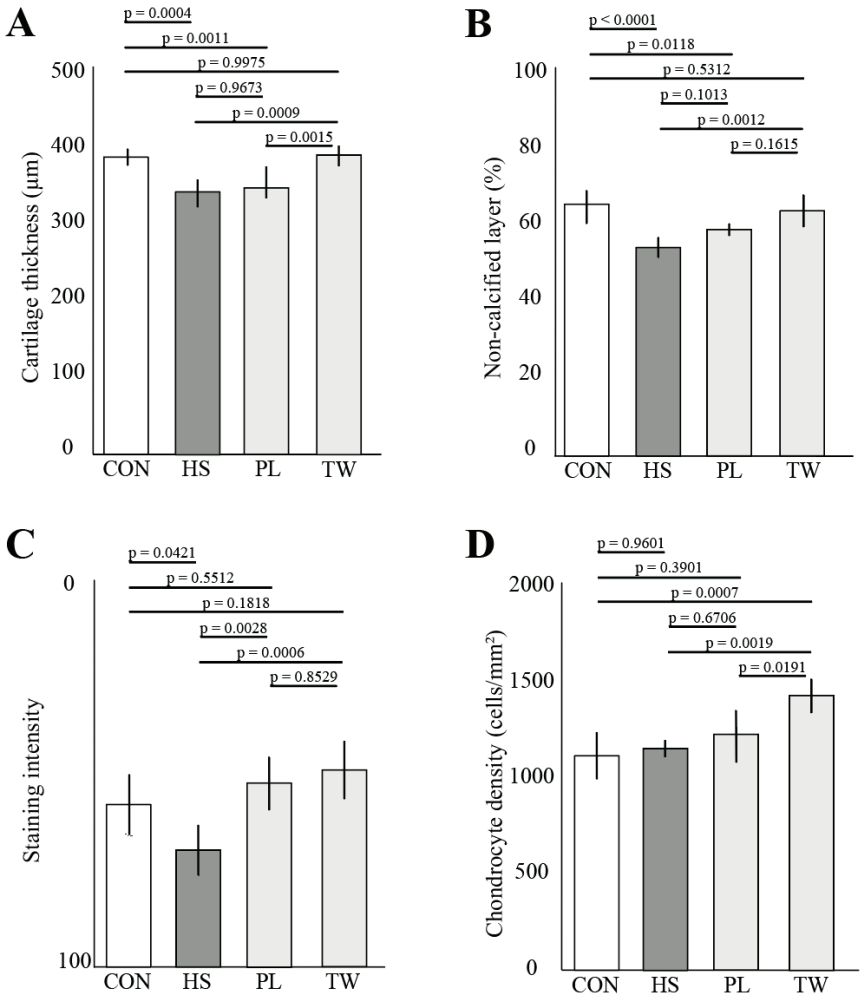

Figure 6 Histological findings associated with loading and walking for articular cartilage atrophy prevention

Loading during the unloading period did not prevent cartilage atrophy. However, walking during the unloading period prevented articular cartilage disuse atrophy. CON, control group; HS, experimental group (kept in an unloaded environment for 4 weeks). PL is the physiological loading group (1 hour/day, 5 days/week), and TW is the treadmill walking (12 m/min, 20 min/day, 5 days/week) group. Figure credit: Takahashi et al.[22]

atrophy as a therapeutic target and contribute to the development of evidence-based physiotherapy protocols.

Conclusion

Articular cartilage is not a “static” tissue with low repair capacity; rather, it is a "dynamic" tissue that changes its histological properties to meet the unique demands of individuals’ mechanical stressors. Although this review focuses on basic research and currently has limited clinical application, these histological findings may be useful and crucial in clinical conditions. We hope that this review will be of some help to physiotherapists who see patients with joint damage in their clinical practice settings.

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