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Review

Advantages of exercise in rehabilitation, treatment and prevention of altered morphological features in knee osteoarthritis. A narrative review

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Summary. Knee osteoarthritis (OA) represents one of the most common causes of disability in the world. It leads to social, psychological and economic costs with financial consequences, also because a further increase is expected. Different knee OA treatments are usually considered in relation to the stage of the disease, such as surgical management and pharmacologic and non-pharmacologic treatments. Treatment should begin with the safest and least invasive one, before proceeding to more invasive, expensive ones. Non-pharmacologic, behavioral treatments of knee OA are recommended not only in rehabilitation but also in prevention because many risk factors, such as excess weight, obesity and joint tissue inflammation, can be monitored and thus prevented. In the present review, we analyze data from the most recent literature in relation to the effects of physical exercise on prevention, therapy and rehabilitation in knee OA. All data suggest that physical exercise is an effective, economical and accessible tool to everyone, in the treatment and prevention of knee OA. The literature search was conducted on PubMed, Scopus and Google Scholar using appropriate keywords in relation to knee osteoarthritis.

Key words: Knee osteoarthritis, Exercise, Rehabilitation, Prevention

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Introduction

Osteoarthritis (OA) is a degenerative disease of the articular cartilage associated with hypertrophic bone changes (Schroeppel et al., 2011; Sinusas, 2012; Musumeci et al., 2011a, 2013a; Pichler et al., 2013a). The knee is one of the most affected joints in OA, and knee OA represents one of the most common causes of disability in the world with about 15% of the world population involved (Egloff et al., 2012; Vincent et al., 2012a, Musumeci et al., 2013a,b). Knee OA is characterized by progressive loss of articular cartilage and formation of osteophytes with consequent chronic pain and functional restrictions (Lorenz and Richter, 2006). It leads to social, psychological and economic costs with financial consequences, also because a further increase in Knee OA is expected in relation to the increase in obesity and ageing of population (Gupta et al. 2005; Egloff et al., 2012). The start and progression of knee OA is caused by many factors, such as genetics, gender, sex, trauma, age, obesity and kinematics which lead to alterations in the joint cartilage (Lorenz and Richter, 2006; Vincent et al., 2012a; Sinusas, 2012). Radiography may be useful, while laboratory tests do not usually have an important role in the diagnosis (Sinusas, 2012). Knee OA has a multifactorial etiology, including increased mechanical stress, ligament derangements, cartilage degradation, subchondral bone changes and muscular impairments (Egloff et al., 2012). In healthy knee, articular cartilage shows adaptations in morphology and mechanical properties in response to weight-bearing activity and these adaptations permit

only some areas of the articular cartilage to respond to loads, whilst other areas are less able to accommodate loading, leading to the beginning and progression of degenerative processes typical of knee OA (Vincent et al., 2012a). Generally, OA occurs when the dynamic steady-state between destructive forces and repair mechanisms alters the joint homeostasis (Kouri and Lavalle, 2006; Egloff et al., 2012). The tibiofemoral mechanics and loading patterns, during walking, influence the regional development of articular cartilage (Vincent et al., 2012a). Alterations in normal gait mechanics due to trauma, acute injury, ligamentous laxity, weight gain, and improper footwear can shift the loading patterns to areas of articular cartilage not well adapted to accept improper loads (Vincent et al., 2012a).

There are many and different types of knee OA treatments, in relation to the stage of the disease: non-pharmacologic, pharmacologic, complementary and alternative, and surgical (Sinusas, 2012; Musumeci et al., 2013c,d). Treatment should begin with the safest and least invasive treatments before proceeding to more invasive, expensive ones (Sinusas, 2012). Surgical management should be reserved for patients who do not improve with behavioral and pharmacologic therapy or have excessive pain and loss of mechanical function (Sinusas, 2012). Non-pharmacologic, behavioral treatments of knee OA are recommended in rehabilitation but also in prevention because of, for example, the importance of obesity and tissue inflammation as important risk factors for OA.

In the present review, we analyze data from the literature concerning the effects of physical exercise on prevention, therapy and rehabilitation in knee OA. All data suggest that physical exercise is an effective, economic and accessible tool to everyone, in the treatment and prevention of knee OA.

Macroscopic and microscopic aspects of osteoarthritis (OA)

The most representative tissue in the knee joint is the cartilage. Cartilage is a tissue with viscoelastic and compressive properties thanks to the extracellular matrix, mainly composed of collagen type II and the proteoglycan aggrecan (Musumeci et al., 2013b,c,d; Loreto et al., 2012). Healthy joint cartilage has a smooth surface, and four layers are typical in articular cartilage: superficial zone, intermediate zone (or middle zone), radial zone (or deep zone) and calcified cartilage (or calcified zone). In the superficial zone, cells are flat and spindle-shaped, parallel to the joint surface (Lorenz and Richter, 2006; Musumeci et al., 2013b). The superficial zone contains the highest proportion of collagen fibers, parallel to the surface, which results in the high tensile modulus of the tissue and indicates that the main function is to resist the shear stress at the joint surface (Lorenz and Richter, 2006). The middle zone is characterized by round cells forming columns perpendicular to the cartilage surface; cells are embedded in an extracellular matrix (ECM) characterized by randomly oriented collagen fibers (Lorenz and Richter, 2006). The middle zone contains more proteoglycans, which exhibit repulsive negative charges neutralized by positive ions, leading to swelling pressures and its highly stable hydrated structure. The deep zone is located at the cartilage-bone interface, where collagen fibers are aligned perpendicular to the surface. In this zone, cells are round and the columns open out to the tidemark, the border between non-calcified and calcified cartilage that is represented by an unbroken basophile line in optical microscopy (Lorenz and Richter, 2006). A zone of calcified cartilage is adjacent to the deep zone and immediately after the subchondral bone is present (Fig. 1). Articular cartilage is not vascularized and innervated, so nutrients and cellular repair molecules are transported to the chondrocytes by diffusion from the synovial ?uid. As a consequence of its properties, articular cartilage has limited capacities for self-regeneration and when this occurs, the repaired articular cartilage shows reduced mechanical capacities compared to healthy cartilage (Egloff et al., 2012). Though chondrocytes are very active cells, they normally do not divide after adolescence, so only small defects associated with minimal loss of matrix components can be repaired by regeneration of articular hyaline cartilage; wider defects exceed the repair capacity and the damage can become permanent (Lorenz and Richter, 2006). Many healthy and untreated joints also show slight signs of cartilage degeneration like minor surface roughness and minimal fibrillation. Histological alterations of degenerating cartilage are scored according to Mankin et al. (1971) or a modified score by Sakakibara et al. (1994). These scores evaluate various factors such as tissue structure, cell morphology, matrix staining and appearance of the tidemark. The highest possible scores meaning the most severe damage are 14 for the Mankin's score and 32 for the modified Mankin's score, respectively. Alterations to healthy joint cartilage usually do not exceed grades of 1-3 (Le Graverand et al. 2002). The semi-quantitative histological grading criteria of Kraus' modified Mankin score (Mankin et al., 1971; Kraus et al., 2004) and histopathology OARSI system (Kraus et al., 2010; Pauli et al., 2011) are used.

OA is a degenerative process characterized by several radiographically visible changes such as narrowed joint space, thickening, formation of osteophytes and cysts in the subchondral bone (Fig. 2). In animal models of OA, osteophytes and subchondral sclerosis are detected radiographically 24 months after anterior cruciate ligament transection (ACLT) and progress further in the next 2-3 years (Ruan et al., 2013). Unfortunately, radiographs are not suitable to determine the degree of cartilage degeneration (Miosge et al., 2004). In magnetic resonance imaging (MRI), osteophytes are also detected, signal intensity of the menisci is altered and in advanced stages geodes or subchondral cysts are detected (Shibakawa et al., 2003).

In MRI, at first the subchondral bone shows bone loss, which is then followed by increased bone density (Shibakawa et al., 2003) (Fig. 3).

OA involves progressive loss of the structure and functionality of articular cartilage due to an imbalance between anabolic and catabolic processes in the cartilage tissue; as the OA advances, cartilage degradation exceeds reparative processes, and OA progresses (Kouri and Lavalle, 2006; Lorenz and Richter, 2006; Lahm et al., 2012). While the surface of healthy hyaline cartilage appears white, shiny, elastic and firm, OA cartilage shows dull and irregular surface with discoloration, softening, and often more synovial fluid is produced (Ruan et al., 2013). Sometimes newly invaded blood vessels can be found. Osteophytes are also found in early stages of the disease as shown in animal models (Ruan et al., 2013), but become more pronounced in advanced stages of OA. While in early OA cartilage presents a thickening in line with hypertrophy, in far advanced disease stages, hypertrophic villi and full-thickness defect areas can be seen, where the cartilage is missing completely and the subchondral bone is exposed (Ruan et al., 2013). The subchondral plate itself is thicker and more dense (Ruan et al., 2013). At the early stage of the degeneration process, minimal changes are detected in the cartilage surface, glycosaminoglycans remain homogenously distributed and mild fibrillations are found in the superficial zone (Miosge et al., 2004) (Fig. 4). As the disease progresses, there are changes in the cellular structure and a loss of proteoglycans (Lahm et al., 2012). Flat cells of the superficial zone become round and hypertrophic at first, then disappear from the tissue. Cells of the intermediate and radial zone expose mild to moderate hypercellularity (Pritzker and Aigner,

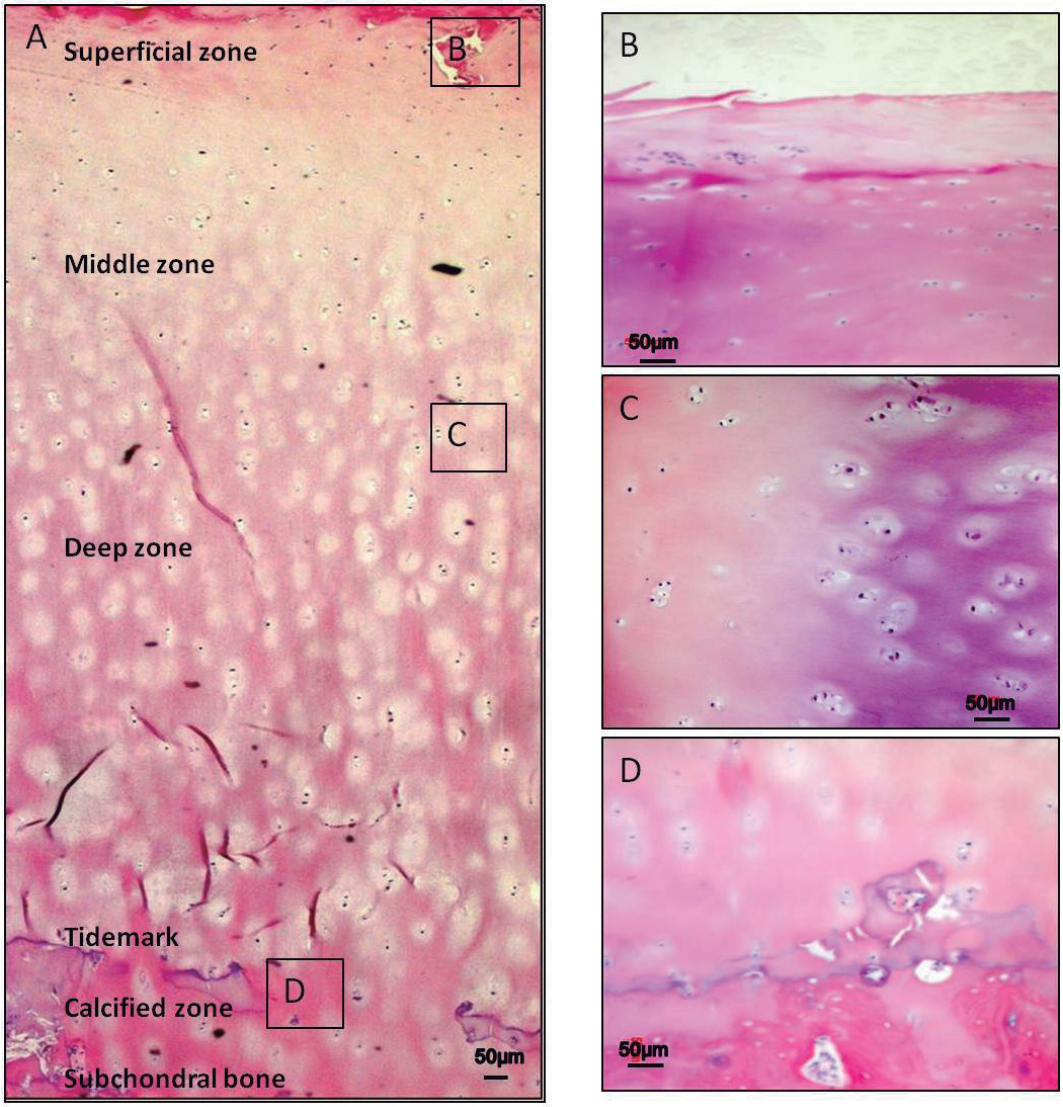

Fig. 1. Articular knee cartilage from Human (male, 60 years old). Hematoxylin and Eosin staining. **A**. Hyaline cartilage layers: superficial zone, intermediate (or middle zone), radial zone (or deep zone) and calcified cartilage (or calcified zone). Tidemark, the border between non-calcified and calcified cartilage. **B.** Magnification of the superficial zone. **C.** Magnification of the middle zone. **D.** Magnification of the tidemark. Scale bars: 50 μm.

2010). Multicellular chondrocyte clusters with large nuclei are found in the superficial zone, and necrotic chondrocytes with pyknotic nuclei in the intermediate and radial zone are found in experimental OA models (Kouri and Lavalle, 2006; Lorenz and Richter, 2006). Histological features of the OA synovial membrane

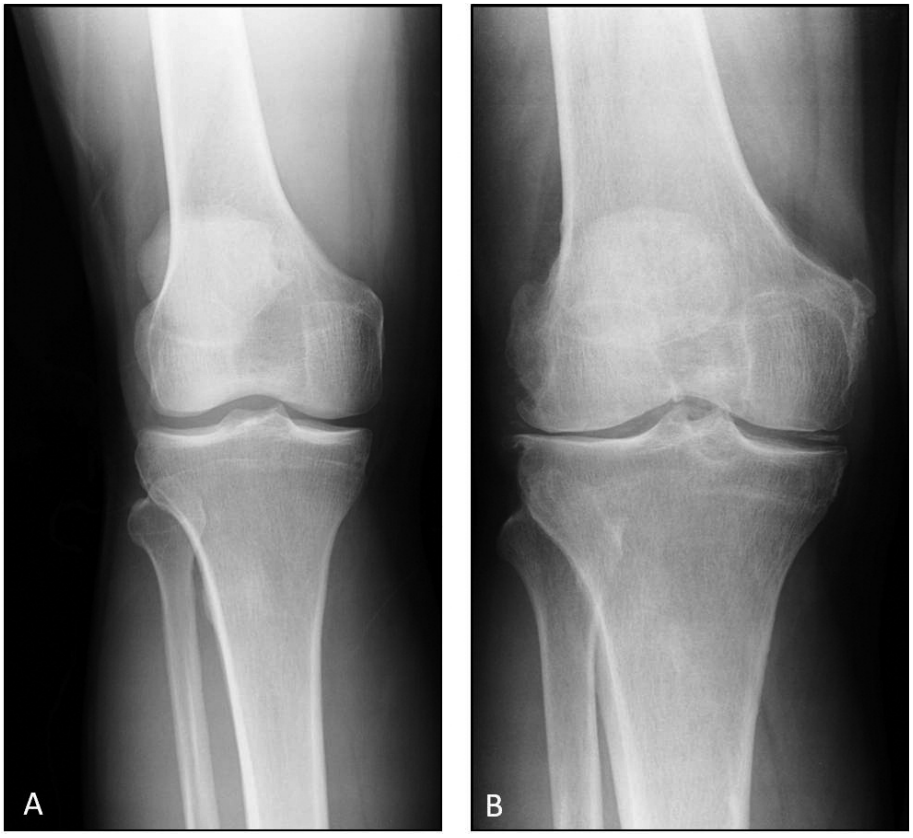

Fig. 2. Xray anteroposterior projection in right normal and osteoarthritic knees from two different adult patients. **A**. Right normal knee. **B.** Right osteoarthritic knee, in the Xray there are radiographically visible changes such as narrowed joint space and thickening of the articular cartilage.

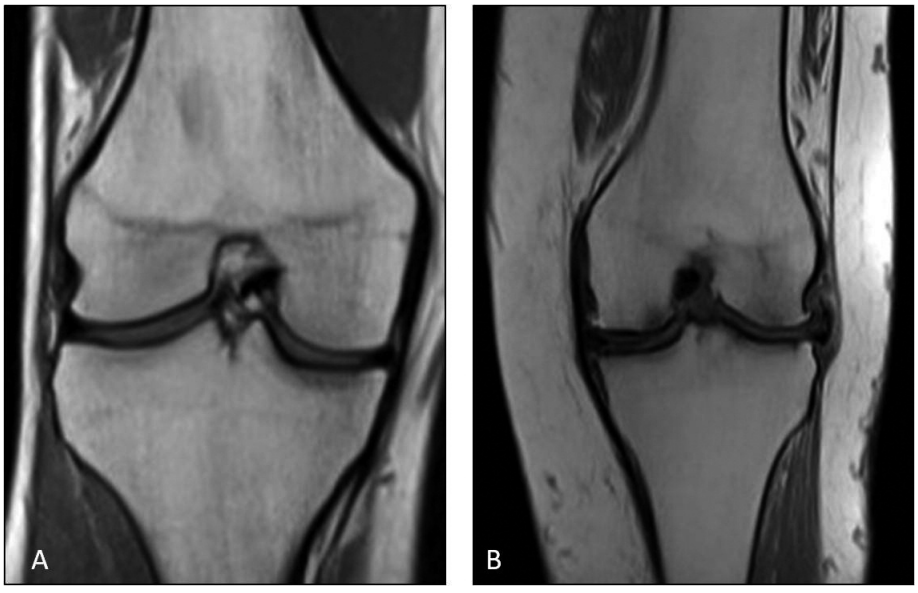

Fig. 3. MRI (magnetic resonance imaging) coronal view in left normal and osteoarthritic knees from two different adult patients. **A.** Left normal Knee. **B.** Left osteoarthritic knee, in which the MRI signal intensity of the menisci is altered, the articular cartilage and the subchondral bone are altered with increased bone density.

include hyperplasia of synovial lining cells, thickening of the synovial membrane, infiltration of inflammatory cells and fibrosis (Kouri and Lavalle, 2006; Pritzker and Aigner, 2010). In advanced stages of OA the cartilage shows signs of complete rupture. The cartilage surface is rough and broken by fissures and cracks, which can reach down to the calcified zone (Veje et al., 2003). Cells are arranged in clusters especially around fissures or disappear completely as the disease progresses. The organization of cartilage is completely disordered and replaced by fibrocartilaginous, scar-like tissue with fibroblast like cells (Miosge et al., 2004) (Fig. 5). In other cases, full-thickness defects develop, where the bone lacks the cartilage completely (Veje et al., 2003). The loss of proteoglycan content reaches the deep zones, until the complete lack of proteoglycan, indicated by the inability of the matrix to stain for safranin O. The tidemark becomes unclear and finally is invaded by blood vessels from the subchondral bone, which penetrate into the calcified zone (Hayami et al., 2003; Lahm et al., 2012). Pannus of various extents can overlay the damaged cartilage tissue, which is described in detail by authors (Shibakawa et al., 2003; John et al., 2007). The extent of damage to the articular cartilage seems to be highly dependent on the joint area, which can be explained by different loading conditions in distinct regions (Ruan et al., 2013). The rate of progression also seems to be related to species and joint localization. Because OA involves progressive loss of the structure and functionality of articular cartilage due to an imbalance between anabolic and catabolic processes in the cartilage tissue, preventive and therapeutic intervention are necessary to improve the regeneration capacities (Schroeppel et al., 2011; Egloff et al., 2012).

Exercise as postoperative rehabilitation

The goal of postoperative rehabilitation exercise program is to restore the full function in patients who

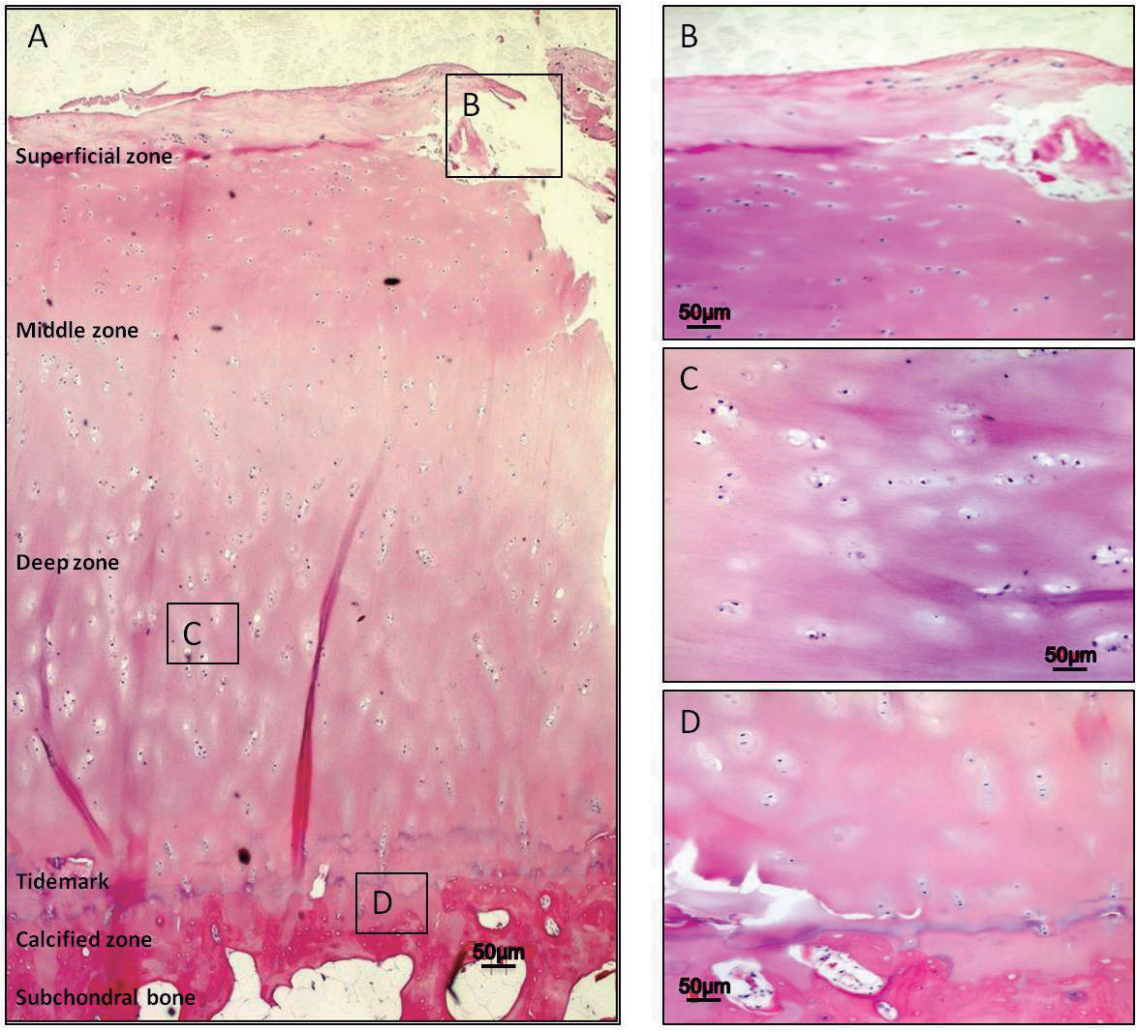

Fig. 4. Articular knee cartilage from Human (female, 65 years old) at early OA stage. Hematoxylin and Eosin staining. Moderate OA cartilage, clear deep fissures in the articular surface, reduction of cells from the superficial, intermediate and deep zone, where chondrocytes are not arranged in columns. The tidemark is not intact in all its extension and the subchondral bone shows fibrillation. **A.** Hyaline cartilage layers: superficial zone, intermediate (or middle zone), radial zone (or deep zone) and calcified cartilage (or calcified zone). Tidemark, the border between non-calcified and calcified cartilage. **B.** Magnification of the superficial zone. **C.** Magnification of the deep zone. **D.** Magnification of the tidemark. Scale bars: 50 μm.

underwent surgical treatment for knee OA, as quickly as possible without overloading the healing articular cartilage. It should be based on the characteristics of the lesion, patient, and surgery. Basic considerations are those related to location, size, depth, and containment of each lesion to create an environment that facilitates the healing process, avoiding deleterious forces to the repair site (Reinold et al., 2006). Previous activities and motivation of the patient should be considered to assure that each patient is successfully involved (Reinold et al., 2006). Surgical procedure should also influence the choice of different exercise rehabilitation programs. Many authors are of the opinion that arthroscopic procedures, such as chondroplasty or microfracture, may resolve faster than procedures with larger incisions and greater tissue involvement, such as osteochondral autograph transplantation (OATS) or autologous chondrocyte implantation (ACI), which require a slower exercise rehabilitation program (Reinold et al., 2006; Mobasheri et al., 2009). Controlled weight bearing and range-of-motion (ROM) are essential to facilitate healing and to prevent degeneration, because immobilization and unloading result in proteoglycan loss in articular cartilage and gradual weakening (Vanwanseele et al., 2002; Waldman et al., 2003; Lahm et al., 2012). Therefore, controlled compression and decompression forces, during weight bearing, nourish the articular cartilage and provide molecular signals necessary to produce an optimal extracellular matrix (Vanwanseele et al., 2002). A force platform is a useful tool in early phases of rehabilitation to perform limited weight-bearing activities in order to facilitate a normal gait pattern and enhance strength, proprioception, and balance (Reinold et al., 2006).

Passive range of motion (PROM) activities are also indicated immediately after surgery in a limited ROM to nourish the healing articular cartilage and prevent the formation of adhesions (Tok et al., 2011). Continuous

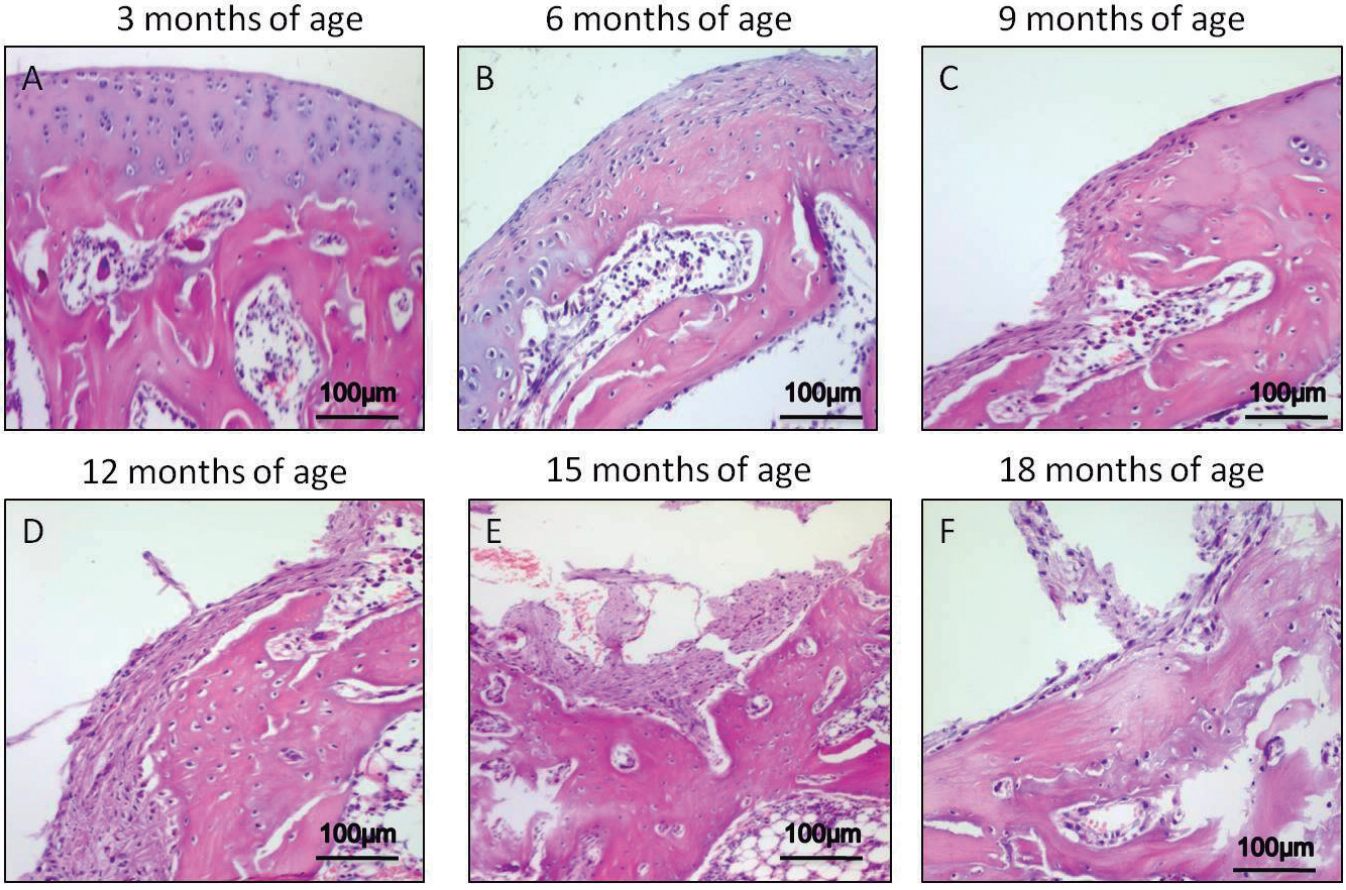

Fig. 5. Articular knee cartilage from rat. Hematoxylin and Eosin staining. **A.** Normal articular knee cartilage from rat (3 months of age). In the superficial zone, cells are flat and small; in the middle and deep zone, cells are organized in columns; the tidemark is evident. **B, C.** Articular knee cartilage from rat (6, 9 months of age) at early OA stage, due to aging. Moderate OA cartilage, the structural alterations included a reduction of cartilage thickness of the superficial and the middle zones. The tidemark is almost intact. **D-F.** Articular knee cartilage from rat (12, 15, 18 months of age) at advanced OA stage, due to aging. Severe OA cartilage, demonstrated deep surface clefts, disappearance of cells from the superficial zone, cloning, and a lack of cells in the intermediate and deep zone, which are not arranged in columns. The tidemark is no longer intact and the subchondral bone shows fibrillation. Cartilage is completely replaced by fibrocartilaginous, scar-like tissue with fibroblast like cells. Scale bars: 100 μm.

passive motion (CPM) has been shown to enhance cartilage healing and long-term outcomes following articular cartilage procedures (Tok et al., 2011). As the lesion heals and symptoms decrease, the ROM, in which exercises are performed, is modified to allow greater muscle strengthening over a greater range of movement (Reinold et al., 2006). With surgical procedures, particularly with the OATS and ACI, because of the large incision and extensive soft tissue trauma, arthrofibrosis can occur and the aim of articular cartilage rehabilitation is to avoid this event (Reinold et al., 2006). This is achieved through the restoration of the full passive knee extension, patellar mobility, and soft tissue flexibility of the knee and entire lower extremity (Reinold et al., 2006). Symptoms, such as pain and effusion, often cause the inhibition of the quadriceps muscle, so electrical muscle stimulation and biofeedback are complementary with the exercise program in order to promote the active contraction of musculature in the acute stage of rehabilitation (Tok et al., 2011). Exercises that strengthen the entire lower extremity should be included as the patient progresses to advanced phases of rehabilitation (Reinold et al., 2006). As the patient returns to functional activities, it is important to increase gradually the amount of stress applied to the treated knee, in order to provide a stimulus for healing to cartilage tissues without causing damage (Reinold et al., 2006). The exercise rehabilitation program following surgical procedures for knee OA is fundamental to the long-term success and functional outcome of patients involved (Reinold et al., 2006).

Exercise as non-pharmacological treatment

In mild to moderate knee OA, pharmacological treatment is indicated primarily to alleviate pain and faulty function of the joint. On the other hand, non-pharmacological treatment, in addition to alleviating symptoms, may also induce a slowing in the progression of knee OA and also avoid the side effects of drugs. In pharmacological treatment, drugs such as topical analgesics, opioid and non-opioid analgesics, non-steroidal anti-inflammatory drugs, intra-articular steroid and hyaluronic acid injections (Zhang et al., 2007) are used. Because drugs often have gastrointestinal side effects, non-pharmacological treatments and alternative medicine are suggested (Schencking et al., 2013). Vitamin supplements, celery extract, fish oil, and garlic extract are some examples of self-medication (Zochling et al., 2004). Alternative medicine includes acupuncture and the use of various herbal agents such as stinging nettle, boswellic acid, and proteins such as glucosamines (Ernst, 2000). Pool therapy, balneotherapy, thermotherapy and hydrotherapy also have beneficial effects on reduction of pain and mobility (Bartels et al., 2007). For example, several studies show that hydrotherapy (alternate cold and warm) has a beneficial effect on cutaneous circulation due to local vasoconstriction followed by reflexive vasodilatation (Silva et al., 2008; Schencking et al., 2013). Hydrotherapy also has positive effects on immuno-regulation, due to an increase in activation of cell-mediated immune reactions (Silva et al., 2008). Hydrotherapy shows improvement in joint mobility with pain reduction and an increase in the quality of life over a period of up to three months (Silva et al., 2008; Schencking et al., 2013). It is clear that non-pharmacological treatment represents a multidisciplinary approach including also instructions for weight loss (Schencking et al., 2013).

The most tested and thus the most suggested non-pharmacological treatment is related to physical activity in the form of a well-defined exercise program. Patients with knee OA often suffer from pain and problems in activities involving the lower limb or prolonged positioning, so exercise should target these specific deficits (Lin et al., 2010). Most studies show that an exercise program, consisting of strengthening exercises with or without range of motion, aerobic exercises or a combination of both, has beneficial effects for both pain and physical function (Fransen and McConnell, 2008; Lin et al., 2010). However, a systematic review, investigating the long-term benefits of exercise, shows that it does not have a significant effect on pain or physical function after 6 months, except when booster sessions are implemented (Pisters et al., 2007). Muscle strengthening, through resistance exercise, increases physical function, decreases pain, and reduces disability (Lange et al., 2008). Resistance exercise often makes use of machines or free weights and includes resistance load, repetitions, velocity of movement and frequency of sessions per week (Vincent and Vincent, 2012). To initiate a resistance exercise program, it is important to assess strength, total knee range of motion, knee pain throughout the range of motion and the patient's access to exercise equipment (Vincent and Vincent, 2012). If access to machines is too expensive, a home-based exercise program could be considered (Jan et al., 2008; Farr et al., 2010; Foroughi et al., 2011). Generally, the exercise program consists of exercise 3 days per week, with 2-3 sets per exercise at 8-15 repetitions per set (Vincent and Vincent, 2012). Resistance loads vary from high to low (Foroughi et al., 2011). Data show that pain decreases by 42%-43%, in a period of 2-9 months of progressive resistance exercise (Jan et al., 2008; Farr et al., 2010). These effects are similar to those achieved from simple analgesia and non-steroidal anti-inflammatory drugs but with much fewer side effects (Zhang et al., 2010). Muscle strength of the knee flexors and extensors increases with resistance exercise (Jan et al., 2008; Foroughi et al., 2011). Isokinetic knee torque can increase more after greater resistance exercise intensity (Jan et al., 2008). These data support that improvements in symptoms and function are directly related to exercise intensity and that higher intensity resistance exercise sustains muscle strength and preserves functionality (Vincent and Vincent, 2012). The initial resistance loads and the joint range of motion for

the different leg exercises should take into account the patient's tolerance (Vincent and Vincent, 2012). During the progression stage, the resistance loads or number of weekly sessions should increase as the patient gains strength and confidence (Vincent and Vincent, 2012). Variety in the exercise program should be provided by using different leg exercises or by substituting free weight exercise (Vincent and Vincent, 2012). Resistance exercise is crucial for some of the mechanisms of knee OA, including muscle strength insufficiency, muscle activation imbalance, aberrant biomechanics and cartilage loading (Vincent and Vincent, 2012). Programs including aerobic exercise activities such as walking, cycling or seated stepper (depending on which is most comfortable and achievable for the patient) have beneficial effects on pain, joint mobility, functional status and respiratory capacity (Mazieres et al., 2008; Bennell and Hinman, 2011). Aquatic exercise for knee OA seems not to have effects regarding walking ability or joint range of motion (Bartels et al., 2007), so it should be an option for exercise prescription in patients with knee OA (Bartels et al., 2007; Bennell and Hinman, 2011). The optimal exercise modality and dosage for knee OA is currently not known (Bennell and Hinman, 2011). Essentially exercise treatment should be established taking into account factors such as age, mobility, co-morbidities and preferences (Bennell and Hinman, 2011). From meta-analyses, beneficial effects for pain and function appear to be higher for land-based exercise than for aquatic exercise and higher for aerobic exercise than for strengthening exercise (Zhang et al., 2010). In overweight patients undergoing dietary-induced weight loss, strength training is important in order to minimize loss of lean muscle mass that worsens muscle weakness (Toda, 2001). A combination of both aerobic training and strengthening exercise is optimal to decrease impairments associated with knee OA (Roddy et al., 2005). Variations in the delivery, content and dosage do not influence outcomes, except that a higher number of sessions leads to greater effects (Lin et al., 2010). The benefits of exercise depend on adherence of patients to the exercise program.

Evidence to date shows that, although exercise has short-term benefits in reducing pain and improving physical function, these benefits may not persist in the long term without adherence to the exercise program (Pisters et al., 2007; Mazieres et al., 2008; Lin et al., 2010). Therefore, strategies to increase long-term adherence to exercise may be necessary to maximize the benefits of exercise for people with knee OA (Lin et al., 2010). Adherence is improved when patients receive attention from health professionals (Mazieres et al., 2008). Self-efficacy is also associated with higher adherence and better outcome (Mazieres et al., 2008). The exercise program should be combined with education and behavioural strategies to promote positive lifestyle change and increase physical activities (Bennell and Hinman, 2011).

Another useful discipline in physical activity is Tai Chi. Tai Chi is a traditional Chinese discipline that enhances balance, strength, flexibility and self-ef?cacy, reduces pain, depression, anxiety and improves physical function in patients with chronic conditions (Wang et al., 2004). Tai Chi should be a treatment especially for older adults with knee OA (Wang et al., 2009). Although Tai Chi has spread worldwide only in the past 2 decades, scientific data support its ef?cacy for knee OA (Lee et al., 2008). The literature shows some positive effects of Tai Chi on pain, functional independence and health-related quality of life in elderly people with knee OA (Wang et al., 2009). Benefits would be mediated by effects on muscle function, muscoskeletal flexibility and mental health (Wang et al., 2009). Significant benefits in the measures of depression and self-ef?cacy are observed in people who practice Tai Chi for a long period (beyond 12 weeks), suggesting that there may be synergy between the physical and mental components of this discipline (Wang et al., 2009). There are several studies testing the effects of Tai Chi in knee OA, but interpretation of results is limited because of low levels of adherence, short follow-up and deployment of varying Tai Chi styles (Brismee et al., 2007). Nevertheless, data show some positive effects on improvements in pain and function (Brismee et al., 2007). Tai Chi may enhance cardiovascular bene?ts, muscular strength, balance, coordination, and physical function, contributing to the reduction of joint pain (Wang et al., 2004). Because the severity of pain is correlated with the degree of muscle weakness (Glass et al., 2013), stronger muscles and better coordination improve the stability of the joints and lessen pain (Wang et al., 2009). Furthermore, data suggest that the mind-body component may in?uence immune, endocrine, neurochemical, and autonomic functioning, leading to improved physical, psychological, and psycho-social well-being and overall quality of life (Wang et al., 2009).

Exercise as prevention

Knee OA has a multifactorial etiology, including trauma, age, obesity, mechanical stress, kinematics, muscular impairments and inflammation that causes cartilage degradation (Kouri and Lavalle, 2006; Lorenz and Richter, 2006; Vincent et al., 2012a; Sinusas, 2012; Egloff et al., 2012), often in correlation between them. It is possible to prevent some of these causes, such as obesity, bad tissue homeostasis in joints and tissue inflammation, adopting some useful changes in lifestyle. Physical activity represents a very good tool for this purpose.

Knee OA is a progressive degenerative disease characterized by deterioration of joints, including loss of articular cartilage, subchondral bone and osteophyte formation (Kouri and Lavalle, 2006; John et al., 2007; Musumeci et al., 2011b,c, 2012a,b). Regular physical activity can decrease bone loss and promote healthy joint

cartilage, improve physical function, reduce some knee OA symptoms and lead to psychological benefits (Callahan et al., 2008). Physical activity can contrast the reduction in fitness, muscular strength and endurance, preventing functional limitations and mitigating their progression and thereby improving quality of life (Kevsor, 2003). The articular joint is a highly complex organ system that requires regular maintenance, and when joints are immobilized a number of negative physiologic consequences result (Cardile et al., 2013; Pichler et al., 2013b; Musumeci et al., 2013e). Hyaluronic acid and lubricin are two major joint lubricants present in the synovial fluid and on the superficial layer of articular cartilage, playing an important role in joint lubrication and synovial homeostasis (Leonardi et al., 2011, 2012a,b). Lubricin is a chondroprotective glycoprotein, which acts as a vital counteragent against aberrant protein and/or cellular adhesion, infiltration and over-proliferation, and serves as a critical boundary lubricant between opposing cartilage surfaces (Musumeci et al., 2011d,e, 2013f). It is recognized to have a major protective role in preventing cartilage wear and synovial cell adhesion, proliferation and reducing the coefficient of friction of the articualr cartilage surface (Schumacher et al., 2005; Musumeci, 2013; Musumeci et al., 2013g,h). Compromising boundary lubrication causes increased friction, load amplification and cartilage damage. Lubricin is involved in several joint diseases and may play a beneficial role against the degradation of articular cartilage (Musumeci et al., 2013f,h). Many studies exist about articular cartilage health, and they highlight that stress deprivation, lack of movement or limb loading results in several articular alterations that do not always recover upon remobilization of the joint (Vanwanseele et al., 2002; Eckstein et al., 2006; Musumeci et al., 2013f,g). Data in the literature examine the effect of physical activity on the knee joint and investigators conclude that physical activity is beneficial to knee joint health (Urquhart et al., 2011). In recent studies, authors reported, and confirmed, the importance of physical activity in conjunction with a particular diet rich in olive oil, typical of the Mediterranean Diet (Catalano et al., 2013; Siniorakis et al., 2013; Kien et al., 2013, Musumeci et al., 2013i), in medical therapy to prevent osteoarthritis disease, in order to preserve the articular cartilage and then the entire joint (Musumeci et al., 2013f,g). The beneficial effects of olive oil have been widely studied and they could be due to its components, which have been shown to possess anti-inflammatory properties (Cicerale et al., 2012; Catalano et al., 2013; Musumeci et al., 2013f,g,h) with phenolic compounds, tocopherol, carotenoids, which possess antimicrobial, antioxidant and anti-inflammatory properties (Cicerale et al., 2012). Phenolic compounds may interact with the inflammatory cascade through their antioxidant action (Berbert et al., 2005). Oleuropein, a polyphenol present in olive oil, inhibits the release of proinflammatory cytokines and chemokines and reduces leukocyte infiltration in the affected joints (Impellizzeri et al., 2011; Musumeci et al., 2013h). Recently, researchers identified molecular events that lead to the destruction and remodeling of joint tissues, including cartilage and bone (Garnero et al., 2000; Schroeppel et al., 2011). Cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and other in?ammatory mediators, are found within the cartilage and are thought to participate locally in cartilage destruction by inhibiting matrix synthesis and stimulating the release of degradative enzymes (John et al., 2007; Chua et al., 2008; Schroeppel et al., 2011). Recent studies demonstrate that low-grade inflammation plays a pathophysiological role in knee OA. The inflammatory cytokine interleukin-1-beta (IL-1-beta) is present in the joint fluids of knee OA patients (Messier et al., 2000; Schroeppel et al., 2011). Severity, mobility, pain, stiffness and radiographic progression may be partly mediated by the level of chronic inflammation in knee OA patients (Messier et al., 2009; Schroeppel et al., 2011). Obese individuals have higher concentrations of inflammatory molecules and this may represent a risk of functional limitation and the start of knee OA (Messier et al., 2009). Indeed, inflammatory mediators can affect muscle function and sensitize nerves leading to increased pain (Bonnet and Walsh, 2005). Studies show that both physical activity and weight loss reduce inflammation (You and Nicklas, 2006, 2008; Musumeci et al., 2013h) and apoptosis in OA (Musumeci et al., 2013f). A dietary intervention producing a 5% weight loss significantly reduces acute-phase reactant C-reactive protein (CRP), IL-6 and tumor-necrosis-factor-alpha (TNF-alpha) concentrations (Nicklas et al., 2004). The Osteoarthritis Research Society International (OARSI) has strongly recommended exercise as part of the standard of care for patients with knee OA (Zhang et al., 2008).

Obesity is one of the major risk factors for knee OA. Several pathways contribute to the onset of knee OA. In relation to obesity, specific mechanisms include loss of muscle mass and strength, mechanical stress, and systemic inflammation (Vincent et al., 2012). An excess of adipose tissue compresses load-bearing joints and creates conditions for tissue inflammation in joints (Vincent et al., 2012b). Obese individuals alter gait patterns and adopt different body transfer patterns to compensate for muscle weakness and instability due to the fact that fat mass increases but the volume of muscle mass remains relatively low and inadequate to deal with loads (Vincent et al., 2012b). In these conditions, joint misalignment may occur (Hinman et al., 2010). During gait, obese adults exert greater forces, and as obesity worsens this compensatory strategy increases, and minimizing these loads is attempted by shortening stride length. Studies suggest that adjusting gait mechanics without reducing body weight does not eliminate the detrimental effects of obesity on the lower extremity (Stephen and Messier, 2010). Indeed, in obese

individuals, intramuscular fat is strongly present and this is associated with elevated systemic levels of proinflammatory molecules (Vincent et al., 2012b). As obesity worsens, proinflammatory molecules induce a self-propagating process of muscle catabolism and loss of strength (Schrager et al., 2007). The cumulative effects of excessive body fat, mechanical loading, aberrant joint motion and inflammation, contribute to the knee OA pathophysiology (Sowers and Karvonen-Gutierrez, 2010). Overall obesity leads to adverse modifications in structure and properties of articular cartilage (Vincent et al., 2012b). Weight loss, through exercise and dietary modification, reduces the load on the knee and lowers pro-inflammatory cytokine activity (Messier et al., 2009), improves joint pain and physical function, preventing the onset of knee OA or combating knee OA symptoms and disability (Vincent et al., 2012b). In obese individuals, caloric restriction combined with an appropriate caloric distribution should be the focus of any dietary intervention (Stephen and Messier, 2010). Obesity is the most modifiable risk factor for knee OA and weight loss should be part of the standard-of-care for overweight and obese persons (Stephen and Messier, 2010).

Conclusion

In the present narrative review, physical activity is considered as an excellent instrument to combat knee OA which, as is well known, is a debilitating disease to varying degrees depending on the stage of the disease. In the most severe cases of knee OA, surgical intervention by chondroplasty, microfracture, OATS and ACI, is necessary, to which it is good and essential practice to associate a rehabilitation exercise program in order to restore full function of the involved joint.

The most common condition is, however, mild to moderate knee OA that is still quite debilitating, in relation to both pain and functionality and to the fluent gait of the patient. In this case, non- pharmacological treatment is strongly suggested.

In particular, physical activity proved to be very useful for both pain mitigation and function of the knee joint with an increase in both physical and psychological well-being of considerable intensity.

Finally, physical activity is also a prevention tool, especially when combined with a proper diet, since a major cause of the onset and progression of knee OA is represented by excess weight often followed by obesity. Furthermore, physical activity is very useful for both the good maintenance of joint tissue homeostasis and the control of possible inflammatory processes in the joint caused by various accidental (or not) conditions.

With this narrative review, we wished to underline the importance of exercise in the treatment and prevention of knee OA as an effective, economical and accessible tool to everyone, analyzing the data of the literature published up to now which strongly supports this position.

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