CE

Osteoarthritis

Detection, Pathophysiology, and Current/ Future Treatment Strategies

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Osteoarthritis (OA) is a disease of the joint, and age is the major risk factor for its development. Clinical manifestation of OA includes joint pain, stiffness, and loss of mobility. Currently, no pharmacological treatments are available to treat this specific joint disease; only symptom-modifying drugs are available. Improvement in imaging technology, identification of biomarkers, and increased understanding of the molecular basis of OA will aid in detecting the early stages of disease. Yet the development of interventional strategies remains elusive and will be critical for effective prevention of OA-associated joint destruction. The potential of cell-based therapies may be applicable in improving joint function in mild to more advanced cases of OA. Ongoing studies to understand the basis of this disease will eventually lead to prevention and treatment strategies and will also be a key in reducing the social and economic burden of this disease. Nurses are advised to provide an integrative approach of disease assessment and management in OA patients' care with a focus on education and implementation. Knowledge and understanding of OA and how this affects the individual patient form the basis for such an integrative approach to all-round patient care and disease management.

Osteoarthritis (OA) is the most common form of arthritis that causes joint pain, joint stiffness, and loss of mobility in older adults. Based on 2007–2009 data from the National Health Interview Survey (Dillon, Rasch, Gu, & Hirsch, 2006) in the United States, 50 million (22%) adults have self-reported doctor-diagnosed arthritis. According to 2003 National Health Interview Survey data (Hootman & Helmick, 2006), 67 million (25%) adults aged 18 years or older are projected to have doctor-diagnosed arthritis by the year 2030 and an estimated 37% (25 million adults) of those will report arthritis-attributable activity limitations. Osteoarthritis is also known to affect more women than men after the age of 50 years (Lawrence et al., 1998). The economic burden of OA is estimated to be $128 million per year (2% of gross domestic product) ("National and state," 2007). Currently, only symptom-modifying treatments are available.

Osteoarthritis can affect one or more than one joint at the same time. The weight-bearing joints in the lower limbs (hips and knees) are affected in OA. Other joints such as the distal interphalangeal, proximal interphalangeal joints, and the metacarpophalangeal joint of the thumb are also affected (Krug, 1997). Osteoarthritis is a degenerative joint disease that eventually leads to failure of the joint by progressive degeneration of articular cartilage (AC) also known as hyaline cartilage and surrounding tissue including subchondral bone, ligaments, periarticular muscles, menisci, local fat pads, nerves, or synovium (Brandt, Dieppe, & Radin, 2009; Dieppe, 2011; Loeser, Goldring, Scanzello, & Goldring, 2012) by a combination of mechanical and molecular mechanisms (Loeser, 2006). Because of the damage and loss of cartilage that otherwise covers the bones, the bones rub against each other, causing pain, stiffness, and immobility.

The second most common form of arthritis is rheumatoid arthritis (RA; Firestein, 2008; O'Dell & Mikuls, 2011). Rheumatoid arthritis is an autoimmune disease that causes inflammation of joints and affects the whole body causing fatigue and a feeling of sickness (O'Dell, 2004). Unlike OA, RA can affect organs other than joints and can occur in any age group. Similar to OA, there is no cure available; however, disease-modifying therapies have shown to be effective (O'Dell, 2004).

In this review, we focus on knee OA, whereas excellent overviews on hip OA can be found by a number of recent reviews (Adatia, Rainsford, & Kean, 2012a, 2012b; Bierma-Zeinstra & Koes, 2007; Lapaj, Markuszewski, & Wierusz-Kozlowska, 2010; Veenhof, Huisman, Barten, Takken, & Pisters, 2012; Vissers et al., 2011).

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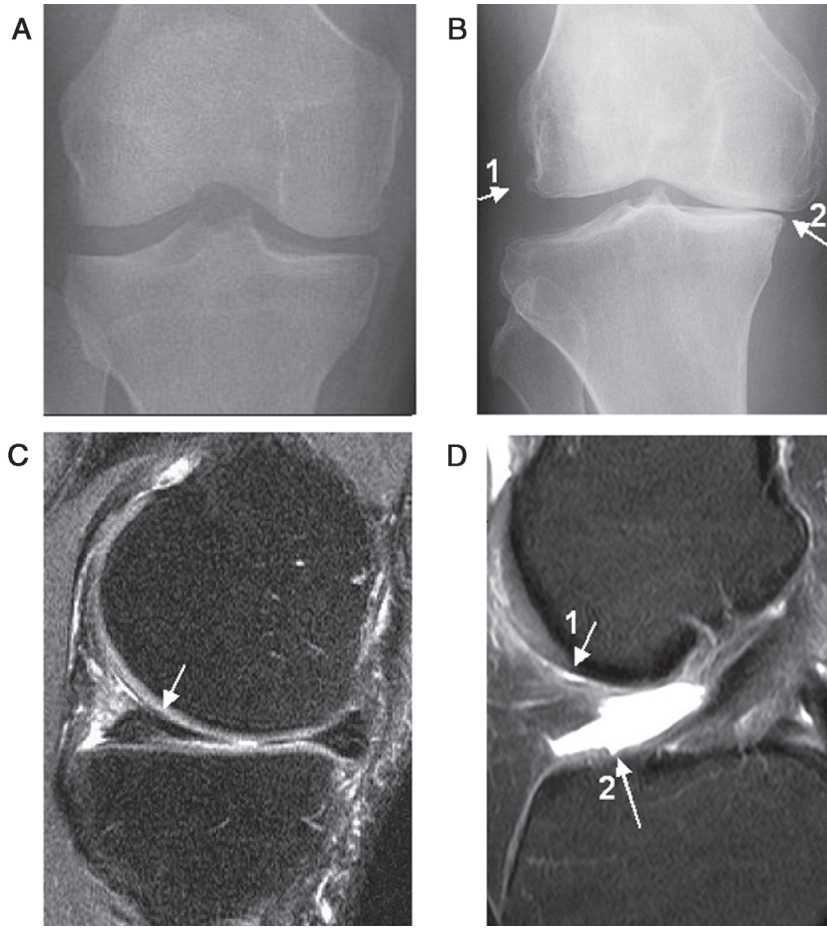

FIGURE 1. Radiographic and magnetic resonance imaging of normal and osteoarthritis (OA) knee joints. (A) Radiograph of a normal healthy knee and (B) radiograph of a knee with advanced OA with typical joint space narrowing. Arrows point to (1) osteophyte formation and (2) joint space narrowing (C). Magnetic resonance imaging of a normal knee. Arrow pointing to healthy cartilage around the rim and (D) OA knee. Arrow pointing to (1) thinning of cartilage and (2) excess synovial fluid in the joint space.

Pathophysiology and Diagnosis of OA

The onset of OA is marked by morphological changes in the otherwise-smooth and well-lubricated AC that lines the joint surfaces. Pathological changes in OA include loss of AC, subchondral sclerosis, and marginal osteophytes (bony projections).

Osteoarthritis is diagnosed pathologically, radiographically, or clinically. Radiographically, osteoarthritis is defined using the Kellgren-Lawrence grading scheme and a standard atlas as a template. This system grades OA into five levels from 0 through 4 on the basis of presence of osteophytes, joint space narrowing, cysts, deformity, and sclerosis (Kellgren & Lawrence, 1963) (see Figure 1). Magnetic resonance imaging (MRI) is also emerging as a visual diagnostic method more sensitive than conventional radiographs (Day et al., 2004; Hunter & Felson, 2006; Kawcak, Frisbie, Werpy, Park, & McIlwraith, 2008; Schneider et al., 2011). Magnetic resonance imaging sequences are capable of detecting changes in water and collagen content that are known to be associated with degenerative changes in OA (Eckstein & Glaser, 2004; Kornaat et al., 2005; Peterfy et al., 2004) (see Figure 1 and Table 1). Although OA is largely noninflammatory in nature, as compared with RA, high sensitivity assays for detecting C-reactive protein indicate presence of inflammation in OA (Saxne, Lindell, Mansson, Petersson, & Heinegard, 2003). Clinical diagnosis includes pain and stiffness in the joints and loss of mobility in the absence of systemic presentations such as fever. The source of pain could be from vascular regions such as subchondral bone, synovium, periosteum, ligaments, or muscle but not cartilage because it is avascular and lacks a nerve supply (Creamer & Hochberg, 1997; Goncharov, 2011).

Molecular Basis of OA

Over many decades, researchers have been trying to understand OA at the cellular and molecular levels. At the molecular level, the AC is composed of chondrocyte cells embedded in a complex meshwork of extracellular matrix (ECM) proteins principally collagen type II, proteoglycans with associated binding proteins like link protein, laminin, fibronectin to name (etc) to name a few, and water. Collagen fibrils give AC its tensile strength, while collagens, together with proteoglycans, bear load and resist compression (Wang et al., 2011). The AC has robust mechanical properties but poor capacity for

Table 1. Charge-Based Imaging Methods

Method	Description	Reference
MRI method of T2 mapping and T1ρ	Detect early biochemical changes in cartilage before joint pain and degeneration	Li et al. (2007)
Delayed gadolinium-enhanced MRI imaging (dGEMRIC)	Evaluate the proteoglycan content of cartilage, thereby to assess its macromolecular structure	Burstein, Gray, Mosher, and Dardzinski (2009)
Sodium-23 MR spectroscopy	Assess the degenerated cartilage, decreasing sodium-23 with loss of negatively charged proteoglycans.	Biswal, Resnick, Hoffman, and Gambhir (2007)
Cathepsin-B sensitive near-infrared fluorescent probes	Detect matrix-degrading enzymes released during the process of cartilage degradation.	Biswal et al. (2007)

repair, most likely due to its avascular nature. Chondrocytes respond to various biochemical and biomechanical stimuli and produce either anabolic factors (tissue maintenance) or catabolic factors (tissue degrading/remodeling). Anabolic factors include bone-morphogenetic proteins and growth factors that promote new ECM to be formed, whereas catabolic or proteolytic enzymes come under the group of matrix metalloproteinases (MMPs) and aggrecanases that degrade the ECM. Under homeostatic conditions, anabolic and catabolic events are regulated by tissue inhibitors of metalloproteinases. At the molecular level, an imbalance between anabolic and catabolic factors leads to excessive matrix degradation (Kirkwood, 2005). Pathways that lead to AC degradation in OA consist of chondrocyte activation, abnormal differentiation, ECM degradation, and cell death (M. K. Lotz & Carames, 2011). During chondrocyte activation, the resting state of chondrocytes changes to a proliferating one and leads to the formation of cell clusters and to a response that results in matrix remodeling, cartilage degradation, and calcification (Goldring & Marcu, 2009; see Figure 2). The degraded ECM protein products can cause further ECM destruction through activation of inflammatory cytokines, chemokines, and MMPs

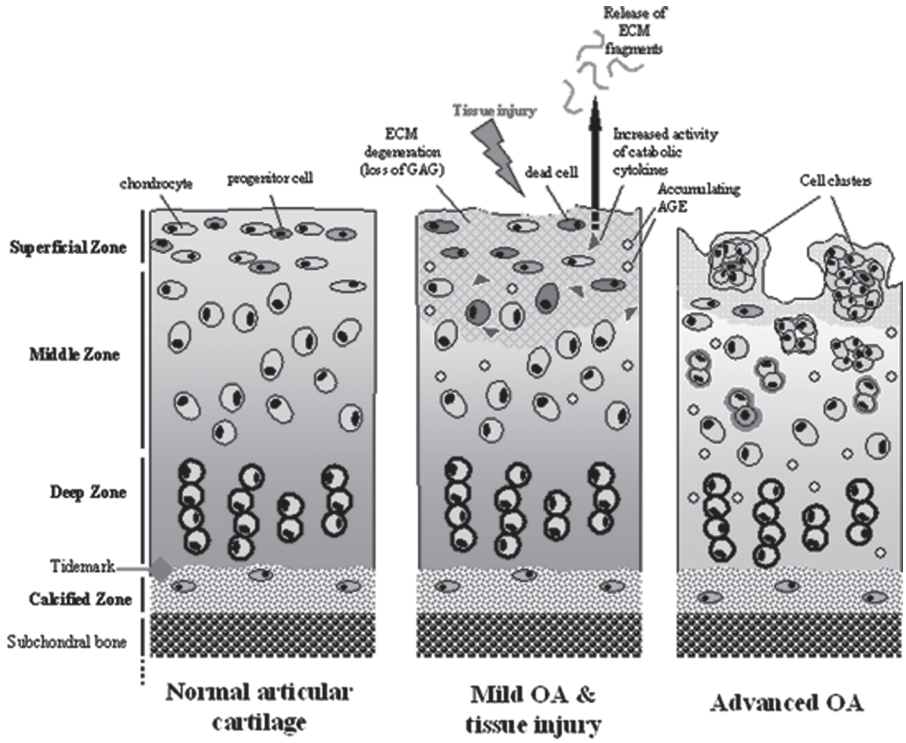

Figure 2. Overview of cartilage structure and changes that occur during aging, after injury, and mediators of osteoarthritis (OA). In normal articular cartilage, the extracellular matrix (ECM) is surrounded by collagen type II and glycosaminoglycans (GAG). Cartilage progenitor cells are located predominately in the surface (superficial zone) aid to maintain tissue surface integrity and the tissue as a whole. As a consequence of normal aging, a natural loss of cells and an accumulation of advanced glycation end products (AGE) alter the tissue's mechanical properties and predispose the tissue to injury. This leads to increased cell death and a homeostatic imbalance that leads to increased catabolic mediator activity and degeneration of the ECM. Progression of this leads to loss of more cells, tissue ECM, and final cartilage destruction. A hallmark of late OA is the formation of cell clusters containing cells that indicate a hopeless attempt of tissue regeneration. Strategies that harness and properly direct this regenerative capacity in this challenging environment may be one means for successful cell-based tissue regeneration.

Table 2. Biomarkers

Biomarker	Description	Reference
Urinary C-terminal cross-linked telopeptide of type II collagen (uCTX-II)	A biomarker that correlates with osteophytes in the body	Patra and Sandell (2011)
Ratios of serum type II collagen cleavage neoepitopes (sC2C) and uCTX-II to C-propeptide of type II procollagen (sCPII)	Shown to be high in early OA	Patra and Sandell (2011)
Serum type II collagen cleavage epitope (CIIM)	Higher in mild to severe OA	Ishijima et al. (2011)
Changes in serum tumor necrosis factor alpha levels	Shown to be associated with joint space narrowing	Denoble et al. (2011)
Soluble receptor for advanced glycation end-products (sRAGE) levels	Shown to decrease with OA advancement	Bierhaus, Stern, and Nawroth (2006)
Ratios of three amino acids (BCCAs) to histidine	Thought to increase in serum with collagen breakdown due to OA	Zhai et al. (2010)
V65 vitronectin fragment	Recently identified and its role is under study	Zhai et al. (2010)
c3f peptide	Recently identified and its role is under study	Zhai et al. (2010)
Connective tissue activating peptide III	Recently identified and its role is under study	Zhai et al. (2010)

(Fichter et al., 2006; Pulai et al., 2005). Biochemical changes related to aging can also cause cartilage turnover similar to that occurring in OA (refer to the Aging section under the Systemic Risk Factors for OA section).

Additional Detection Techniques

A number of imaging methods are being developed to detect changes in the composition of joint tissues including MRI and near-infrared fluorescent probes (see Table 1). During the progression of cartilage degradation, a number of products are released from the cartilage ECM or cytokines are released by other joint tissues. These products have been investigated as biomarkers to detect and monitor OA conditions including type II collagen cleavage neoepitopes, vitronectin and amino acids, as well as changes in the release of soluble receptor for advanced glycation end-products and the cytokine tumor necrosis factor alpha (see Table 2).

Risk Factors

The risk factors for knee OA are numerous. Systemic factors that are largely immutable include aging, genetics, and gender. Among the identified local risk factors, the ones that can be most easily modified consist of reducing weight (obesity), preventing injury (acute or repetitive stress), or correcting the mechanical alignment of the limbs.

Systemic Risk Factors for OA

Aging

Although a close correlation has been observed with advancing age and occurrence of OA (Felson et al., 2000; Felson & Zhang, 1998; Lawrence et al., 2008), radiographic and symptomatic changes associated with aging do not occur in the AC of all individuals (Temple-Wong et al., 2009). During the process of aging, an imbalance between the catabolic and anabolic processes occurs in all tissues (Kirkwood, 2005). Aging-related changes in cells and ECM are a precursor for initiation of OA (M. Lotz & Loeser, 2012). Although aging is a significant risk factor for OA, not all aged joints develop the disease. Figure 3 displays the spectrum of joint states in normal young joints, normal aging, mild OA, and one of severe joint destruction, whereas Figure 4 shows the histology micrographs of cartilage sections corresponding to the same spectrum.

Advanced glycation end-products (AGE) are the products of uncontrolled, nonenzymatic glycation, and oxidation reaction between proteins and sugars, and accumulate in the AC as a part of aging and make the tissue brittle (Loeser, Im, Richardson, Lu, & Chubinskaya, 2009). Fragments of collagen and fibronectin are also formed because of aging (Loeser et al., 2009). These fragments can induce production of inflammatory cytokines and MMPs to continue ECM destruction and also activate innate immune responses (Fichter et al., 2006; Homandberg, Wen, & Hui, 1998; Pulai et al., 2005) or the classic complement pathway (Heinegard & Saxne, 2011). The combination of changes in the mechanical properties of the cartilage tissue, the procatabolic environment, and the innate low capacity for self-repair leads to a tissue that is unable to withstand normal joint loading, which gradually leads to total joint failure.

Genetics

Several studies have shown the inherited nature of OA. Studies conducted on twins and families have shown between 50% and 65% of OA to be genetically linked with a larger incidence occurring for hip and hand OA compared to knee OA (Felson & Zhang, 1998; Palotie et al., 1989; Spector, Cicuttini, Baker, Loughlin, & Hart, 1996). A genomewide association study (Kerkhof et al., 2010) showed that a single mutation, also known as single nucleotide polymorphism on chromosome 7q22, was associated with a 30% higher risk of knee OA and a 1.14-fold higher occurrence of knee and/or hand OA. Kizawa et al. (2005) reported an aspartic acid repeat polymorphism in the protein known as asporin that increases the susceptibility to OA. The D14 allele of aspartic acid repeat polymorphism was found to be

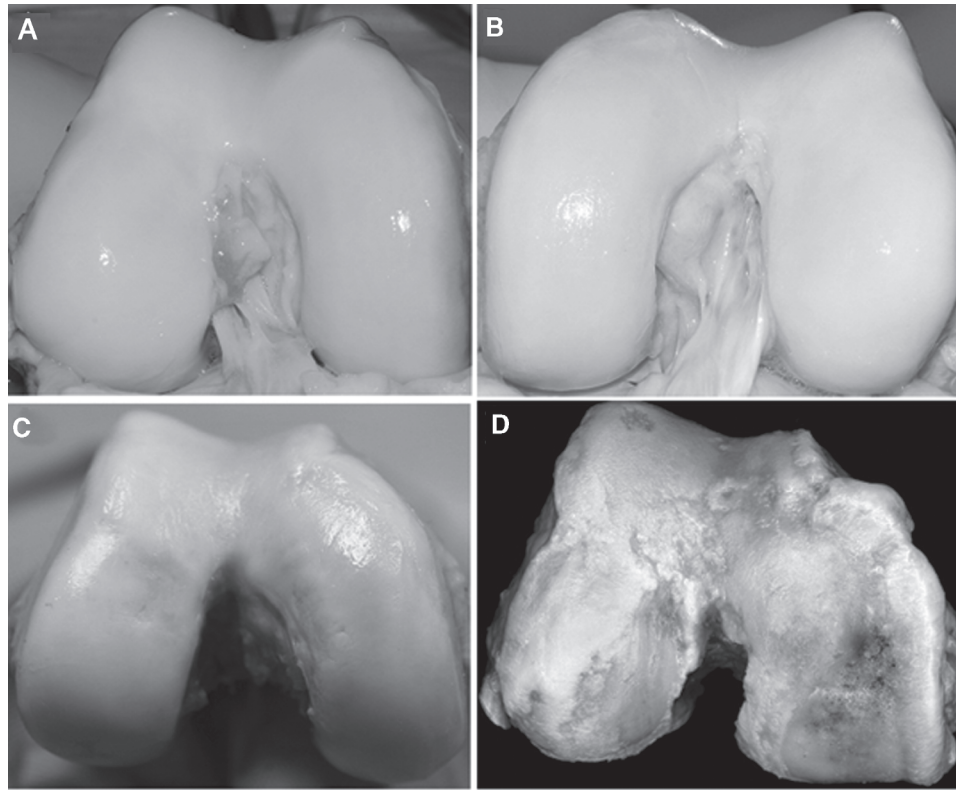

Figure 3. Macroscopic images of human knee joints (femoral condyles). (A) Normal young cartilage (24 years old); (B) normal aged cartilage (61 years old); (C) mildly degenerated cartilage surface (63 years old); and (D) severely degenerated cartilage surface (89 years old).

overrepresented relative to the common D13 allele, and its frequency increases with disease severity in both knee and hip OA.

Gender and Other Risk Factors

Statistically women after the age of 45 years are twice as likely to have OA than men (Hart, Doyle, & Spector, 1999). Some studies show that estrogen and estrogen receptor modulators have a chondroprotective effect (Christgau et al., 2004; Felson & Nevitt, 1998; Nevitt et al., 1996). Occurrence of knee OA has been observed to be higher in postmenopausal women than in premenopausal women (Felson et al., 1995; Wilson, Michet, Ilstrup, & Melton, 1990), which could be attributed to the loss of cartilage protective role of estrogen (Hudelmaier et al., 2001). Other factors identified for OA include race, congenital conditions, and diet (for details, please refer to Y. Zhang & Jordan, 2010).

Local Risk Factors

Obesity

Obesity is one of the potent risk factors for knee OA (Felson et al., 2000). Weight loss has been associated with a decreased risk of radiographic and symptomatic knee OA (Felson, Zhang, Anthony, Naimark, & Anderson, 1992), reduced pain (Christensen, Bartels, Astrup, & Bliddal, 2007; Messier et al., 2004), and improved physical function (Christensen et al., 2007). One of the outcomes of weight loss is reduced mechanical load on the entire knee joint. A possible role of metabolic factors such as insulin resistance and adipose-derived hormones such as leptin in the progression of OA in obese population is reviewed in more detail elsewhere in the literature (Eaton, 2004).

Injury/Surgery

Knee injury or fracture that causes structural damage to the knee tissues predisposes the knee to OA in the long run. A study found that meniscal tissue damage was present in 82% subjects who had radiographic knee OA whereas only in 25% who had no OA (Englund et al., 2008). Another study published in 2010 reported that ruptures in anterior cruciate ligaments and torn menisci increased the risk of narrowing joint space, osteophyte formation, and defects in cartilage. The study also concluded that surgical removal or menisectomy did not reduce the risk of developing OA (Huetink, Nelissen, Watt, van Erkel, & Bloem, 2010). One significant consequence of joint injury is cell death, which is a known major contributing factor to the development of posttraumatic OA (Grogan & D'Lima, 2010). Preserving cell viability following traumatic injury has been shown to prevent the onset of OA in animal models (Blanco, Guitian, Vazquez-Martul, de Toro, & Galdo, 1998; D'Lima, Hermida, Hashimoto, Colwell, & Lotz, 2006; Hashimoto, Ochs, Komiya, & Lotz, 1998; Kuhn, D'Lima, Hashimoto, & Lotz, 2004) and is a prime target for future intervention strategies in the clinic.

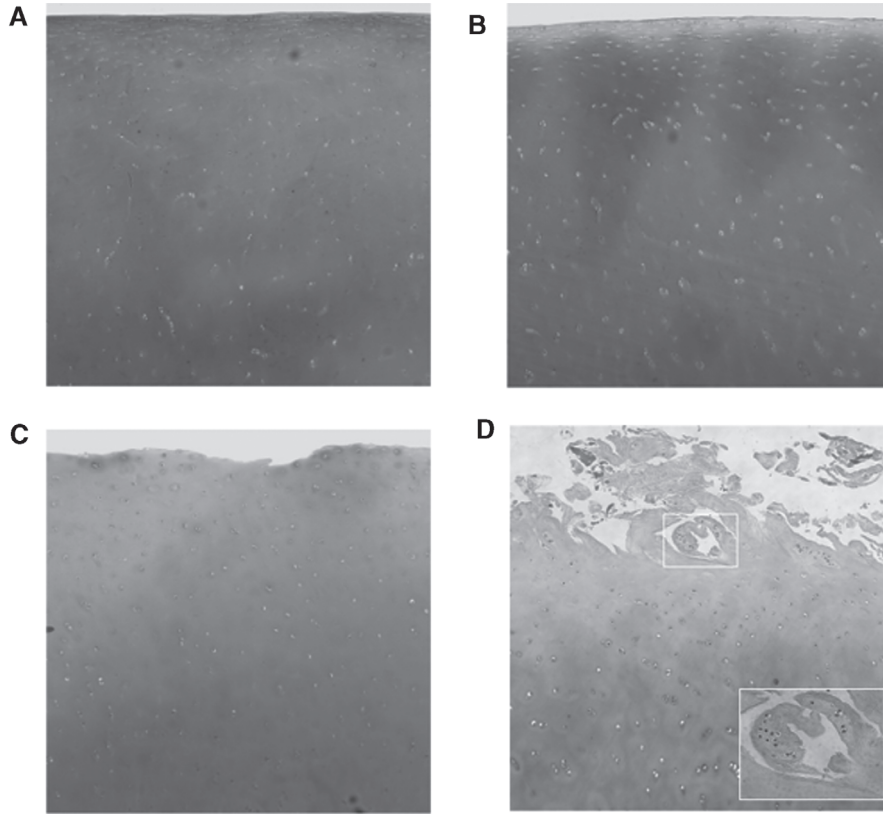

FIGURE 4. Histology micrographs of cartilage sections derived from human knee joint (Safranin O stain). (A) Normal young cartilage (24 year old) and (B) normal aged cartilage (61 years old). Typical staining profile showing uniform Safranin O stain throughout the depth of tissue, with low staining at the immediate surface (superficial zone); (C) mildly degenerated cartilage surface (51 years old). Loss of Safranin O stain and reduced cell density; (D) severely degenerated cartilage surface (89 years old) with severe loss of Safranin O stain, marked fibrillation, fissures, and cell clusters (see the inset). (Magnification 10×.)

Repetitive Stress Injury

Repetitive use of joints based on occupation or activities, for example, lifting at least 55 pounds regularly, kneeling, and squatting, has shown to pose a two times higher risk of developing OA (Felson et al., 1991). Certain types of sports that require repetitive activities have also shown to be a risk factor for OA in a study that found a higher prevalence of knee OA in male elite athletes than expected (Tveit, Rosengren, Nilsson, & Karlsson, 2012).

Mechanical Alignment

According to a study published online in 2010 involving 2713 volunteers who already had arthritis or were at risk of OA, varus knee alignment (bow-legged deformity) and not valgus (knock-knee deformity) had an increased risk of OA development. Varus knee alignment increases medial tibiofemoral load, whereas valgus knee alignment increases lateral tibiofemoral load (L. Sharma et al., 2010).

OA Treatment

So far no cure is available for OA. The current treatments available focus on management of pain for symptomatic relief and management of certain risks such as weight reduction combined with exercise, injury prevention, or correction of malalignment to slow down the progression of OA. Research in the field of disease-modifying aspects of OA is ongoing and is outlined later.

Pain Management and Functional Improvement

Paracetamol is most commonly used in symptomatic OA treatment per international guidelines for pain management (Jordan et al., 2003; W. Zhang et al., 2005) but may not be effective in alleviating stiffness and improving mobility (Towheed et al., 2006). Nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2 (COX-2) inhibitors, have been shown to alleviate pain and improve function (Bannwarth, 2006), yet because of the gastrointestinal complications and cardiovascular risks associated with conventional NSAIDs and COX-2 inhibitors, respectively, these are not advised for long-term OA treatment. Topical NSAIDs do not have the adverse effects of oral ones and have been recommended for OA treatment (W. Zhang et al., 2010). Cardiovasular implications of COX-2 selective inhibitors are reviewed in an article by McGettigan and Henry (2006).

Chondroitin Sulphate and Glucosamine

Conflicting results have been reported regarding the efficacy of glucosamine and chondroitin sulphate therapies.

Glucosamine and chondroitin sulphate alone or in combination did not show significant pain reduction or functional improvement in one study (Clegg et al., 2006). But the Cochrane review found an improvement in pain and function by glucosamine therapy (Towheed et al., 2005). Another study has shown that glucosamine, along with physical training, can alter cartilage turnover as indicated by serum cartilage oligomeric matrix protein and urinary c-terminal telopeptide of type II collagen levels (Petersen et al., 2010). In a clinical trial using glucosamine sulphate, no significant joint space narrowing was observed using MRI as compared with placebo (Pelletier, Martel-Pelletier, & Raynauld, 2006).

Intra-articular Injections

Intra-articular corticosteroid injections have been shown to reduce pain and inflammation (Bellamy et al., 2005) and have been shown to be safe in a 2-year study without adverse effects (Bellamy et al., 2006). Data on efficacy of intra-articular injections of hyaluronic acid for reducing pain and improving function are inconsistent (Bellamy et al., 2005); however, hyaluronic acid may have a positive effect on reducing joint pain and improving function in OA.

Surgical Approaches

The knee joint has three compartments, the patellofemoral (between the knee cap and the thigh bone), the medial tibiofemoral joint (the inside of the knee), and the lateral tibiofemoral (outside of the knee). Osteoarthritis can cause wear in any or all of these compartments. Total joint or total knee arthroplasty (TKA) replaces all of the three compartments in the knee OA joint, whereas unicompartmental surgery is carried out on a single compartment (most commonly the medial tibiofemoral compartment). Minimally invasive surgery is a newer surgical approach that uses special retractors and guides to perform arthroplasty through an incision that is typically less than half the size of that used in conventional arthroplasty. The benefit of minimally invasive surgery is reduced postoperative pain and faster recovery. Knee arthroscopy is a minimally invasive outpatient procedure to repair meniscus or ligaments. Arthroscopic lavage and debridement are not effective in changing the course of OA (Kirkley et al., 2008; Lutzner, Kasten, Gunther, & Kirschner, 2009).

A number of biological-based repair strategies have been used in the clinical setting, whereas a number are still undergoing development in the laboratory.

The microfracture (MF) procedure surgically creates holes into the subchondral bone to induce bleeding so that stem cells from the bone marrow can migrate into the cartilage defect to form a fibrocartilagenous tissue repair. The benefits with this procedure are short term because this tissue has limited weight-bearing capacity due to the poor mechanical properties of fibrocartilage and a decline over time is observed, more so in athletes due to the type of activities involved (Mithoefer, McAdams, Williams, Kreuz, & Mandelbaum, 2009).

In 1994, Brittberg et al. (1994) introduced the first cell-based cartilage repair strategy called autologous chondrocyte transplantation or also referred to as autologous chondrocyte implantation (ACI). In this procedure, chondrocytes are harvested from non–load-bearing areas of the knee, enzymatically isolated, cultured, and implanted back in the knee of the patient. Autologous chondrocyte implantation has shown better results than MF (Saris et al., 2009). Matrix-induced autologous chondrocyte implantation (MACI) is the next-generation ACI technique, in which the harvested chondrocytes are grown on a collagen membrane ex vivo and then implanted in the patients. Autologous chondrocyte implantation and MACI have shown to form partly hyaline-like cartilage and partly fibrocartilage formation (Bartlett et al., 2005; Moriya et al., 2007). Although MACI is approved for clinical use in Europe, it is not yet approved by the US Food and Drug Administration.

Another generation of the ACI technique involves the use of three-dimensional scaffolds. Recently chondrocytes embedded in three-dimensional bioresorbable gel scaffolds have shown positive results even four years after graft implantation (Kreuz, Muller, Ossendorf, Kaps, & Erggelet, 2009).

Osteochondral autograft transplantation is another procedure that involves harvesting osteochondral plugs (cartilage and bone) from non–weight-bearing areas of the knee to implant in the defect. This procedure can be carried out either using autologous grafts (mosaicplasty) or from cadavers (Choi, Potter, & Chun, 2008). It is a minimally invasive and laboratory-independent procedure and follow-up studies have shown hyaline cartilage and healing (Chow, Hantes, Houle, & Zalavras, 2004; Hangody, Feczko, Bartha, Bodo, & Kish, 2001).

Osteotomy is a procedure that is performed to correct for varus or valgus deformities of the knee. In this procedure, the load on the worn-out compartment of the knee is shifted to the unworn compartment by cutting away a wedge of a bone from the damaged compartment of the knee joint. TKA have a finite life span because these wear out with time and hence osteotomy is generally carried out in younger patients allowing them to postpone TKA by 8–10 years.

Role of Nurses in OA Assessment and Management

Nurses are advised to carry out an integrative approach in OA patients' care. This care consists of disease assessment and management with a focus on educating patients on OA and its implications on their daily lives (Porcheret, Jordan, & Croft, 2007), exercise and dietary weight-loss consultation (in case of obese patients), injury-prevention advice (in case of activities involving acute or repetitive stress), and coordination with other departments for physical therapy, and psychological support (Hill, Lewis, & Bird, 2009; McDonald & Fedo, 2009; Porcheret et al., 2007). Self-reporting tools such as the Health Assessment Questionnaire, and the Medical Outcomes Study Short Form 36-Item Health Survey, and Western Ontario and McMaster Universities Osteoarthritis Index can be helpful to assess progression of OA (Baron, Tubach, Ravaud, Logeart, & Dougados, 2007; McGinley, 2006; Roux et al., 2008). Once a patient has decided to pursue the surgical option for care,

nurses are involved in the preoperative and postoperative care of OA patients. Together knowledge and understanding of OA and how this affects individual patients form the basis for an all around patient care and disease management role (Antonelli & Starz, 2012).

Future Perspective on Cell Therapies

Apart from preventing or slowing the process of cartilage degeneration, the need for knee replacements will be the standard means to restore joint function over longer durations until biological-based repair approaches mature.

As outlined previously, ACI-related procedures do not always lead to the formation of hyaline-like cartilage (Clar et al., 2005; Zeifang et al., 2010). However, strategies to form organized/stratified tissues in vitro have improved over the past decade (Kim et al., 2003; Klein et al., 2003; C. S. Lee et al., 2007; Ng et al., 2005; B. Sharma et al., 2007; Woodfield et al., 2004). Although few laboratory approaches are ready for the clinic, engineered tissues are currently being evaluated in clinical trials.

Crawford, DeBerardino, and Williams (2012) recently reported a 2-year evaluation of a Food and Drug Administration Phase II prospective, randomized clinical trial, using NeoCart, an autologous cartilage tissue implant, in comparison with MF. The NeoCart procedure is considered as safe as MF, and patients with the implanted NeoCart showed improved clinical efficacy (http://clinicaltrials.gov/ct2/show/study/NCT00548119). Another clinical trial (now in Phase III) uses a neocartilage tissue implant called DeNovo ET (engineered tissue graft) to treat lesions no larger than 5 cm^2 in patients between 18 and 60 years of age. This trial started in July 2011 and the primary outcome data are expected in mid-2014 (http://clinicaltrials.gov/ct2/show/NCT01400607). Both studies indicate improved translation of tissue engineering into clinical trials, albeit only for small lesions and not for patients with advanced disease status.

One other challenge of cell-based procedures is the choice of cells. Chondrocytes, the principal cells in cartilage, represent the most ideal cells to produce cartilaginous tissue; however, a limited number of cells obtainable from biopsies and a change in cell phenotype after cell culture expansion (to increase cell numbers for therapy) hinder successful new cartilage formation (Giovannini, Diaz-Romero, Aigner, Mainil-Varlet, & Nesic, 2010; Mandelbaum et al., 2007). Mensenchymal stem cells from the bone marrow are a promising cell source for regeneration of many skeletal tissues (De Bari, Kurth, & Augello, 2010; Lim et al., 2011). One significant problem using mensenchymal stem cell is the tendency of these cells not to remain cartilage, but rather to continue to develop into bone-like tissue (Bian, Zhai, Mauck, & Burdick, 2011). Alternative promising stem or progenitor cell sources include adipose (fat) tissues (Gimble, Grayson, Guilak, Lopez, & Vunjak-Novakovic, 2011; Minteer, Marra, & Rubin, 2012), skeletal muscle (Andrades et al., 2012; Usas et al., 2011), and even tissues within the knee joint such as the synovium and the infrapatellar fat pad (S. Y. Lee, Nakagawa, & Reddi, 2010). Although researchers investigate and elucidate which cell source will lead to regenerated cartilage, the most intriguing possibility is to utilize and guide "cartilage progenitor" or "cartilage stem cells" that reside in the cartilage tissue itself (Gerter, Kruegel, & Miosge, 2012; Grogan et al., 2009; Pretzel et al., 2011).

Conclusion

In this review, we have presented an overview of the current methods used to detect OA, provided a brief synopsis of the molecular basis of OA, and identified risk factors associated with this disease, as well as the current limited means of treatment. The future of OA treatment will involve prevention of degeneration by reducing risk factors such as obesity, or by pharmacological intervention following trauma as well as early detection with the help of new biomarkers. For an advanced disease state, the need for prosthetic replacement will remain the standard for patients older than 50 years. However, the continued improvements of various cell-based therapies will eventually emerge as the standard therapy for the young and middle-aged population.

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