2 The Osteochondral Unit: The Importance of the Underlying Subchondral Bone

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Principle of the Osteochondral Unit

The term osteochondral unit reflects the fact that the articular cartilage, the calcified cartilage, and the underlying subchondral bone form a tight functional association (Fig. 2.1) [11]. These tissues are interdependent: mechanically, physiologically, and biochemically. Together they are responsible for transferring loads during weight-bearing and joint motion [7, 10].

Articular and Calcified Cartilage

Hyaline articular cartilage is an avascular and aneural tissue, consisting of chondrocytes (1–2% of the total cartilage volume) embedded in an extracellular matrix. The extracellular matrix contains mainly water (>70%) and two major organic components: type II collagen and the proteoglycan aggrecan, which provide tensile strength and compressive resilience to the tissue [10, 14]. Aggrecan is composed of a core protein and hydrophilic glycosaminoglycan side chains. Multiple (20–30) aggrecan molecules bind to a long, central hyaluronic acid chain by link proteins and form proteoglycan aggregates. This structure draws a large quantity of water that is extruded during compression and reabsorbed after the stress is released, resulting in restoration of the original cartilage dimensions [10]. In lower quantities other collagens, like collagen types XI and IX, are also present in the matrix. Histologically, the non-calcified articular cartilage layer, from the side facing the synovial fluid to the subchondral bone, can be divided into the superficial, transitional, and deep (radial) zones based on the general orientation of the collagen fibrils, the morphology and arrangement of the chondrocytes, and the staining properties of the matrix [15, 24].

Between the deep zone and the calcified cartilage layer, a radiologically denser, 5-μm-thin discrete band of mineralized cartilage, called tidemark can be found on sections stained by various histological methods. The tidemark represents a calcification front, at which non-mineralized cartilage matrix comes to contain hydroxyapatite [20]. It is not well understood how the tidemark is formed, and knowledge of its precise composition is also limited. Duplication of the tidemark can be observed in aging and osteoarthritis [13].

Located below the tidemark, the calcified cartilage is a 20–250-μm-thick transitional zone, which reduces the "stress riser" between the much stiffer bone and cartilage. The term "modulus of elasticity" is useful in differentiating

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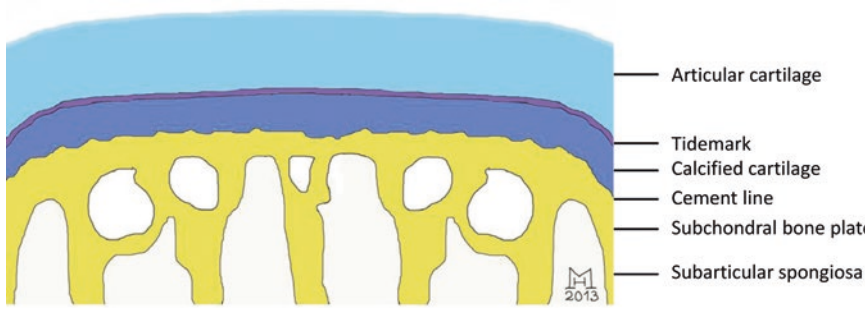

Fig. 2.1 Schematic representation of the osteochondral unit. The articular cartilage is separated from the calcified cartilage by the tidemark. The subchondral bone consists of two layers, the subchondral bone plate and the subarticular spongiosa. Between the bone and the cartilage the cement line forms a boundary. (Reprinted with permission from Orth et al. [32])

material stiffness. The modulus of hyaline cartilage is 1–15 MPa [1], the calcified cartilage is ~0.3 GPa, and subchondral bone is ~2 GPa [27], representing transitions of 20–300-fold between the former and ~7-fold between the latter, which increases the ability to resist shear loads over an abrupt cartilage to bone interface about 100–2000-fold. Its physiological function is to form an interface between cartilage and bone for transmitting force, attaching cartilage to bone, and limiting diffusion from bone to the deeper layers of cartilage [31]. It is characterized by small rounded chondrocytes distributed in an extracellular matrix composed of collagen type II, collagen type X, glycosaminoglycans, and alkaline phosphatases which contribute to the hydroxyapatite mineral (Ca-P) deposition in the matrix [13]. The type II collagen fibrils of the articular, non-calcified cartilage are anchored within the calcified cartilage, thus crossing the tidemark [24].

The Subchondral Bone

Under the calcified cartilage lies the subchondral bone which is separated from the calcified cartilage by the cement line, a less-distinct boundary compared to the tidemark (Fig. 2.2). No collagen fibers cross the interface between the two tissues; they are held together only by three-dimensional interdigitation [31]. Importantly, its undulated organization aids to transform shear stresses into compressive and tensile stresses during joint loading and motion [10]. The subchondral bone plays a key role in mechanically and metabolically supporting the articular cartilage, maintaining the joint shape, and absorbing shock [15]. The subchondral bone attenuates about 30% of the loads through joints, while cartilage attenuates only 1–3% of them. The main collagen isoform of subchondral bone – similarly to other bone regions – is type I collagen.

The subchondral bone consists of two parts with different macroscopic structures: the subchondral bone plate (also termed cortical endplate) and the subarticular spongiosa (also termed subchondral trabecular or cancellous bone).

The subchondral bone plate is a dense bony lamella, similar to the cortical bone of other bony structures, separating the calcified cartilage from the marrow cavity. It consists of 0.2–0.4-mm-thick plates which join together to enclose intervening spaces. The thickness and mineral density of the subchondral bone plate vary by age, bodyweight, location, function (stresses), and genetics, but in general, the central, more heavily loaded contact areas are thicker and more mineralized, reflecting the long-term stress acting here [14]. This pattern, however, can alter if the direction of the loading changes: e.g., in conditions such as genu varum and genu valgum, the density patterns deviate from the normal, reflecting the altered load distributions [24].

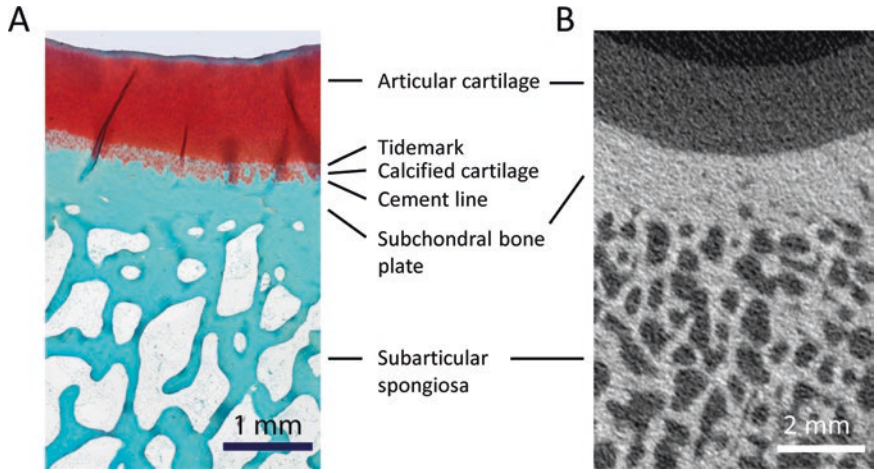

Fig. 2.2 Observation of the osteochondral unit. The osteochondral unit is studied mostly by histological methods and high-resolution imaging techniques. (**a**) A Safranin O/fast green-stained section of a sheep tibial plateau showing all regions of the osteochondral unit. (**b**) Micro-computed tomography images are valuable resources for studying the structure of the subchondral bone

The bone in the subchondral bone plate merges into a network of trabecular bone that is more porous and metabolically active than cortical bone. This region is the subarticular spongiosa, and it can be recognized by its large, elongated spaces between the trabeculae at right angle to the articular surface. This spatial organization is adapted to the local mechanical influences via the continuous remodeling activity of osteoblasts and osteoclasts. The strength of the bone correlates with its trabecular density, reflecting the load-bearing areas [24]. The mean bone strength is greater in men than in women, and it rapidly decreases with the distance from the surface [12].

The subchondral bone is innervated by sensory and sympathetic nerve fibers, which modulate bone regeneration, bone remodeling, and articular cartilage homeostasis [35]. Additionally, the subchondral bone contains a high number of blood vessels which metabolically support the cartilage from below. The development of vascularization correlates with the distribution of stress. Narrow canals and wider ampullae provide connection between the marrow cavity and the cartilage, across the subchondral plate [24]. One type of these cavities are relatively large (>100 μm) extensions of the marrow cavity, lined with endothelial cells, containing fat cells. The second type consists of 30–70-μm-wide cylindrical canals, frequently branching off the larger cavities and containing marrow cells and an occasional blood vessel. The third type has fingerlike, narrow canals, sheathed in the lamellar bone, and contains blood vessels. These blood vessels penetrate into the zone of calcified cartilage [31] and enable nutrients to reach the deeper layers of cartilage. This perfusion accounts for at least 50%, if not more, of the glucose, oxygen, and water requirements of cartilage. Where these canals are missing, the cartilage relies solely on nutrients coming from the synovial fluid [15] (Fig. 2.3). Signaling molecules can also traverse between the bone and cartilage via these blood vessels and the osteocyte lacuna-canalicular network of bone [7]. The vascular channels also nourish osteocytes in the subchondral bone plate, but not the osteocytes in subarticular spongiosa, which receive nourishment from the marrow tissue [17]. The blood flow in the long bones radiates outward after delivery to the marrow cavity. The cortical bone is perfused by a mixture of arterial blood originating from the main nutrient arteries as well as from the separate, smaller periosteal arteries [25].

Repetitive microinjuries to the subchondral bone and calcified cartilage may initiate a repair

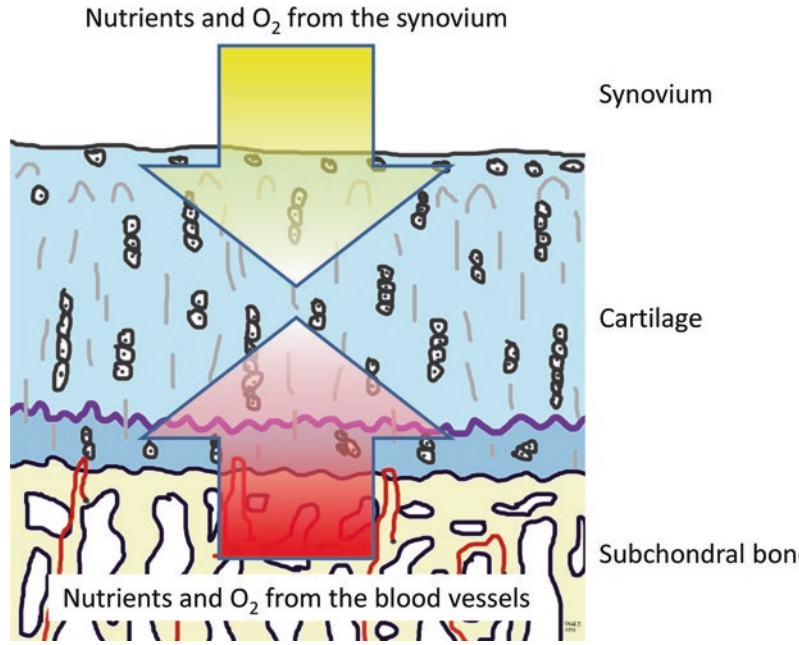

Fig. 2.3 Schematic of the perfusion of the cartilage from the synovial fluid and the blood vessels of the subchondral bone

mechanism, ultimately resulting in the formation of new bone (subchondral sclerosis) and establishment of a new, cartilaginous mineralization zone (duplication or triplication of the tidemark) [15]. Of note, mesenchymal stem cells (MSCs); nonhematopoietic, multipotent cells of the bone marrow; and other tissues with reparative and trophic properties can be found in the subarticular spongiosa. In the case of an osteochondral defect or as a result of marrow stimulation for chondral defects, the MSCs migrate from the subchondral bone into the defect where they differentiate into chondrocytes and osteoblasts. Over time, they establish a fibrocartilaginous repair tissue in the defect while simultaneously closing the connection with the subchondral bone [22].

Pathological Alterations of the Subchondral Bone

During spontaneous and orthopedic surgical repair of chondral and osteochondral defects, several pathologic features of the subchondral bone emerge, including the formation of intralesional osteophytes, residual microfracture holes, peri-hole bone resorption, and the appearance of subchondral bone cysts [23, 32]. Their possible causes include impaired osteochondral crosstalk and regeneration, pathologic vascularization or angiogenesis, and pathologic consequences of altered biomechanical loading. Interestingly, many translational studies showed a lack of correlation between cartilage and subchondral bone repair, suggesting that independent repair pathways take place within these tissues [23, 32]. For making precise distinction between the subchondral bone alterations with high-resolution imaging methods such as microcomputed tomography, subtle analyzing algorithms were developed in translational animal models [8]. From a clinical standpoint, the different cartilage restoration techniques used to treat (osteo)chondral injuries [5] are not only indicated based on patient- and defect-specific factors such as size and location but also on the status of the subchondral bone [21].

Osteoarthritis

Osteoarthritis (OA) is considered a disease of the entire joint, affecting the articular cartilage, subchondral bone, synovium, menisci, capsule,

ligaments, and muscles [10]. There is a considerable biochemical and molecular crosstalk between them, which leads to abnormal joint remodeling once the natural repair processes fail. The subchondral bone plays an important role in the development of OA. In early OA, thickness of the subchondral bone plate and subarticular spongiosa is increased, their mineral content is reduced, and the trabecular integrity is altered [23]. In OA, the duplication of the tidemark and the advancement of the calcified cartilage into the overlying hyaline cartilage are also frequently observed. Other pathological processes include the presence of microcracks, microedema, microbleeding within the subchondral region, and the development of subchondral bone cysts and osteophytes [10, 24]. These patterns co-localize with regions of articular cartilage damage, indicating that both tissues are responsive to the effects of loading [10, 23].

In early stages of OA and for patients that are too young to undergo total joint arthroplasty, reconstructive surgical therapy is indicated. It aims at preserving joint function and includes debridement, removal of osteophytes, unstable articular cartilage flaps or loose bodies, the treatment of degenerative meniscal lesions, marrow-stimulating techniques to induce fibrocartilaginous repair, and correction of axial malalignment among other procedures [24].

Bone Marrow Changes on MRI that Suggest "Edema"

Bone marrow edema is a misnomer coined by radiologists early in the history of MRI as they observed signal changes in bone that were similar to fluid signal within the joint cavity [36]. However, histological studies of such regions have revealed the presence of fat necrosis, localized bone marrow fibrosis, and vascular changes associated with microfractures of the trabecular bone at various stages of healing [10]. These findings suggest that the MRI signal is not generated by actual edema but rather by an active cellular process that is associated with local regions of bone damage [10], and thus a better term might be "bone marrow lesions," yet this term "scares" radiologists who associate the term bone marrow lesion with bone sarcoma. In many settings, the micro-trabecular fractures play a major role, and thus the term "bone marrow stress reaction" or even "bone marrow stress fracture" may be useful.

Bone marrow lesions tend to be associated with regions of cartilage pathology in OA, and their presence generally correlates with joint pain and with the progression of cartilage loss first brought to light by Felson et al. in 2001 [6] and more recently by Goldring et al. in 2016 [10]. In a normal situation, the overlying cartilage distributes mechanical forces and in this way protects the subchondral bone from the adverse effects of excessive load. In OA, however, its protective effect is reduced [10]. Of note, bone marrow edema-like lesions are also observed in the healthy, asymptomatic population and may predict an increased risk of OA. In their pathogenesis, damaged cartilage, an inflammatory reaction to cartilage breakdown products or other factors in intruded synovial fluid, and microtraumatic changes associated with altered biomechanics are proposed to be involved. They also have a profound relationship with subchondral bone cysts, which could develop in pre-existing regions of bone marrow edemas [19].

Bone marrow edema-like lesions with a history of antecedent trauma, e.g., soft tissue injuries of the knee, including anterior cruciate ligament (ACL) tears and patellar dislocations, has been referred to as a "bone bruise" [18]. Although their rate of healing is unpredictable, it is generally agreed that bone contusions as a result of trabecular fracture heal in the short term. It has been proposed, however, that increased stiffness of the healed bone may decrease the potential for the joint to dissipate load by deformation, and this may also increase shear stress at the bone cartilage interface, precipitating cartilage degeneration [18].

Little data is available on the relationship of bone marrow edemas and cartilage repair procedures. A case series of 86 patients on long-term outcomes after first-generation autologous chondrocyte implantation (ACI) for cartilage defects

of the knee showed defect-associated bone marrow edema in 78% of the cases but did not identify correlations with the clinical results [30]. How bone marrow edemas affect the success of cell-based cartilage restoration therefore remains controversial. Some authors see the persistence of edema-like signals for more than 1 year as a predictor for poor clinical outcome, while other studies regard edema as a sign of undetermined importance [11]. Following marrow stimulation, it is possible that a bone marrow edema simply reflects the osteochondral adaptation and repair of the subchondral bone perforations. Recent data in animal models suggest that such changes may be significant at early time points [9] and persist for a longer periods of time than previously expected [33].

Subchondral Bone Cysts

Subchondral bone cysts usually develop in late-stage osteoarthritis, characteristically in focal areas of cartilage loss, bone damage, and necrosis (Fig. 2.4) [10]. Subchondral bone cysts are cavitary lesions in subchondral bone, without an epithelial lining, not uniformly filled with fluid [19]. Many of the cysts develop at sites of pre-existing bone marrow lesions, which suggests a common causal mechanism related to local tissue damage [10]. There are two main conflicting hypotheses that explain the origin of subchondral bone cysts in OA [19]. The "synovial fluid intrusion" theory proposes that synovial fluid intrudes into subchondral bone and leads to formation of subchondral bone cysts, which is due to the breach of the osteochondral junction. The "bone contusion" theory suggests that abnormal mechanical stress and subsequent microcracks, edema, and focal bone resorption induce necrotic lesions in subchondral bone, leading to the formation of subchondral bone cysts [19].

A subchondral bone cyst has its largest expansion within the subarticular spongiosa [32]. Subchondral bone cysts appear at sites of greatest cartilage loss, both in humans and animal models. Osteoclastic bone resorption, activated osteoblasts, and new bone formation were detected to be present surrounding subchondral bone cysts in OA, indicating high bone mineralization and bone turnover [19].

Marrow stimulation procedures (microfracture, drilling, or the generalized thinning of the subchondral bone plate following abrasion arthroplasty) may induce pathological bone resorption and subchondral cyst formation in translational animal models. Clinical studies suggest that subchondral bone cysts do not occur in the first weeks after articular cartilage resurfacing procedures but are detectable as early as 6 months postoperatively [32]. They appear as well-defined areas of fluid signal on MRI, which correspond to well-defined lucent areas surrounded by sclerotic rims on radiographic images [19].

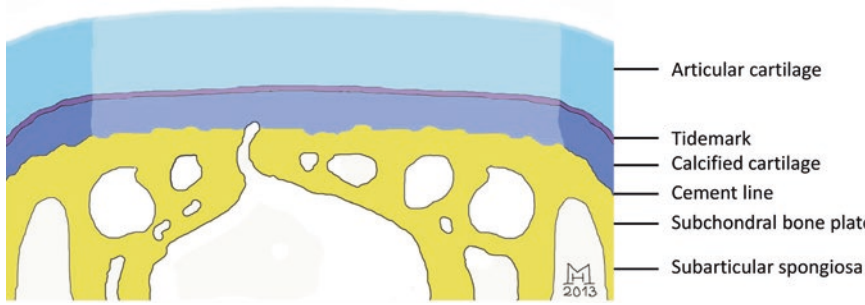

Fig. 2.4 Schematic representation of a subchondral bone cyst located mostly in the subarticular spongiosa. The less intense blue color of the cartilage represents osteochondral repair tissue. (Reprinted with permission from Orth et al. [32])

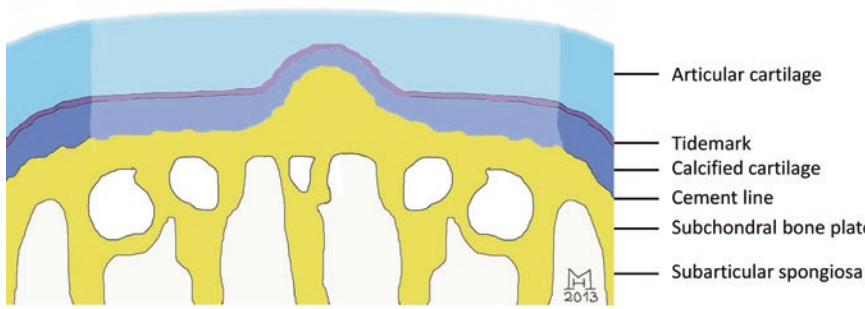

Fig. 2.5 Schematic representation of an intralesional osteophyte. The less intense blue color of the cartilage represents osteochondral repair tissue. (Reprinted with permission from Orth et al. [32])

Intralesional Osteophytes

Intralesional osteophytes can develop in central or peripheral locations within articular cartilage defects (Fig. 2.5). They are focal, newly formed bone outgrowths located apical to the original cement line and projected into the cartilaginous repair tissue layer. Contrary to genuine (chondro-)osteophytes, which always arise in the region of contact between the periosteum and the articular cartilage in diarthrodial joints, intralesional osteophytes are surrounded with articular cartilage or exposed bone within a cartilage defect. The effect of focal intralesional osteophytes on cartilage degeneration remains poorly understood [32].

It is sometimes difficult to distinguish intralesional osteophytes from generalized thickening of the subchondral bone plate. Mithoefer and colleagues summarized intralesional osteophytes and the elevation of the subchondral bone plate as bone overgrowth [28]. Intralesional osteophytes are increasingly described in high-level clinical studies [32]. In microfracture-treated patients, sclerosis, subchondral cysts, and osseous overgrowth resulting in the formation of intralesional osteophytes were observed, which may be among the factors causing increased failure of autologous chondrocyte implantation after microfracture. Following their surgical removal, intralesional osteophytes may regrow in approximately one third of the patients [4]. Aggressive deep debridement of the calcified cartilage layer, high body mass index, and location of the defect in the lateral compartment have been identified as risk factors to result in "subchondral overgrowth," associated with an increased rate of postoperative failure after microfracture [28].

Avascular Necrosis (Osteonecrosis)

In avascular necrosis (AVN) or osteonecrosis, the blood supply of the bone is interrupted, causing necrosis of the bone components, finally resulting in the collapse of the bone and the overlying cartilage. It is a devastating disease that can lead to end-stage arthritis of various joints including the hip and the knee. There are three categories of osteonecrosis that affect the knee: spontaneous, secondary, and post-arthroscopic [16].

The spontaneous osteonecrosis of the knee (SONK) is the most prevalent form of osteonecrosis, most commonly seen in elderly, postmenopausal women who may have osteoporosis [24]. This typically unilateral disease presents with severe knee pain of sudden onset [34]. SONK is classically described as a single, shallow, focal, superficial subchondral lesion, mainly affecting the medial femoral condyle. The pathological mechanisms that lead to spontaneous osteonecrosis of the knee are not fully understood [24]. Repeated minor trauma may result in subchondral insufficiency fractures, permitting the synovial fluid accumulating in the bone marrow and increasing intraosseous pressure, which results in subsequent edema with focal ischemia,

that eventually results in bone necrosis, collapse, and subchondral cyst formation [16, 24].

The secondary or atraumatic osteonecrosis of the knee usually affects patients younger than 45 years of age and frequently involves multiple lesions affecting numerous joints with insidious onset of vague pain [16, 34]. It is usually apparent on X-rays at the onset of symptoms, involving large portions of the epiphyses and metaphyses [24]. Most of the patients who have this pathology have bilateral involvement (>80%). Similarly to spontaneous osteonecrosis, it has a female predominance. Secondary osteonecrosis has been associated with numerous conditions and risk factors interfering with the blood flow in the vessels that can be separated into direct causes (sickle cell disease, caisson disease, Gaucher's disease, myeloproliferative disorders) and indirect associations (alcohol, corticosteroids, tobacco, obesity) [16].

Post-arthroscopic or post-meniscectomy osteonecrosis of the knee is the rarest type of osteonecrosis, mostly reported after routine chondroplasty and meniscectomy. There are varying theories on the etiology. Altered biomechanics of the knee following meniscectomy, which causes increased contact pressures, may lead to insufficiency fractures and intraosseous leak of synovial fluid and eventually the development of osteonecrosis. The lesion is probably better be described as being, in fact, a subchondral stress fracture and not true osteonecrosis as traditionally described. Additional theories include thermal energy or photoacoustic shock to be the causing factor of knee osteonecrosis [16].

To identify AVN, radiographs and MRI can be used. Regardless of osteonecrosis categories, the treatment of this disease aims to halt further progression or delay the onset of end-stage arthritis of the knee. As above, it is important to differentiate a stress fracture etiology from probably a more metabolic pathology. That is, the stress fracture may respond to stabilization with one of the commercially available calcium phosphate or bone marrow concentrate injection techniques or unloading. Currently, the nonoperative treatment options consist of observation, nonsteroidal anti-inflammatory drugs (although they may slow bone healing), protected weight-bearing, bisphosphonates, and analgesia as needed. Operative interventions include arthroscopic debridement, osteotomy, marrow stimulation, or total knee arthroplasty depending on the extent and type of disease [16, 34]. Joint-preserving procedures are usually attempted in pre-collapse and some post-collapse lesions, when the articular cartilage is generally intact with only the underlying subchondral bone being affected. However, after severe subchondral collapse has occurred, joint arthroplasty is often necessary [16].

Osteochondritis Dissecans

Osteochondritis dissecans (OCD) is a disease that chiefly affects children and adolescents. In OCD, a well-circumscribed segment of the subchondral bone becomes necrotic and is at risk to be separated together with the overlying articular cartilage from the surrounding osteochondral unit. As a result, the osteochondral fragment becomes a loose body and the resulting void an osteochondral defect. The most common joints affected by osteochondritis dissecans are the knee, ankle, and elbow joints.

A variety of etiologies have been proposed, the main ones including lack of vascular supply, trauma and repetitive injury, malalignment, vitamin D deficiency, or genetic causes. Its incidence is 9.5 per 100,000 individuals between 6 and 19 years of age, with a higher prevalence in males and in the 12–19-year age group. Knee OCD most commonly affects the lateral aspect of the medial femoral condyle (64% of knee OCDs). OCD can also occur in other locations of the knee including the patella [3, 29].

OCD is diagnosed by radiographs and often by MRI. A CT scan is a useful technique to analyze the subchondral bone [2], whereas a CT arthrography is highly accurate to evaluate the stability of the osteochondral fragment [26].

Treatment of knee OCD always attempts to preserve the osteochondral fragment, thus preventing osteoarthritis. It is depending on patient factors such as age, location, and stage of

OCD. Conservative treatment includes activity modification with temporary cessation of sports, as well as protected weight-bearing on crutches, or unloader bracing. Surgical treatment of OCD may include subchondral drilling, fragment (re) fixation, and ACI with concomitant subchondral bone reconstruction [3, 29].

Conclusions

Recent translational and clinical studies unambiguously support the concept that the osteochondral unit is a strong functional association between the articular cartilage and the subchondral bone. Many pathological conditions affect this important structure. Yet, our knowledge about the natural history and therapeutic options is far from complete. Targeting the entire osteochondral unit will lead to success of future reconstructive therapies for cartilage restoration.

Conflicts of Interests Neither Henning Madry, Tamás Oláh, nor any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article.

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