Abstract

In a brief review of the literature, specific structure and function of articular cartilage, its possibility for spontaneous healing after local mechanical damage is presented. The data of review confirm, that defects of the articular cartilage that do not penetrate to the subchondral bone fail to heal spontaneously. Defects that penetrate the subchondral bone, repair with a fibrocartilaginous or hyaline-like tissue which over the time develops into the degenerative osteoarthrosis. In this review current concepts in the development of surgical methods for restoration of the injured articular cartilage surface, comparison and evaluation of outcome results by different surgical methods are present. This review evaluates advantages and faults of the used different surgical methods, talks over about perspective for the treatment of joint cartilage damage.

Keywords:
joint cartilage injury, surgical treatment, autologous chondrocyte transplantation

Chondral defects are joint lesions that can cause pain and functional disability, with the potential progression to an early osteoarthritis (OA). Diseases of the articular joints present a major medical, social and economic burden of the society. Therefore the proportion of these diseases in the elderly population inevitably increases [1]. Patients, who are sixty-five or more years old, and have an arthritic condition, can obtain a marked relief from the pain and restoration of the joint function after the total joint replacement [2]. However, O’Driscoll [3] refers that such procedures have the higher rates of failure in young and early- or middle-aged patients, because of the risk of the early prosthesis loosening and “wearing out”. Therefore the lifetime of the patient is likely to be well beyond the lifetime of the prosthesis. So, for this large group of young patients, this problem might be possible to solve, if the damaged segment of the articular cartilage could be regenerated. After restoration, the joint would be able to function indefinitely, or until the patient would reach the age at which joint replacement would appropriate [4, 5].

Articular cartilage lesions are common after acute joint trauma, and patients often suffer from joint effusion, pain, locking and loss of function. It has been reported that about 10% of young, active patients who present with haemarthrosis of the knee after specific traumatic event will have a focal chondral injury [6]. In the study of population with cartilage injuries, Johnson et al. [7] found the accompanying articular cartilage defects. The
incidence of 1.9% defects were observed after acute injuries, but the overall incidence of 19% defects there appeared to be a close relationship between ligament injury and articular cartilage deterioration. Cartilage defects also may be found in healthy subjects, without knee pain or radiographic OA, so called asymptomatic lesions [8, 9]. Although articular cartilage has a durability which, in many people, lasts throughout their life, but it is also a well-established fact that articular cartilage has a very limited potential to regenerate after injury [10, 11].

Partial-thickness articular cartilage defects do not heal spontaneously. Small chondral lesions that involve the subchondral bone may fill up with fibrocartilage and render to patient as asymptomatic, but the large osteochondral defects are less likely to benefit for fibrocartilaginous healing response. An understanding of the degeneration of the articular cartilage, osteoarthrosis (OA), and the potential for restoring of the articular surface, depends on the large extent of an appreciation of the biological behavior and the responsiveness of the articular cartilage to injury and disease [12].

Until recently, treatment was limited with [to] abrasion and drilling of the subchondral bone, resulting in fibrocartilaginous repair tissue [13, 14]. During the past two decades, interest in the management of cartilage lesion has grown. With the increasing use of the arthroscope, chondral lesions of the knee are being diagnosed more frequently. Surgical procedures, supported by basic science principles of cartilage physiology and known responses to injury, are evolved to treat these lesions [15].

Selection of the proper treatment algorithm for the particular patient depends on a careful evaluation of the patient, including the recognition of comorbidities such as ligamentous instability, deficient menisci, or malalignment of the mechanical limb axis or extensor mechanism. These comorbidities may need to be treated in conjunction with symptomatic chondral injuries to provide a mutually beneficial effect [16].

The goal of surgical treatment, however, is to produce a repair tissue that has the same functional and mechanical properties of the hyaline articular cartilage. The poor reparative potential of cartilage has led to many strategies and numerous new therapeutic techniques [17]. These techniques may be classified as 1) debridement of loose or impinging chondral flaps; 2) stimulation of the intrinsic repair mechanism from subchondral bone; 3) to fill up the defect with transplantation of autografts or allografts; 4) cell-based therapy to regenerate the chondrocytes and surrounding matrix; or 5) combinations of these techniques with growth factors or biologically active carriers to influence the repair process [18].

The purpose of this article is to present concepts with respect to the articular cartilage damage, histologic, and clinical allusion, and contemporary opportunities for the biological restoring of the structure, and function of the articular cartilage.

**Cartilage tissue composition**

The structure and composition of articular cartilage provides unique mechanical properties which effectively damp and distribute loads through a range of motion and functional activities. This function depends on the specific composition and organization of it composite structure [19]. Articular cartilage is composed of matrix, chondrocytes, and water. The matrix is composed of collagen fibers (principally of type II collagen) and proteoglycan aggregates which provide the architectural structure and biomechanical strength of the tissue and is responsible for the structural properties of the articular cartilage, including its tensile strength and resiliency. The collagen fibers are firmly embeded in the subchondral bone, giving stability to what ensures the stability of the cartilage [19]. The chondrocyte is mesenchymal stem cell origin. It is primarily responsible for the synthesis of proteoglycan monomers, link proteins and hyaluronan and secretes them into the extracellular matrix where they aggregate spontaneously [20]. The synthesis and degradation of the matrix are carefully regulated by the chondrocytes and there is an intimate interplay between the chondrocytes and the extracellular matrix [21]. Water comprises 60–80% of the wet weight of cartilage and its flow plays an important role in cartilage nutrition, and provides the mechanical properties of the cartilage. Other components include biglycan, decorin, fibromodulin, fibronectin, lipids, and link proteins [22]. The fundamental problem of cartilage is that it has no innervation and direct blood supply and is therefore not sensitive to early injuries and is lacking in inflammatory or cellular response to injury. Thus, the defect does not repair spontaneously [23].

**Cartilage tissue response to injury**

Arthroscopic explore and Magnetic Resonance Imaging have provide to classify articular cartilage injuries. Buckwalter [24] presents three types of articular cartilage injuries which repair response from the cartilage tissue is distinct: 1. The integrity of the articular surface is pre-
served, but the macromolecular matrix and/or the population of cells and/or the subchondral bone show signs of damage. 2. Chondral fractures or ruptures, are sparing the subchondral bone. 3. Osteochondral fractures, are breaking through both the cartilage and the subchondral bone.

The articular cartilage injuries may be explained by interstitial water flow through the permeable matrix and the generation of frictional drag force on the matrix. The ability of interstitial water flow damps and distributes compressive loads to deal with internal stress, gives the articular cartilage viscoelastic behaviour and nutrition under compression. However, if the impact is heavy or sharp enough, it may leads to damage of the matrix framework, cells and the subchondral bone [25, 26]. Cartilage damage injures chondrocytes, limits their metabolic capacity for repair, and leads to decreased proteoglycan concentration, increased hydration, and altered fibrillar organization of collagen. These changes lead to rapid elevation of the metalloproteinase enzyme stromelysin and other cytokines that cleave articular cartilage [27, 28].

However, unanswered question is the natural course of traumatic articular cartilage injury. It is not known what chondral lesion may heal spontaneously and what will progress to OA. It is generally believed that lesions larger than 2 cm in diameter are more likely to be symptomatic and degenerate further. Some smaller lesions, however, may become symptomatic and progress in size [29]. Convery et al. [30] found that osteochondral defects less than 3mm in diameter healed within nine months, and were difficult to detect them from the adjacent cartilage [and their detection from the adjacent cartilage was difficult], while larger defects failed to heal. Maletius [31] performed the 14-year follow-up arthroscopy study on 28 young athletes with isolated chondral injuries. According to the Lysholm evaluation system, 21 patients were able to resume previous sports activities. But the recently published study of the same author showed that intra-articular knee injury was related to an increase in the risk of the development of OA [31]. Clinical experience has shown that, remained untreated lesions do not heal and may progress to degeneration of the joint, and symptoms tend to worsen over time [32–34]. Therefore, the treatment of selected isolated chondral and osteochondral defects may help to delay or prevent the development of OA [35]. Articular cartilage response to the injury depends on the severity and depth of the damage. In partial-thickness cartilage injury, the response is limited or does not exist, so, the defect is not repaired. A full-thickness injury of articular cartilage that penetrates subchondral bone provides access to cells, blood supply, and theoretically, has a higher capacity for reparation [3, 36, 37].

**Treatment options for articular cartilage injury**

During the last three decades clinical and basic scientific investigations have brought a plenty of research and technical innovations, which stimulate the formation of cartilaginous tissue in osteochondral and chondral defects in damaged joints. The apparent potential of these techniques and methods is to influence the regeneration of new sufficiently stable joint surface that has the same functional and mechanical properties of hyaline articular cartilage [37, 38, 39, 40]. The common target of all utilized methods is to produce a sufficiently stable quality of the cartilage reparation or regeneration. Clinical efforts to treat articular cartilage injuries can be divided into symptomatic (debridement, joint irrigation, shaving of fibrilated cartilage tissue) and the healing or reparative methods (penetration of the subchondral bone, soft tissue grafting, autologous cell implantation).

**Arthroscopic lavage and debridement**

The early signs of OA are follows: localized fibrillation, roughened and irregular articular surface, free fragments are released into the joint space and destined enzymatic degradation of the matrix is observed. Debridement has not been shown to enhance the repair of cartilage lesions, but it may has a palliative effect on the patient’s symptoms such as pain and joint dysfunction. Lavage is the basic irrigation of the inflammatory mediators from the knee joint. Debridement performed by the simple shaving of fibrilated cartilage surfaces, removes damaged tissue, debris and any kind of loose pieces of cartilage from the joint. Both of these procedures have been shown to be successful in the treatment of early stages of OA and have been used since the early 1980s [41, 42]. The most of people that receive some benefit from these procedures are the patients with very small defects (less than 1 cm²) or with the loose pieces of the articular cartilage. The improvements might be due to the removal of damaged tissue, which can act as a synovial irritant causing inflammation and the joint effusion and/or create mechanical problems in the joint [43].

Both of these procedures may provide only the short-term relief because nothing fills up the defect and it leaves behind [33]. [as nothing ever fills in the defect
Penetration of the subchondral bone plate

Few methods of articular cartilage repair involve the penetration into the vascular subchondral bone to generate a fibrin clot within the defect. Undifferentiated pluripotential marrow stem cells migrate into the clot, proliferate and differentiate into the chondrocytes, that leads to formation of reparative cartilage. Methods to penetrate the subchondral bone traditionally include the arthrotomies or arthroscopic drilling, microfracture with a sharp awl, or abrasion chondroplasty with a Burr [46]. An animal experiment has shown that creating perforations with subchondral drilling or abrasion burr arthroplasty can cause cells to die for thermal necrosis and repair tissue is fibrocartilage [47]. However, the defects displayed degenerative changes, which increased over time [48]. The arthroscopical microfracture technique uses angled awls, what avoids the potential risk of the heat necrosis but it is easier and probably more effective than drilling [49]. Each of these techniques is combined with removal of loose bodies and debridement. Reports of the clinical outcome of these procedures are varied. It is due to the inferiority nature of the repair tissue, depends to the age, and patient’s activity. Defects as a result of a sudden injury seem to heal better than the defects from wear and tear damage. About 80% of patients have improved pain relief and function in the short term, but after 4 or 5 years, however, these results are deteriorated [41, 49]. Johnson [44] examined joint surfaces after penetration of the subchondral bone and found that 10% of patients had the restoration of hyaline cartilage, but the remaining patient’s repair tissue was fibrocartilage. He reported that this procedure was resulted in the formation of a fibrocartilaginous tissue, that varied in composition from fibrous tissue to hyaline cartilage-like tissue, and which was not so good mechanically as hyaline cartilage. Rand found fibrocartilage in 11 of 28 patients, worsening in 9 patient’s after 3 years [of follow-up], and half of the patients went on to the total knee arthroplasty [50]. Optimal outcome has been noted in younger patients with smaller lesions, because bone marrow of younger patients has much more mesenchymal cells [33]. As things stand today, a limited effect, with only a short- to medium-term duration can be expected, makes the clinical value of these methods uncertain [51]. As it is mentioned above, all of these techniques generate a fibrocartilaginous repair that appears to deteriorate over time.

Soft tissue grafting

Treatment of OA joints with soft-tissue grafts involves debridement of the joint and interposition of fascia, joint capsule, muscle, tendon, periosteum or perichondrium. Animal experiments and clinical experience have shown that perichondral and peristomal grafts placed in articular cartilage defects can produce new cartilage [52]. Recently, encouraging results with use of peristomal and perichondrial grafts for the treatment of isolated osteochondral defects have been reported [53, 54].

Periosteal and perichondrial arthroplasty

De Bari et al. demonstrate that the adult human periosteum contains cells that upon enzymatic release and culture expansion, are multipotent MSCs at the single cell level [50]. The chondrogenic potential of periosteum is attributed to chondrocyte precursor cells in the inner, juxta-fibrous portion of the cambium layer that lies adjacent to the bone [56]. Periosteum has been used alone for biological resurfacing arthroplasty in humans for more than a decade. The periostal graft is implanted into the defect with the cambial layer facing upwards towards the articular surface. The graft is held in the place by fibrin glue. There are much debates as concerns the orientation of the cambial layer: whether it should face the joint space or the subchondral bone [57]. Perichondrium has also been used as a graft source. It has been shown that there is no significant difference between repair tissue formed from perichondrium or periosteum. But O’Driscoll [3], by using the periosteum in the rabbits and humans, has confirmed that it can be transplanted into defects of various sizes, shapes, and depths. Include the accessibility and the amount of the available tissue as well as its chondrogenic potential, periosteum appears to be preferable against perichondrium for the biological resurfacing of the joints. It has been demonstrated clinically that the age and the use of continuous passive motion post-operatively are important factors in the successful outcome of soft tissue transplantation [58].
Transplantation of articular cartilage

Osteochondral transplantation of auto and allografts has been widely used to treat predominantly large osteochondral defects. Clinical and experimental works have suggested that osteochondral transplantation have the advantage of providing a fully formed articular cartilage matrix and restore the subchondral bone [59, 60]. Allogeneic materials derived from cadaveric donors have been used to treat osteochondral defects with varying degrees of success [61]. Also it has been demonstrated experimentally that fresh tissue is more successful than frosted tissue in terms of the cell death and mechanical stability, despite the fact that the immunological response is still a potential problem of this approach [62].

Autologous osteochondral grafts

Both animal and clinical studies of immunology and osteochondral transplantation have shown that transplanted fresh cartilage is viable [63]. Autologous osteochondral grafts involve the removal of an osteochondral plug from non-load bearing regions of the articular cartilage, such as the femoral trochlear groove, patella, and they are transplanted into the debrided full-thickness defect. Osteochondral grafts have the advantage of providing a formed articular cartilage matrix and the potential for transplanting viable chondrocytes to heal to the surrounding recipient tissue [64, 65]. This method has attraction because it is carried out in one procedure and can be performed through a small incision. The application of the technique is limited by the amount of donor tissue available in the joint [66]. It is important to maintain a perpendicular relationship with the articular surface to create well-defined vertical walls in the recipient hole, which will facilitate congruent plug placement. Supported grafts heal well, but unsupported grafts tend to subside, they eventually become covered by fibrous tissue [67]. The results have shown, that in a small number of patients with transplantation of autologous grafts, this technique can restore an articular surface [68] and provide satisfactory function of the joint for more than a decade [69]. Recently the graft substitution replacements have become popular for small, of 1- to 2 cm, lesions and are referred as “mosaicoplasty” [70]. The procedure requires the use of multiple cylindrical plugs, which must be obtained, and inserted into the cartilage defect. The grafts are comprised of hyaline cartilage but the spaces around the grafts fill up with fibrocartilage as the donor site does. Wakitani et al. [71] described a technique employing collagen as a carrier in which to transplant and maintain chondrocytes in defects. Hendrickson et al. [72] showed that at eight month, using the fibrin as the matrix to carry the cells, healing was superior in the defects which contained 61% of collagen type-II compared with 25% of it in the controls. Donor site pathology in “mosaicoplasty” is an issue of concern mainly if more than six plugs are removed from the femoropatellar joint, and this alone can create clinical symptoms [73]. Limitations for this technique include the inability to treat defects greater than 6-8 cm² due to limited availability of donor site and integration with the surrounding native cartilage. However, for moderate-sized lesions, osteochondral autografts appear to offer an excellent treatment option [74].

Fresh osteochondral allografts

This is basically the same procedure as osteochondral autograft, but for the reconstruction of joint defects the plugs are taken from the deceased donor. Fresh, unfrozen allografts have the best preserve chondrocyte viability and are recommended to use for the treatment of post-traumatic defects as well as for osteochondritis dissecans and avascular necrosis of femoral condyle. But they are contraindicated in the lesions caused by diffuse diseases processes [75]. If the defect is localized and the surrounding bone is healthy, or defect is limited to one joint surface, allograft implantation may be considered. It is generally recommended that fresh articular cartilage allograft be transplanted within days of harvest, with the understanding that the longer the wait, the greater the death of cartilage cells [76]. One of the advantages of the using of allografts over autografts is that more osteochondral tissue can be taken and so larger areas of defects can be repaired. Ghazavi et al. [77] demonstrated clinical success of 85% in 126 knees at a mean of 7.5 years following surgery of the osteochondral allografts. Clinical improvement in follow-ups of intermediate range (up to 10 years) has been reviewed by other authors [61, 78]. Although these results have stood the test time, the logistical problems of tissue procurement by using fresh, unirradiated osteochondral grafts coupled with the potential for disease transmission (infection such as HIV and hepatitis) and immune response have limited the widespread applications of these techniques [79, 80]. The upper limit of the patient’s age for these procedures remains an area of controversy. Although the majority of investigators recommend an age limit of 40 to 45 years, others have extended this to 60 years of age.
**Autologous chondrocyte implantation**

Technique of autologous chondrocyte implantation (ACI) was originally developed in experiments performed by Grande et al. [81]. In the human it was firstly described in 1994 by Brittberg et al. [82]. Recently the authors reviewed the good or excellent results in 88% of patients with femoral lesions [83]. Over the last two decades this surgical technique has become more widespread. ACI is a 2-stage procedure. The first stage involves an arthroscopic evaluation of the chondral lesion. The biopsy of the normal hyaline cartilage is performed from a non-load bearing region of the articular cartilage. It is released from the matrix by enzymatic digestion and grown in culture to increase the cell population. The second stage of the procedure is cell implantation and a periosteal flap suture over the cartilage defect. Chondrocytes do not possess the capacity to induce subchondral bone-healing, whereas periosteal flap have the potential to regenerate both the cartilage and the underlying subchondral bone [84]. Present indications for ACI include younger (age of 20 to 50 years), active patients with an isolated, traumatic, femoral chondral defect greater than 2 to 4 cm² [18]. This technique is used in clinical practice with a number of clinical studies and demonstrates the satisfactory results [85–87]. In accordance with short- and long-term experimental and clinical studies, it has been observed that transplanted cells retention in the defects is a problem, because the cells can not grow in the empty space. For this reason, scaffolds and matrices have been used for the cell transplantation. The chondrocytes were grown employing carbon-fiber pads, absorbable polyactic-polyglycolide scaffolds, collagen gels, human fibrin glue as the matrix to carry the cells, hyaluronan and collagen based matrices and etc. [38, 88]. Hyaluronan and collagen based matrices are among the most popular natural scaffolds that are implanted into the cartilage defect without the need of the periostial flap. Early clinical findings are encouraging, with 96.7% of repair tissue and hyaline-like cartilage formation [89]. Polyglycolic and polylactic based scaffolds, however, have shown to enhance the promotion of proteoglycans, proliferation, differentiation and maturation of chondrocytes in comparison to collagen based scaffolds [90]. One of the major biological problem is the lateral integration of the graft. Chondrocytes do not have a durable articular surface, and after two years may reduce the risk of later failure [94]. In accordance with short- and long-term experimental and clinical studies, a few problems which complicate the production of repair tissue, that biologically and mechanically will be equivalent to the native cartilage, have been observed. One of the major biological problem is the lateral integration of reparative tissue into the host cartilage at a predictable level. Several experimental studies demonstrate that chondral lesion induces irreversible lose and death of chondrocytes from the cartilage tissue bordering to the wound edge, whereas adjacent chondrocytes do not participate in the reparation of the defect. The inevitable spaces that develop between the graft and margins of the defect with loss of chondrocyte viability, are the hindrance to lateral integration of the graft. On the other hand, the chondrocytes of the mature cartilage have no ability to migrate throughout a dense and complex extracellular collagen matrix to the defect site. However, it is known that chondrocytes are released from the matrix by delicate enzymatic digestion which alters the type II collagen scaffolding. Hunziker and Rosenberg [95] after enzymatic treatment of articular defects determine that it evoke the initial increase in the coverage of the cartilage defect with mesenchymal cells presumably from the synovial tissue. Other investigators reported about the migration of mesenchymal cells from the perichondral region to the middle zone of cartilage after delicate depletion.

**Conclusions and future challenges**

Chondral lesions caused by mechanical damage do not heal, and efforts to induce the healing and repair of injured surface with hyaline cartilage continue, despite of great importance of recent advances. Recent reports of the methods that promote the formation of new cartilage surfaces in the local cartilage defects, show that none of these methods has been produce the repair tissue that duplicate the structure, composition and function of the native articular cartilage. The repair tissue is often hyaline-like or a fibrocartilaginous nature and does not have a durable articular surface, and after two years may reduce the risk of later failure [94]. In accordance with short- and long-term experimental and clinical studies, a few problems which complicate the production of repair tissue, that biologically and mechanically will be equivalent to the native cartilage, have been observed. One of the major biological problem is the lateral integration of reparative tissue into the host cartilage at a predictable level. Several experimental studies demonstrate that chondral lesion induces irreversible lose and death of chondrocytes from the cartilage tissue bordering to the wound edge, whereas adjacent chondrocytes do not participate in the reparation of the defect. The inevitable spaces that develop between the graft and margins of the defect with loss of chondrocyte viability, are the hindrance to lateral integration of the graft. On the other hand, the chondrocytes of the mature cartilage have no ability to migrate throughout a dense and complex extracellular collagen matrix to the defect site. However, it is known that chondrocytes are released from the matrix by delicate enzymatic digestion which alters the type II collagen scaffolding. Hunziker and Rosenberg [95] after enzymatic treatment of articular defects determine that it evoke the initial increase in the coverage of the cartilage defect with mesenchymal cells presumably from the synovial tissue. Other investigators reported about the migration of mesenchymal cells from the perichondral region to the middle zone of cartilage after delicate depletion.
Surgical Treatment Options of Articular Cartilage Injury

Future research needs to clarify biological challenges of this process of chondrogenesis and its regulation at the cellular and molecular levels. The role and application of chondrogenic potentiating growth factors such as transforming growth factor, basic fibroblast growth factor, insulin like growth factor will need to be elucidated. Further investigations are required to identify the most effective factors or their combination, the optimal doses and methods of maintaining and releasing them at the site of damaged cartilage. Scaffolds have been used in combination with growth factors and chondrocytes, however nonabsorbable materials have not proved successful in the restoration of cartilage. Absorbable polymers when used with cells and growth factors have shown promise. As reported Piscoya et al. [96] transplanted scaffold with its architectural and biomechanical strength must conform to the mature cartilage with its adequate hydraulics possibilities at load bearing action. Cyclic loading and static compression, however, enhance the solute diffusion and transport of larger molecules which might alter the nutritional and metabolic status of the cartilage. In connection with the all new developments, O’Driscoll [84] prescribes that all current methods for the healing and regeneration of the cartilage should be considered to investigation until they can be proved in rigorous clinical trials, which must be randomized, controlled, and blinded.

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Santrauka

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