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The role of biodegradable materials in the treatment of articular cartilage defects

Eklem kıkırdak defektlerinin tedavisinde biyobozunur malzemelerin rolü

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Objectives: This prospective randomized study was designed to evaluate the safety and efficacy of polymer Polyactive B as a bone-graft substitute for filling up donor defects caused by removal of mosaicplasty grafts.

Patients and methods: The study included 10 patients (7 males, 3 females) who underwent mosaicplasty using 6.5-mm grafts. The donor sites of the grafts were filled up with 2 to 6 pieces (average 3.5 pieces) of Polyactive B cylinders, 7.5 mm in diameter. The control group consisted of 10 patients in whom the donor sites were left empty. Surgical interventions were performed either arthroscopically or by open exposure. All the patients had preoperative, 3- and 9-month clinical scores; preoperative, 7-day, and 3-month magnetic resonance imaging (MRI) scans. Control arthroscopy was performed in all Polyactive B-filled patients and in four control patients nine months postoperatively.

Results: No postoperative bleeding or other complications occurred. Clinical scores were similar in two groups. Magnetic resonance imaging showed congruent surfaces in all cases. In control arthroscopies, no signs of inflammatory reaction were seen. All surfaces of the filled donor areas were congruent, whereas mild protrusions were observed on the surfaces of the control areas. Macroscopically, the Polyactive B plugs were well integrated into the surroundings. Histological analysis showed proper subchondral ossification in each Polyactive-B case, and a large number of polymer fragments, suggesting partial biodegradation.

Conclusion: The absence of inflammation and evidence of mild foreign body reaction suggest that the Polyactive B is biocompatible and may be appropriate to fill up the donor areas.

Key words: Biocompatible materials; cartilage, articular/surgery; extracellular matrix; polymers; tissue engineering.

Amaç: Bu ileriye dönük randomize çalışmada, mozaikplasti için greft alımından sonra oluşan defektlerin doldurulmasında kemik grefti yerine kullanılan Polyactive B polimerinin güvenilirliği ve etkinliği değerlendirildi.

Hastalar ve yöntemler: Çalışmaya, 6.5 mm boyutta greftlerle mozaikplasti uygulanan 10 hasta (7 erkek, 3 kadın) alındı. Greftlerin alındığı yerlerdeki defektler çapı 7.5 mm olan silindir şekline getirilen Polyactive B ile dolduruldu. Uygulamada ortalama 3.5 silindir (dağılım 2-6) kullanıldı. Kontrol grubunu oluşturan 10 hastada greftlerin alındığı yerler boş bırakıldı. Cerrahi girişimler artroskopi ile ya da açık görüş altında yapıldı. Tüm hastalar ameliyat öncesinde ve 3. ve 9. aylarda klinik skorlamayla; ameliyat öncesinde ve 7. gün ve 3. ayda manyetik rezonans görüntülemeyle (MRG) değerlendirildi. Polyactive B kullanılan tüm hastalara ve kontrol grubundaki dört hastaya ameliyat sonrası dokuzuncu ayda kontrol artroskopisi yapıldı.

Bulgular: Hiçbir hastada ameliyat sonrasında kanama veya başka bir komplikasyon görülmedi. Klinik skorlar iki grupta benzer bulundu. Manyetik rezonans görüntülerinde hiçbir olguda eklem yüzeylerinde düzensizliklere rastlanmadı. Kontrol artroskopisinde enflamatuvar reaksiyon bulgusu yoktu; doldurulan alanlarda tüm yüzeyler düzgün idi; kontrol grubunda ise hafif yüzey düzensizlikleri gözlendi. Makroskobik olarak, Polyactive B tıkaçlarının çevre dokularla çok iyi bütünleştiği görüldü. Histolojik incelemede, Polyactive B uygulanan tüm olgularda yeterli subkondral ossifikasyon ve kısmi çözünmeyi gösteren çok sayıda polimer fragmanı gözlendi.

Sonuç: Enflamasyon olmaması ve yabancı cisim reaksiyonunun çok hafif derecede olması Polyactive B'nin biyouyumlu olduğunu ve verici alanlardaki defektlerin doldurulmasında kullanılabileceğini göstermektedir.

Anahtar sözcükler: Biyouyumlu materyal; eklem kıkırdağı/cerrahi; ekstraselüler matriks; polimer; doku mühendisliği.

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The typical consequences of articular cartilage injuries are pain, disability, and joint dysfunction. Surgical treatment of articular cartilage defects never achieves formation of new hyaline cartilage. The defects are filled with fibrocartilage, which does not take on the functions of a normal articular surface. These problems call for new procedures that might allow the regeneration of functional hyaline cartilage tissue. One of such procedures involves transplantation of cultured human autogenous chondrocytes in combination with a periosteal flap.[1]

Tissue engineering approach exploits the possibility of using constructs consisting of autogenic chondrocytes cultured on suitable biodegradable matrices - scaffolds. After the implantation of chondrocyte culture-impregnated scaffolds, the biodegradable network is resorbed. Bioresorbable refers to a material that, upon placement within the human body, starts to dissolve (resorbed) and is slowly replaced by advancing tissue (such as bone). Common examples of bioresorbable materials are tricalcium phosphate [$Ca_3(PO_4)_2$] and polylactic/polyglycolic acid copolymers.[2] Calcium oxide, calcium carbonate, and gypsum are other common materials that have been utilized during the last three decades.[3,4]

Materials for scaffolds could be medical ceramics or polymers of natural or synthetic origin. The use of bioresorbable polymers for scaffolds is especially attractive as the cartilaginous tissue may replace the space occupied by the scaffold. The term 'polymer' is associated with synthetics; however, polymers are found in the nature in large quantities. In optimal circumstances, the construct implanted into a cartilage defect could potentially induce the regeneration of functional hyaline cartilage. Such scaffolds have more or less chondroinductive capacity.[5,6]

Ideally, the filling substance must not inhibit cellular and vascular invasion to the donor areas, and it has to promote fibrous cartilage formation on the surface, which is comparable to the characteristics of the tissue created on the surface of donor areas left empty.

This prospective randomized study was designed to test a different material, the Polyactive B (used in oral surgery) and to evaluate its safety and efficacy for filling up the donor channels. On the basis of promising animal experiments and human oral surgery practice, it was supposed that this filling would satisfy our expectations not only as a bone replacement, but as an initiator of fibrous cartilage formation on the surface (Fig. 1).[7,8]

PATIENTS AND METHODS

Polyactive B (polyethylene glycol terephthalate/polybutylen terephthalate) polymer (Polyactive, IsoTis NV, Bilthoven, The Netherlands) is an osteoinductive and osteoconductive substance, which is easily modulable due to its physicochemical properties. It has been used in maxillofacial surgery for years and has the FDA approval. The form we used was spongious in structure and highly porous (75%), with the average size of pores being 200 microns (dynamic stiffness at 0.1 Hz: 2 MPa).

Easily modeled Polyactive B cylinders of 7.5 mm diameter were implanted in 10 patients (7 males, 3 females; mean age 37 years) who underwent mosaicplasty using 6.5-mm grafts (Fig. 2a, b).[9] The donor sites of these grafts were filled up with 2 to 6 pieces (average 3.5 pieces) of FDA approved elastic, spongious Polyactive B cylinders. The control group consisted of 12 patients (4 males, 8 females; mean age 35 years) in whom the donor sites were left empty.

Surgical interventions were performed either arthroscopically or by open exposure. Other interventions performed parallel to mosaicplasty were not considered to be an exclusion factor. Postoperative bleeding and healing of the donor sites were assessed, and articular surface congruence was evaluated with magnetic resonance imaging (MRI) and arthroscopy (Fig. 3). Magnetic

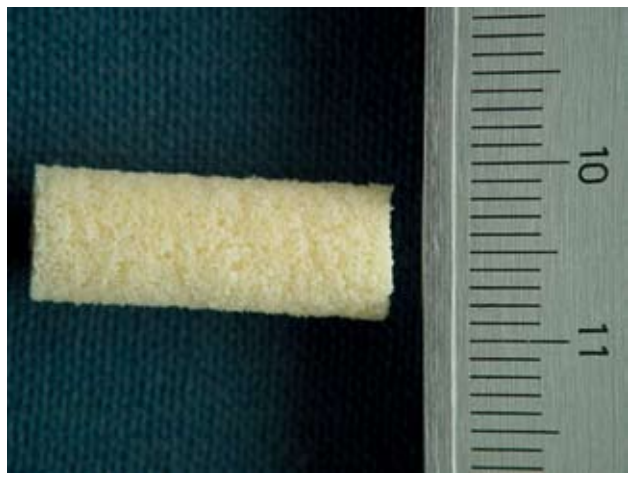

Fig. 1. Polyactive donor site plug.

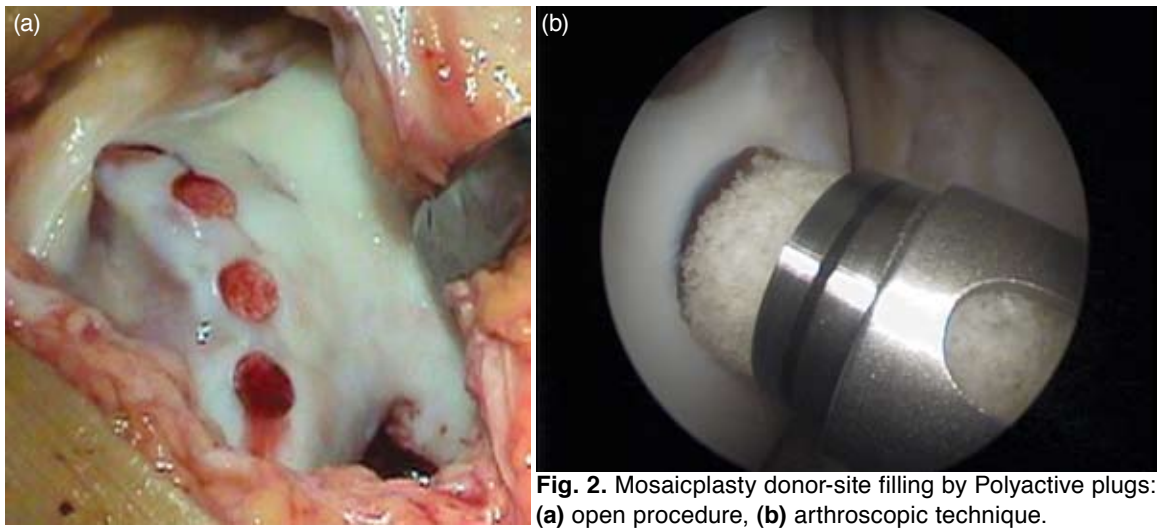

Fig. 2. Mosaicplasty donor-site filling by Polyactive plugs: **(a)** open procedure, **(b)** arthroscopic technique.

resonance imaging was obtained before the operation, on the seventh day, in the third month, and one year postoperatively.

The patients were evaluated before the operation, and 3, 9 and 12 months postoperatively using the following scoring systems: modified HSS (Hospital for Special Surgery), Lysholm, ICRS (International Cartilage Repair Society), and Cincinnati.

Of the control group, only four patients were available for complete follow-up. All the patients had preoperative, 3- and 9-month scorings, and preoperative, 7-day, and 3-month MRI assessments.

Control arthroscopies - with approval of the ethic committee - were performed in all Polyactive B-filled patients and in four control patients nine months postoperatively, during which the congruency of cartilaginous surfaces was assessed and histological specimens were taken from donor areas. Biopsies were taken from 10-mm depth with the use of a 2.7-mm tubular chisel.

RESULTS

No postoperative bleeding or hemarthrosis or other complications (reactive synovitis, arthritis) occurred. Clinical scoring systems did not indicate any difference between the two groups. Magnetic resonance imaging showed congruent surfaces in all cases. During control arthroscopies, it was noted that "soft fibrous cartilage" of the reparative tissue formation on the top of the Polyactive B plugs reached the surface. No signs of synovitis, arthrofibrosis, or inflammatory reaction were seen. All surfaces of the filled donor areas were congruent and the reparative tissue was yellow-whitish in color, whereas mild protrusions were observed on the surfaces of the control areas. Macroscopically, the Polyactive B plugs were well integrated into the surroundings. The surface of the filled areas was in the same height with the neighboring surface, and when checked with the probe, it had similar firmness, or was even more firm than the reparative tissue at the donor sites left empty. No signs of hemosiderosis or bleeding were found. Inside the plugs, excellent tissue integration was observed. Microscopic analysis showed proper subchondral ossification in each Polyactive-B case. Regeneration

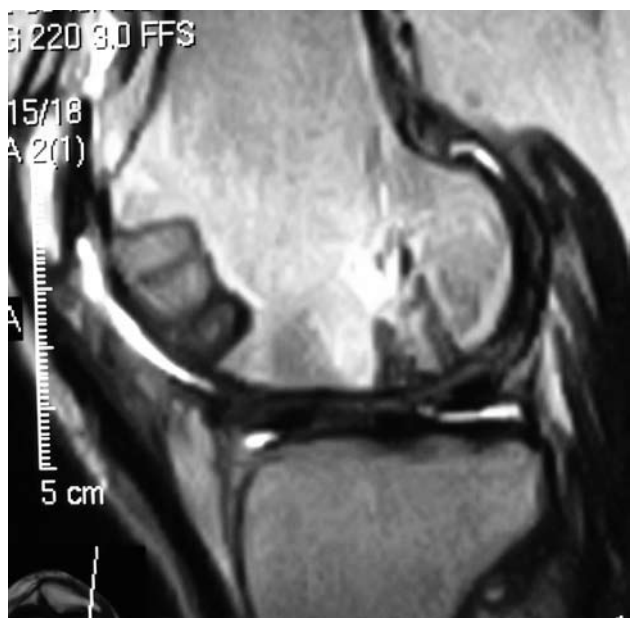

Fig. 3. A magnetic resonance image obtained three months after Polyactive donor tunnel filling of the medial femoral condyle.

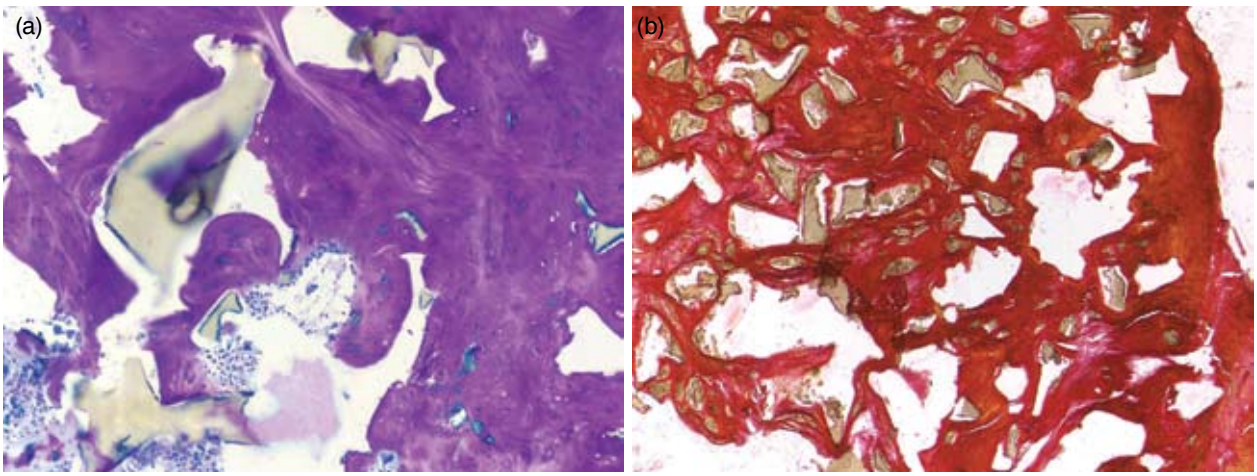

Fig. 4. Histological evaluation of Polyactive filling nine months after surgery: **(a)** implant degradation and new bone formation inside the plug (Dimethylmethylene blue x 20); **(b)** fibrocartilage formation on the articular surface of the plug (Picrosirius red x 4).

of superficial tissues showed fibrous cartilage formation in two cases, and fibrous tissue in two cases. The absence of chronic inflammation and evidence of mild foreign body reaction suggested that these grafts might be biocompatible in the long run. There were a large number of polymer fragments in histological samples, suggesting partial biodegradation (Fig. 4a, b).

DISCUSSION

Natural bioresorbable polymers used in scaffolds are collagen, gelatin, fibrin, and alginates. The first entirely synthesized polymer is the Bakelite, produced in 1909. Synthetic bioresorbable polymers are primarily polyhydroxy acids, including polylactides, polyglycolide, and copolymers of lactide or glycolide units, and other monomers.[10,11] Polymer terminology was born in 1933, when cellulose was created. Those synthetic polymers, which have become the basis of the polymer industry, like nylon, polyethylene, Teflon, and silicon were created in 1920.

Optimally, scaffolds for tissue repair, regeneration and engineering should be biocompatible, bioresorbable or biodegradable and have adequate degradation profile and micro and/or macroporous structure to allow ingrowth of blood vessels, tissues, and flux of nutrients. Scaffolds should support attachment, activity, and proliferation of cells and allow for the formation and maintenance within the porous structure of extracellular matrix. The success of tissue repair and regeneration when using polymeric scaffolds will, to a great extent, depend on the interactions of implants with cells and tissues. The biological quality of the polymer, biocompatibility of the released byproducts, chemistry and texture of the scaffold surface and its mechanical compatibility with tissues influence these interactions. Additional factors include the technique of the scaffold preparation and post-treatment care, i.e. cleaning and sterilization. During the last two decades scaffolds from various polymers have been extensively tested for their capability to support the growth of chondrocytes harvested from various animal species.[12-17]

The polyesters, which degrade by hydrolysis, have been used as a stitch material with the FDA clearance like polylactate, polyglyconate and their copolimers and are utilized as biodegradable materials.[5,6] The speed of degrading can be controlled through mixing different amounts of these two polymers. These materials are sterilized easily, and it is essential that they enter the metabolism of the body and leave it by excretion.

There seems to be a universal consensus that gels from collagen type I enhance the growth of bovine, rabbit, and canine chondrocytes.[12,14] Collagen type II is a better scaffold material than collagen type I is.[14] It was reported that collagen scaffolds stimulated the synthesis of collagen and was better for bovine chondrocytes compared to polyglycolide or poly(lactide-co-glycolide). The latter, however, enhanced the synthesis of proteoglycans.[15] A porous polylactide matrix promoted growth of neocartilage at the articular surface of the rabbit knee.[17] Bovine and human chondro-

TABLE I

The most promising matrix-associated chondrocyte implantation (MACI) or transplantation (MACT) procedures for cartilage surface repair in weight-bearing joints

Cartilink-1	Autologous chondrocyte culture injected under periosteal membrane
Cell Tec	Autologous chondrocyte culture on collagen matrix
Cartilink-2	Autologous chondrocyte culture injected under collagen membrane
BioSeed-C	Autologous chondrocyte culture on gel-like fibrin matrix
Hyalograft C	Autologous chondrocyte culture on 3-dimensional hyaluronic acid matrix
ViesCart	Polyactive B scaffold structure with autologous chondrocyte culture (IsoTis)

cytes seeded on a polyglycolide nonwoven mesh or porous poly(L-lactide) scaffold produced neocartilage *in vitro* and *in vivo*. Porous scaffolds from poly(L/DL-lactide) supported the attachments and growth of sheep articular chondrocytes.[17]

Animal experiments

Biodegradable scaffolds seeded with autologous chondrocytes can be a viable treatment for chondral lesions (Table I). However, there is insufficient clinical experience to evaluate the long-term efficacy of hyaline-like repair tissue developed by implantation of a chondrocyte matrix.[6] The type of tissue repair achieved demonstrated histological characteristics similar to those of normal articular cartilage. According to the current data collected from histological evaluation of human biopsies, it seems that an optimal outcome – an excellent type II collagen and glycosaminoglycan formation – can be observed, with certain minor differences regarding the organization of the extracellular matrix compared to the normal articular hyaline cartilage. Long-term investigations are needed to determine the durability of the repair produced with this technique.[18]

Culturing hyaline cartilage cells has become a milestone of cartilage repair surgery, because, with this new method, autologous chondrocyte culture can be implanted to the damaged cartilage area. The defect is filled up with the autologous chondrocyte culture injected under a periosteal flap stitched to the intact cartilage to ensure the positioning of the culture mass. Autologous chondrocyte culture impregnated to a special scaffold structure proved to be a more reliable method to fix the autologous chondrocyte culture to the area of destruction.

The use of the Hyalograft C is an innovative tissue-engineering approach for the treatment of knee cartilage defects and involves the implantation of a three-dimensional hyaluronan-based scaffold on which autologous chondrocytes are grown.

Because no periosteal coverage is required to keep the graft in place, surgical time and morbidity are reduced, and handling of the graft is much simpler than currently available autologous chondrocyte implantation techniques. This technique has recently been introduced into clinical practice, with more than 5,000 patients treated in 14 European countries in the last five years.[19]

Our working team has also performed over 20 successful cartilage surface repairs with the Hyalograft C. However, the firmness of the replaced cartilage was found suboptimal in the medium-length follow-up.

Mosaicplasty and donor site cartilage surface repair

The autologous osteochondral mosaicplasty has become a well-established therapeutic modality in

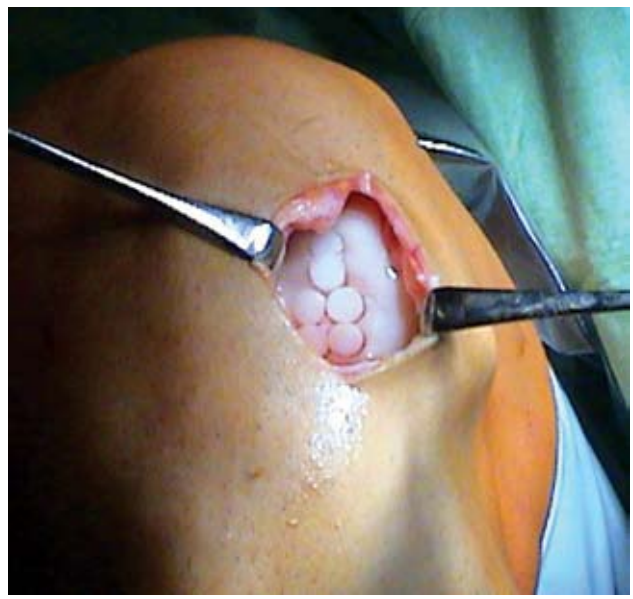

Fig. 5. Miniarthrotomy mosaicplasty in the medial femoral condyle.

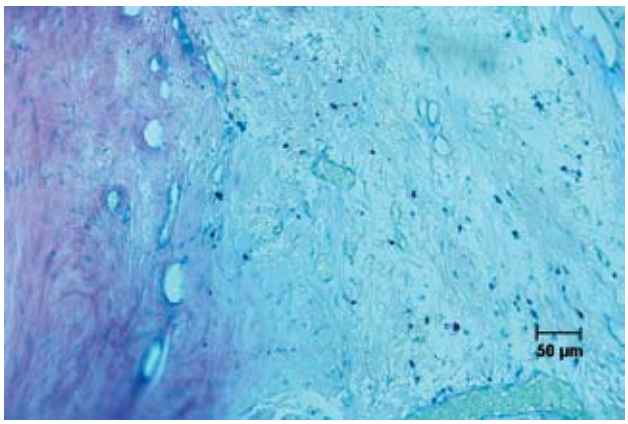

Fig. 6. Histological evaluation of compressed collagen implantation into mosaicplasty donor tunnel: fibrocartilage formation in the replaced area (DMMK x 20).

treating focal chondral and osteochondral defects (Fig. 5). In mosaicplasty, a small-sized cylindrical osteochondral graft is harvested from the less weight-bearing periphery of the femoral condyles at the level of the patellofemoral joint. The original places of harvesting are routinely left empty as in our clinical practice. Healing of these areas starts with bleeding-mediated mesenchymal stem cell invasion from the subchondral cancellous bone. Data from animal experiments, histological studies, and human second-look arthroscopies demonstrate that filling of donor sites with cancellous bone is accomplished by the fourth postoperative week, and by 8 to 12 postoperative weeks, their surface is covered by reparative fibrous cartilage tissue. At the same time, clinical practice shows that these donor channels may sometimes be sources of major bleeding. The risk for bleeding increases with grafts higher in number or in diameter. Based on our experience and other reports, this complication arises in 7% to 8% of cases in the immediate postoperative period.[20-23]

In the development of arthroscopic mosaicplasty technique, animal studies were pursued with different bioresorbable materials to decrease excessive bleeding from the donor channels. On the other hand, limited amount of bleeding impregnates the scaffold, resulting in fibrocartilage coverage of the donor site due to mesenchymal stem cell invasion. Many modern biodegradable materials have been tested including hydroxilapatite, polyglyconate-B, polylactate, polycaprolactone, and carbon rods.[24]

The use of hydoxilapatite, polycaprolactone materials, and carbon rods failed to provide an acceptable fibrocartilage formation on the gliding surface. Repair tissue generated by hydoxilapatite and polycaprolactone fillings was poor and resembled only a weak connective tissue. Carbon material produced a reasonable granulation at 26 and 30 weeks, but the quality of the repair tissue was poor. The polyglyconate filling did not provide acceptable good results. Continuous fibrocartilage coverage occurred after compressed collagen fillings in 12 weeks and this coverage achieved an excellent quality in 26 to 30-week-old samples. Fibrocartilage coverage of good thickness was the only acceptable surface for the less donor-site requirements.[24] Based on these histological observations, the use of compressed collagen material seems to be more promising than other materials used to fill donor areas (Fig 6).[24]

The Polyactive plugs prevent joint bleeding, at the same time they do not interfere with the healing capacity of donor sites. They promote formation of superficial fibrous cartilaginous tissue and do not hinder vascular and tissue integration in deeper layers.[9]

Better surface congruence was observed at the donor sites filled with Polyactive B, compared to that of the control group. Disintegration was observed in some parts of the implanted material; nevertheless, on the surface, fibrous cartilage of good quality appeared together with islands of hyaline type regeneration.

Based on the findings of this pilot study carried out in a small cohort of patients, the Polyactive B may be appropriate to fill up the donor areas. However, our observations should be verified by further studies.

The occurrence of hyaline islands in some cases is difficult to explain and requires further research. One possible suggestion is that the Polyactive B plug acts as a frame for the reparation of an osteochondral defect. Healing of the osteochondral defect results in bone replacement of good quality. On the other hand, one of the most important result is that reparative fibrous cartilage tissue is not of poorer quality compared to that of the reparative tissue developing at the donor sites that were left empty. Moreover, filling of the donor sites with Polyactive B resulted in better congruence compared to empty sites where some protrusion of reparative tissue was observed.

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