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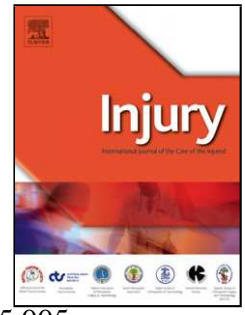

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History of osteochondral allograft transplantation

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Abstract

Osteochondral defects or injuries represent the most challenging entities to treat, especially when occur to young and active patients. For centuries, it has been recognized that such defects are almost impossible to treat. However, surgeons have never stopped the effort to develop reliable methods to restore articular cartilage and salvage the endangered joint function. Osteochondral

allograft transplantation in human was first introduced by Eric Lexer in 1908. Since that era, several pioneers have been worked in the field of osteochondral allotransplantation, presenting and developing the basic research, the methodology and the surgical techniques. Herein we present in brief, the history and the early clinical results of osteochondral allograft transplantation in human.

KeyWords: Osteochondra; transplantation; Allograft; history;

Osteochondral defects or injuries represent the most challenging entities to treat, especially when occur to young and active patients. Such lesions involve the articular cartilage and the subchondral bone. For centuries, it has been recognized that such defects are almost impossible to treat. Back in 1743, William Hunter (1718-1783) stated that "from Hippocrates down to the present age, ulcerated cartilage is a troublesome disease; when destroyed, it is not recovered" [1, 2] (**Figure 1**). Almost 100 years later, in 1851, Sir James Paget wrote, ''There are, I believe, no instances in which a lost portion of cartilage has been restored, or a wounded portion repaired, with new and well-formed permanent cartilage, in the human subject.'' [3]. Since that era, tremendous effort has been made by orthopaedic surgeons to develop reliable methods to restore articular cartilage and salvage the endangered joint function.

Both mechanical or biological methods have been developed for the treatment of the symptomatic osteochondral lesions. Osteotomies, arthroplasty, micro-fractures, abrasion arthroscopy, mosaic-plasty and autologous chondrocyte transplantation techniques are currently used as treatment options. However, each method has limitations. Arthroplasty is generally not recommended for young active patients due to the risk of early failure or infection. Microfractures and abrasion arthroscopy leads to the formation of fibrocartilage or mixed hyaline and fibrocartilage. Mosaic-plasty has the limitation of donor site morbidity and autologous chondrocyte transplantation demands two operations and is an expensive procedure. Even more importantly, all these methods are generally limited to defects less than 2-3 cm^2 and 1-2 cm deep [4-6].

On the other hand, fresh osteochondral allograft transplantation involves the transfer of size-matched allograft cartilage and subchondral bone into chondral or osteochondral defects. This method not only restores true type II hyaline cartilage but also directly address any associated bone defects. The nature of allograft chondral tissue is ideal for transplantation as it is avascular and

aneural tissue. Moreover, studies have shown that it is also relatively immunologically inactive and privileged, as the chondrocytes are embedded in the extracellular matrix [7].

Henri Judet, first reported the implantation of osteochondral grafts in animals [8] but the clinical use of allograft joint transplants was first introduced by Lexer in 1908. Eric Lexer (**Figure 2**) was born in Freiburg, Germany in 1867. He graduated medical school in Wurzburg in 1890 and he received his surgical training in Berlin. He was appointed Professor of surgery in Koninsberg, Jena, Freiburg and finally Munich in 1928. He died in 1937, leaving a tremendous amount of work in the fields of anatomy, bone infections and tissue transplantations. In the clinical setting, he was famous as a general and plastic surgeon [9].

Lexer published his early experience with "joint allotransplantation" by three different methods; half joint replacement, both articular surfaces replacement and total joint transplantation, including joint capsule. The first case to present was a 38 years old male with proximal tibia sarcoma. The affected part of patient's proximal tibia was surgically removed and replaced by a proximal tibia osteochondral allograft. The allograft was taken, in a synchronous way, by a man whose leg was amputated due to gangrene. At the 8 month follow up, Lexer evaluated the outcome of this procedure as excellent. Interestingly, he described the procedures of allotransplantation of half joints and even total joints with good and fair results. All transplants were obtained by fresh amputated legs at the same day of surgery. However, he acknowledged that joint transplantation is not an easy procedure and that he was not able to promise successful and permanent results [10]. By 1925, Lexer had documented 34 hemi or whole knee allogenic implants in humans and reported a 50% success rate. [11]

The following years a few more case reports [12, 13] had been published but the interest on osteochondral allograft transplantation remained limited, until the early 1970's, when early reports of large series appeared. Volcov, from the Central Institute of Traumatology and Orthopaedics in Moscow, published in 1970 a series of 145 operations of joint allotransplantation. He reported four groups of operations; focal osteochondral transplantation, one joint surface with its supporting bone replacement, two joint surfaces replacement and whole joint complex replacement [14]. In most of the cases allografts harvested by persons that have died by injury or myocardial infraction, were preserved by freezing in -70 ^{o}C for 24 hours, followed by storage at -30 ^{o}C. Volcov reported good results in all fifteen cases of partial joint replacement and 60% good

results in patients with half joint replacement. In fifteen cases with total joint allotransplanations he reported inferior results eighteen months after transplantation [14].

Approximately at the same period, Ottolenghi [15] and Parrish [16] published their experience with osteochondral allograft transplantation. In 1972, Carlos Ottolenghi presented the results of 62 patients with osteoarticular or metadiaphyseal bone allograft transplantation. From these patients 16 received osteoarticular transplant, mainly due to bone tumor resection. All grafts were obtained from dead people due to accidents or from amputated extremities of patients with congenital defects. The grafts were removed within 6 hours of death, under sterile conditions, and were stored in sterile boxes or bottles. Then, they were presented in freeze of -15 ^{o}C to -25 ^{o}C. All grafts were used within 6 months of harvesting. Before implantation grafts were thawed in a solution of penicillin for 30-60 mins. Overall 59% of patients had finally good results. Interestingly, Ottolenghi reported that in cases of osteoarticular allografts, results were good, (good range of joint motion and pain-free) even in cases that there were signs of graft absorption and necrosis [15].

Similarly, in 1973, Frank Parrish, from Texas published the results of massive osteochondral allograft transplantation in patients with tumor of the end of long bone [16]. Overall, 22 massive allografts were transplanted in 21 patients. Eleven patients had total and five partial replacements of different large joints, including the distal femur, the distal and proximal end of the tibia and the proximal end of humerus. The grafts were removed from adult donors, whose cause of death was trauma or heart disease. The osteochondral grafts were harvested within the first twelve to eighteen hours after the death of the donor, under usual sterile conditions. Cultures were taken and grafts were stored in -20 ^{o}C for at least three weeks. Twenty-four hours before transplantation, the grafts were removed from deep freeze and were submerged in solution containing neomycin and bacitracin and kept in ordinary refrigeration temperature. Parrish reported that at the latest follow-up, sixteen patients still had their limbs, three had amputations and one was lost to follow-up. The clinical results and functional status of patients varied extensively but he did mention that these results appeared to justify continuation of the osteochondral allograft transplantation procedure [16].

The revived interest in osteochondral allograft transplantation that was observed in the late 60’s and early 70’s can be attributed to the better understanding of the grafts immunogenicity and

the optimal methods of preservation and storage. Early experimental studies by Paul Curtiss [17-19], and Herndon [20], effectively showed that freezing the cadaveric bony parts reduce immunological activity and thus reduce the rejection rate. Fred Langer and co-workers from Canada, have also shown that a blocking antibody was produced by the temperature reduction [21]. Also Langer and Gross, in 1974 concluded that chondrocytes are relatively immunoprivileged, as the surrounding matrix protects them from the immunocompetent cells assault [7] . On the other hand, also early studies have shown that preservation of the grafts by freezing cause chondrocyte death in 90% to 50%, depending on the freezing methods [22]. Thus, different centers, mainly in North America and elsewhere have started to use different methods of cryopreservation of osteochondral allografts with mixed results. Generally, the standards for grafts cryopreservation have been established at either -70 to -80 ^{o}C for frozen grafts or 4 ^{o}C for "fresh" grafts. Additionally, Ringer's lactate or cryoporotectants, such as ethylene glycol, dimethyl sulfoxide or glycerol were used during the freezing process to minimize chondrocyte death. At the same time the first bone banks were developed [23] and relatively large series with the first results in humans have started to be published.

Allan Gross has been a pioneer in the use of osteochondral transplantation for traumatic defects of the hip and knee. Gross and co-workers published in 1975 the first results of allotransplantation of osteochondral allografts in the treatment of knee osteoarthritis in eight patients [24]. Grafts were harvested within 24 hours of the donor's death and were stored in Normasol M with Gentamycin and cephaloridine at 4 ^{o}C until implantation. They reported the early follow-up from 6 months to 2 years post-surgery. Results were very encouraging, as there was no rejection, all patients were fully ambulatory and developed good functional range of movement. In one patient they performed histological testing that revealed cartilage viability at 14 months [24].

Few years later, the same group published the results of 110 osteochondral transplants in patients with deficits due to degeneration, trauma, and neoplasm, mainly involving the knee joint [23]. They have used fresh grafts stored at 4 ^{o}C in Normosol M with cefazolin and gentamycin or frozen grafts stored at -70 ^{o}C. Fresh grafts were used within 24 hours from harvesting. They analyzed results of small fragment grafts (mainly fresh) and large fragment grafts (fresh or frozen). Overall, they reported 78 small fragment grafts and 32 large fragment grafts. Interestingly they reported that graft success depended more on the fate of bone than that of the cartilage, meaning

that if the bony part of the graft was compressed or fragmented, instability and malalignment occurred and the donor cartilage could be replaced by host fibrocartilage. Grafts with better results were those done for plateau fractures, trauma and giant cell tumors [23].

Beaver and co-workers, from the same center in Canada, reported the survivorship analysis of fresh osteochondral allografts of the knee in 98 patients (99 knees) [25]. In this series, donors were chosen to be less than 30 years old, to maximize cartilage quality. Grafts were harvested within 24 hours of death and when possible within 12 hours. Storage was made in antibiotic containing sterile Ringer's solution and temperature of 4 ^{o}C. The mean follow-up time was 68 months. Survival analysis showed that at five, ten and fourteen years after transplantation, the clinical success rate was 75%, 64% and 64% respectively. Authors analyzed that clinical success depended more upon biomechanical factors than upon graft rejection. Additionally, they stated that for the long term survival of the fresh allograft, there are three perquisites; firstly the transplanted chondrocytes must remain viable. Secondly chondrocytes must continue to produce sufficient proteoglycan and collagen and thirdly the subchondral bone must be preserved [25].

Marvin Meyers and co-workers from Texas, presented their experience with fresh osteochondral allograft transplantation in 20 (21 hips) relatively young patients suffering from segmental collapse, in osteonecrosis of the hip [26]. Donors were 16-40 years old and the whole femoral head graft was harvested within 12 hours from death. Allografts were placed in antibiotics containing Ringer's solution and stored in 4 ^{o}C for up to 72 hours. Authors reported that 15 of the 21 hips had successful results. Nine patients had more than 18 months follow-up, five more than two years and two five years follow-up. The overall success rate was 71%. Patients with steroid induced avascular necrosis did worst [26].

John Garrett, also published the early results of osteochondral transplantation in 24 patients, suffering from osteochondral defects of a femoral condyle [27]. He has used fresh allografts from young donors. Transplantation was done within 12 hours from harvesting. The follow-up time was between 1 and 4 years. Garrett reported good results, as all patients improved at the latest follow-up. He was able to arthroscopically evaluate 11 allografts and concluded that in all cases graft appeared viable [27].

These are some of the earliest follow-up studies, demonstrating good to excellent clinical results of osteochondral allograft transplantation, mainly in the fields of hip and knee surgery.

Following these encouraging results research efforts have been intensified and better methods of allograft harvesting, handling, preservation and implantation have been presented [28-30]. Use of osteochondral allografts has been expanded to almost all the fields of orthopaedic surgery, including the patellofemoral joint [31], foot and ankle [32, 33] and shoulder and elbow [34-36] surgery. Long follow-up studies have recently been published confirming excellent long-term graft survival [37-39].

There is no dough that as research continues in several areas, results will further be improved. Surgical techniques will be simplified and better tissue banking networking will allows a greater number of osteochondral allografts to become available for patients. Thus the "miracle" performed by Saints Cosmas and Damian, at the sixth century AD [40], known as "The miracle of the black leg" (**Figure 3**), will come as closer to reality as ever.

Conflict of Interest: The authors declare no conflict of interest

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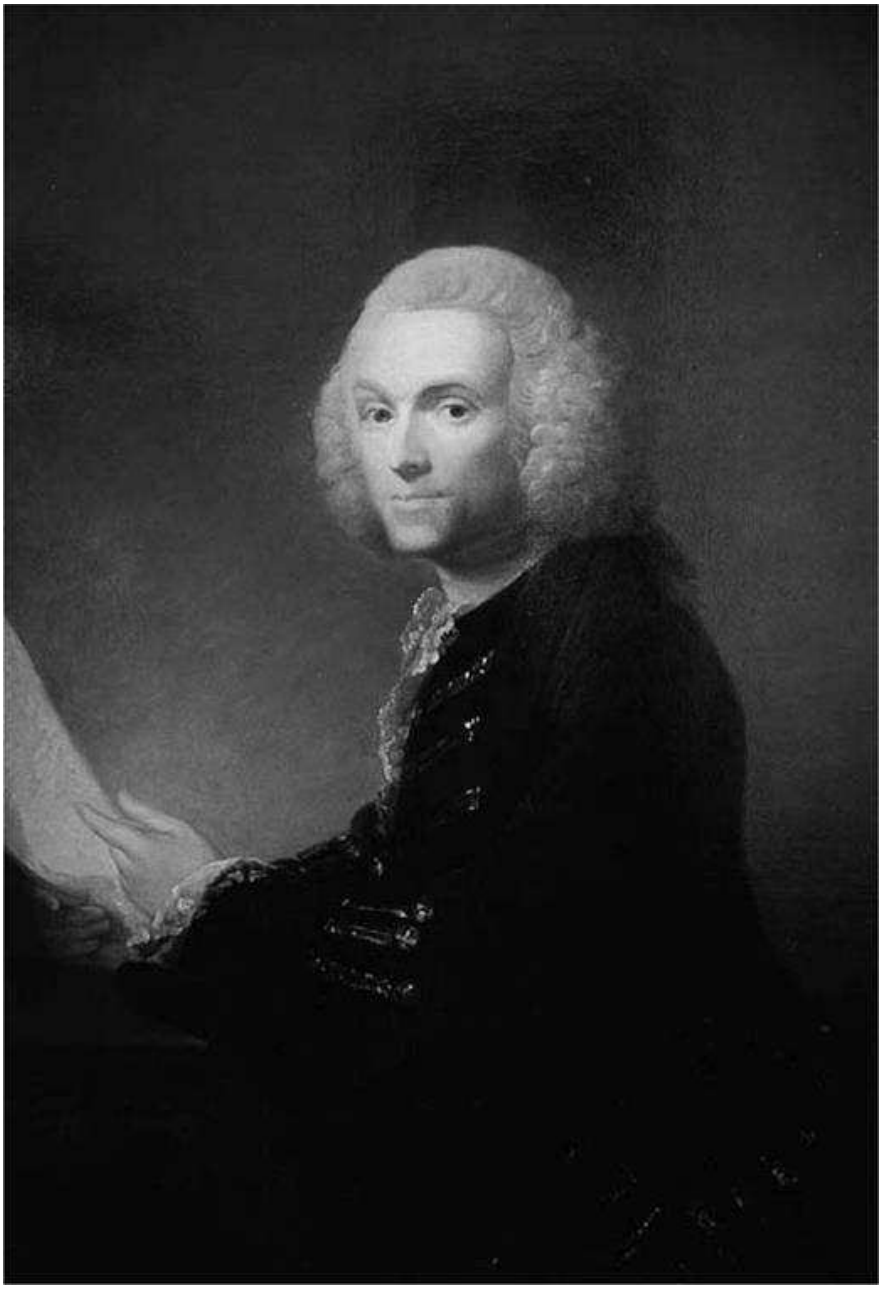

Figure 1: William Hunter (1718–1783).

Figure 2: Dr. Erich Lexer (1867–1937)

Figure 3: Spanish altarpiece of Saints Cosmas and Damnian, performing the miracle of transplanting a leg (the miracle of black leg).