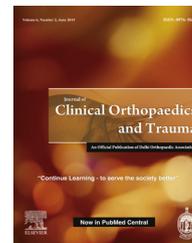


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Review article

2016 barriers to cartilage restoration

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ABSTRACT

Cartilage restoration has flourished since the 1990s. The early pioneering work included cell therapy by Peterson, marrow stimulation by Johnson, osteochondral autograft treatments by Hangody, and osteochondral allografts by Gross. Since those early days, many scientists and clinicians have created “variations on a theme”, markedly expanding the potential options for treating patients with symptomatic chondral lesions. Nevertheless, a variety of barriers exist between these new cartilage products and their clinical applications. These barriers may be categorized as cost, regulatory, insurance, and logistical issues. While absolute solutions will remain elusive, the current goal is to define these barriers as the first step toward solving these problems.

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1. Historical background

Cartilage restoration is a relatively new field of orthopedic surgery, yet the value of preserving the joint instead of replacing it has long been attractive to surgeons and patients alike. In the beginning, osteochondral allograft transplantation arose in the academic setting where tissue harvest and brief storage was possible. The pioneers (Gross et al.,¹ Mankin et al.,² Malinin et al.,^{3,4} Convery et al.,⁵ and Myers et al.⁶) demonstrated the efficacy, but widespread adoption was limited by procurement

and processing hurdles. Marrow stimulation techniques were developed based on the early work of Pridie⁷ and expanded into the general orthopedic community with the advent of arthroscopy and pioneering work of Johnson⁸ with abrasionoplasty. However, not until the introduction of microfracture as popularized by Steadman et al.⁹ in the 1990s did marrow stimulation truly gain widespread adoption. In the mid-1990s, Bobić et al.¹⁰ and Hangody et al.¹¹ added the technique of small osteochondral autografts in the form of osteochondral autograft transfer and mosaicplasty, respectively. Cellular-based (cultured) chondrocyte therapy was introduced by Peterson et al.¹²

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Abbreviations: ACI, autologous chondrocyte implantation; AMIC, autologous matrix-induced chondrogenesis; ICRS, International Cartilage Repair Society; MACI, matrix-induced autologous chondrocyte implantation; NICE, United Kingdom National Institute for Health and Care Excellence; QALY, quality-adjusted life year; RCTs, randomized controlled trials.

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with a publication in 1994. In the early 2000s, clinicians and scientists expanded marrow stimulation and cellular applications with a variety of cell and scaffolds approaches. Now a decade later, while cartilage restoration basic science is flourishing and multiple promising techniques are technically available, there remain multiple barriers to routine clinical application around the world. These barriers include the expense of technology, as well as regulatory and logistical hurdles. Understanding these barriers is the first step in overcoming them.

2. Cost

The absolute costs of different techniques are highly variable; however, cost should not be the only consideration, but also quality of the restoration and its durability over time, i.e. cost effectiveness. Across medicine, the attempt to calculate this is typically termed Quality-Adjusted Life Year (QALY), which is a measure of both the quality and the quantity of life lived. In 1998, Minas¹³ reported that the cost per additional quality-adjusted life year for autologous chondrocyte implantation (ACI) was \$6791, an amount that was in line with other routine orthopedic procedures. This was supported by Lindahl et al.¹⁴ in 2001 who reported on cost savings of \$88,000 due to reduced sick leave over 10 years when used on defects greater than 2 cm². However, conflicting data exists: the UK National Institute for Health and Care Excellence (NICE) reviewed various types of cartilage restoration in 2005, concluding that the data was inconsistent and quoting one analysis where cost effectiveness was better for microfracture than ACI.^{15,16}

Overall, however, for the individual patient in a specific country, this overview is of lesser concern than limits imposed by their insurance, their social medicine benefits, and what they can personally afford. In the developed world, socialized medical programs typically have limits on expensive new technology. These decisions are based on reviews such as Cochrane, NICE, and other reports, which note a lack of Level 1 evidence-based studies that, to them, would clearly demonstrate sustained superiority of one technique over another. Thus, given the relative lack of long-term data in these situations, the allowed techniques are the ones that are cheapest at time point zero. This approach favors one-stage procedures and excludes culturing cells. Of the one-stage procedures, variations of marrow stimulation (abrasionoplasty, microfracture and drilling) are the most common, followed by osteochondral autograft transfer. With the lesion size constraints of autograft plugs, the majority of cases are therefore currently treated with marrow stimulation. Noting the poor durability of marrow stimulation as shown by Kreuz et al.^{17,18} and Mithoefer et al.,¹⁹ there has been a push to develop cost-effective means to improve the tissue quality, durability, and thus clinical outcomes through the use of various scaffolds.

The issues of allograft are more complex than just cost, but cost does play a role. In 2016, Spalding²⁰ [ICRS Focus Meeting- Allografts] presented cost data for a number of allograft tissues. Costs and availability were generally higher in the developed world, and markedly lower in the developing world. For example, the average cost of fresh osteochondral allograft

in the US is approximately \$11,000, compared with a cost of \$1200 in Iran. Costs will be shown to enter into the complex equation of logistics as well.

3. Regulatory

Each country or region (e.g., EU) has their own unique requirements for medical products to be allowed in the market. As these are agencies founded by law, their mandates change over time. For example, the Japanese agency has recently relaxed the regulatory process by changing the focus to safety and will let post-market release studies and the payers ultimately determine availability. On the other hand, the EU has tightened the process for cell therapy approval and now requires an adequately powered randomized controlled study—similar to the US FDA. However, this remains a process in flux noting that the FDA appears to be considering the use of historical controls for one new product under evaluation for a pivotal study (Gelrin, Regentis, Israel) and the use of EU data for another (MACI, Vericel, USA). The requirements for scaffolds are less clear as it is possible for a product to be approved for one use (dental void filler) and then surgeons apply it “off-label”, as allowed under law. For cartilage restoration in the US, one such example is the BioGide membrane (Geistlich, Switzerland) used with ACI and AMIC.

Even more confusing to the casual observer is allograft tissue. In the US, the FDA oversees the procurement and processing of allograft tissue, but not the use of the tissue if used orthotopically without manipulation (FDA regulation HCT/P 361 vs 351). This is straightforward when a medial femoral condyle allograft is transplanted into a medial femoral condyle defect. The concept becomes more blurred when tissue is “processed”, but declared minimally manipulated through internal company review. Specifically, what is the boundary between minimally manipulated and more than minimally manipulated? Industry currently interprets this on a case-by-case basis with examples including minced tissue (DeNovo NT, Zimmer Biomet, USA) or micronized lyophilized cartilage (Biocartilage, Arthrex, USA), both of which are considered minimally manipulated and thus exempt from the stricter FDA requirements applied to medicinal and cell-based products.

In some countries, allograft may not be allowed under the law. As laws are made by people, people can change them. A recent example occurred in Brazil, where Dr. Luis Tírico from University of Sao Paulo led a legislative effort to change the law, which succeeded. The process has been documented by Tírico et al.²¹ and may serve as a template for other countries where legal barriers exist.

4. Insurance (private and national health care)

Private insurance and national health insurance have a system of medical policies for determining allowed medical and surgical treatments. These are formulated based on evidence-based medicine. Unfortunately, for cartilage restoration, these policies are largely developed using a common framework for all medical policies. While the framework for

policies is laudable, it is largely developed by non-surgeons addressing medical diseases that affect multiple millions of patients, rather than the relatively low numbers of patients needing cartilage restoration. As a result, these policies typically require two or more RCTs (randomized controlled trials) with Level 1 evidence. Recently, Lyman et al.²² reviewed study designs and concluded that RCTs may not be the optimal means of evaluating cartilage restoration procedures, and more broadly, medical and surgical trials need to be approached differently for a variety of statistical, ethical, and equipoise reasons. Nevertheless, at present, cartilage restoration procedures are frequently trapped in medical policies that use circular logic. That is, if the criteria of the medical policy are not met, insurance labels the device, implant or drug as “experimental and investigational”, which is not covered. However, since insurance cannot dictate medical treatment, patients are not prohibited from receiving the treatment. As it is the rare patient who can afford to pay for the more advanced techniques, patients receive only treatments paid for by their insurance. Interestingly, clinical evidence appears to have little influence over these medical policies – although multiple studies show the limited outcomes of marrow stimulation treatments for patients over 40, and large (>4 cm²) or patellar lesions, marrow stimulation remains the one technique covered by nearly all health systems and insurance companies across the world.

5. Logistical

While logistical considerations may seem trivial, in fact, they may be one of the largest barriers. At the 2016 ICRS Focus Meeting on Allografts in Brussels, it became obvious that tissue may be available in concept, yet not functionally. This problem existed in the US in the pre-2000s when only academically based tissue processing was available. Thus, only academic surgeons at these centers had access to the tissue. Once commercial and not-for-profit organizations entered the market, tissue became more widely available to both academic and nonacademic surgeons. At that point, the scale of procurement overcame prohibitive costs. The early growing pains of similar programs in Europe echo the US development: while the demand is there, the cost of procurement, processing, and delivery limit supply. The supply cannot allow development of an adequate demand for the delivery numbers to provide recovery of investment. At some point, government or the private sector need to jump into the chiasm with faith to allow supply and demand to equilibrate and create an adequate return on investment for the loop to become continuous.

6. Conclusions

Cartilage restoration is a desperately needed bridge for young patients with symptomatic cartilage lesions. Left untreated in some patients, these lesions will lead to frank osteoarthritis. To allow multinational evidence-based medicine treatment, concomitant resources must be made available to address the current inadequacies within cost, regulatory, insurance, and logistical aspects of cartilage restoration.

Conflicts of interest

The authors have none to declare.

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