REVIEW ARTICLE

CONTENTS

Biomaterials in cartilage damage

Marta Żerebiec[1], Weronika Woźnica[2], Natalia Kołodyńska[1], Zuzanna Kołodyńska[1], Natasza Jankowska[3], Lena Sobiech[4], Vivek Vasudevan[1], Katarzyna Jóźwik[1], Karolina Turżańska[5], Małgorzata Drelich[5]

[1]STUDENT SCIENTIFIC ASSOCIATION AT THE DEPARTMENT OF REHABILITATION, MEDICAL UNIVERSITY OF LUBLIN, LUBLIN, POLAND

[2]MEDICAL UNIVERSITY OF LUBLIN, LUBLIN, POLAND

[3]SPECIALIST DENTAL OUTPATIENT CLINIC, 5TH MILITARY CLINICAL HOSPITAL WITH POLYCLINIC, INDEPENDENT PUBLIC HEALTHCARE INSTITUTION, CRACOW, POLAND

[4]MEDICAL UNIVERSITY OF GDAŃSK, GDANSK, POLAND

[5]DEPARTMENT OF REHABILITATION, MEDICAL UNIVERSITY OF LUBLIN, LUBLIN, POLAND

ABSTRACT

Aim: Cartilage tissue degradation is a common symptom of diseases affecting the musculoskeletal system. Impairment of its function can occur due to numerous factors, both external and internal. Thanks to advances in imaging techniques, identifying pathologies in cartilage tissue is becoming increasingly common, leading to a search for optimal treatment methods. Human cartilage has a limited capacity for self-repair. Treatments such as transplants have many limitations, which is why biocompatible materials are becoming increasingly popular. This article presents selected biomaterials that may be useful in the treatment of cartilage pathologies. Current research on the use of biomaterials in cartilage regeneration was analyzed.

Materials and Methods: The research material consisted of scientific publications describing the use of natural and synthetic scaffolds in animal models and clinical trials. Particular attention was paid to gelatin, silk fibroin, polylactic acid, polycaprolactone, poly(lactic-co-glycolic acid), and commercial biomimetic scaffolds. Methods included analysis of mechanical properties, biocompatibility, and the ability to support chondrogenesis.

Conclusions: The study results indicate that appropriately modified biomaterials can effectively support cartilage regeneration and improve its structure and function. Further research is needed to improve the treatment of cartilage injuries and diseases, and to optimize biomaterials used in cartilage tissue engineering.

KEY WORDS: cartilage injuries, cartilage tissue engineering, tissue scaffolds, biomimetic materials, biocompatible materials

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INTRODUCTION

There are three types of cartilage tissue in the human body: hyaline, fibrous, and elastic. Cartilage tissue provides support and cushioning, enabling smooth movement of bones within joints, shaping human features (e.g., the nose), and providing support, such as reinforcement of the trachea. The proper functioning of cartilage depends on the composition and structure of its extracellular matrix [1]. Deterioration of cartilage tissue and thus impairment of its function can occur due to factors such as aging, repetitive stress during daily activities, degenerative disease, rheumatoid arthritis, and genetic factors [2]. Thanks to advances in imaging techniques and the widespread availability of magnetic resonance imaging, the identification of cartilage tissue pathologies is becoming increasingly common. Unfortunately, human cartilage has limited self-repair capacity [3]. Interventions such as allografts, autografts, and bone marrow stimulation also have numerous limitations. Allografts are at high risk of cell death during storage, and bone marrow stimulation yields cartilage of much lower quality [4]. These limitations have contributed to advances in cartilage tissue engineering. Thanks to this field of science, we can create cartilage-like structures that mimic the biochemical and mechanical properties of natural cartilage [5]. Both natural and synthetic materials have been studied for use in cartilage tissue engineering. Studies have shown that natural polymers (such as gelatin and fibrin) are bioactive and biocompatible. In contrast, synthetic polymers (such as poly(lactic-co-glycolic acid), polycaprolactone, and polylactic acid) are amenable to modification of their mechanical properties and degradation rate [6]. Furthermore, in recent years, commercialized biomimetic scaffolds designed to achieve cartilage regeneration have also appeared on the market. These include MaioRegen, Agili-C, and TruFit [7].

AIM

This article presents selected biomaterials that may be useful for the treatment of cartilage pathologies.

MATERIALS AND METHODS

To create this article, databases such as PubMed and Google Scholar using keyword combinations: "cartilage defects," "natural biomaterials," "synthetic biomaterials," "commercialized biomimetic scaffolds," and "cartilage tissue engineering," as well as "silk fibroin," "gelatin," "polylactic acid," "polycaprolactone," and poly(lactic-co-glycolic acid)" was searched. Ultimately, we included 39 articles, selected based on their high relevance and innovative nature in the context of biomaterials for cartilage repair.

REVIEW

BIOMATERIALS USED IN THE TREATMENT OF CARTILAGE DAMAGE

The basic classification of biomaterials distinguishes between natural and synthetic biomaterials. Plants and animals have become the source of natural biomaterials, while synthetic biomaterials are produced in laboratory conditions [8].

NATURAL BIOMATERIALS

The basic groups of natural biomaterials include glycosaminoglycans (e.g., hyaluronic acid), polysaccharides, proteins, and extracellular matrix materials (e.g., eggshell matrix). Their advantages in the context of tissue engineering include low production costs and good availability, as well as biocompatibility and biodegradability [8]. The basic classification of biomaterials distinguishes between natural and synthetic biomaterials. Plants and animals have become the source of natural biomaterials, while synthetic biomaterials are produced in laboratory conditions [8].

SILK FIBROIN

Silk fibroin is a protein isolated from silk that is rich in glycine, alanine, and serine [9]. Along with other compounds such as collagen and glycosaminoglycans, silk fibroin forms the extracellular matrix of chondrocytes. It plays a crucial role in the maturation and differentiation of these cells and is therefore essential for maintaining the proper structure and function of cartilage tissue [10].

The advantages of silk fibroin in the context of cartilage tissue engineering include high biocompatibility, controlled biodegradability, and a very low risk of immunological reactions. This protein can be processed into a variety of forms, including solutions, powders, fibers, films, sponges, and hydrogels. These forms can be obtained using techniques such as electrospinning, spin coating, and freeze-drying [11]. By combining silk fibroin with other polymers, we can obtain composite scaffolds that can effectively enhance responses such as cell differentiation, proliferation, and adhesion [8]. For example, combining silk fibroin with glycidyl methacrylate gel demonstrates high cellular biocompatibility in vitro and provides a suitable environment for chondrocyte growth and survival. Furthermore, adding growth factors (e.g., insulin-like growth factor) to silk fibroin-based scaffolds improves chondrogenic outcomes and provides an alternative to autologous and allogeneic cartilage implants [12].

GELATIN

Gelatin is a major component of connective tissue, formed by the breakdown of the collagen triple helix [13]. It is a compound that stimulates the formation of the extracellular matrix. The biocompatibility and biodegradability of gelatin, as well as its affordability and ease of production, have made it a widely used compound in tissue engineering [14]. A study led by Maihemuti showed that 3D-printed scaffolds made from gelatin derived from cold-water fish are promising for repairing cartilage defects in the knee joints of mice [15]. Furthermore, the creation of composite scaffolds combining gelatin with other natural or synthetic polymers has also been shown to be effective in cartilage tissue engineering [16]. For example, chemically modifying gelatin by reacting it with methacrylic anhydride increases its thermal stability while maintaining its natural biocompatibility [17]. This fact has been confirmed by a study by Visser et al., which demonstrated that adding methacryloyl gelatin to equine cartilage matrix particles yields a composite with stiffness and elasticity very similar to those of natural cartilage tissue [18].

SYNTHETIC BIOMATERIALS

In orthopedic applications, there are three basic categories of synthetic biomaterials: metals (characterized by high resistance to deformation), ceramics (characterized by chemical inertness and low thermal conductivity), and biodegradable and non-biodegradable polymers (low density and good processability) [8].

POLYLACTIC ACID

Polylactic acid is a biodegradable, non-toxic plastic. This polymer is currently produced primarily from a non-renew-

able raw material, such as crude oil. An alternative route to its production is through the biotechnology industry, using lactic acid derived from renewable resources such as sugarcane. In addition to its biodegradability and non-toxicity, its advantages in tissue engineering include biocompatibility, thermoplasticity, and good moldability [19].

An in vitro study conducted by Liang et al. demonstrated that nanofibers produced by grafting polylactic acid chains onto lignin can positively influence chondrogenic differentiation, thereby facilitating the regeneration of damaged cartilage. They found that lignin-polylactic acid-containing scaffolds had excellent antioxidant properties and promoted favorable expression of cartilage-specific genes. Additionally, they maintained a balance with the expression of late-stage chondrogenesis genes [20].

POLYCAPROLACTONE

Polycaprolactone is a biodegradable aliphatic polyester that is thermally stable at temperatures above 300 degrees Celsius. It is widely used in medicine due to its properties, including good solubility, long degradation time, and low melting point. Polycaprolactone has been approved by the Food and Drug Administration and hailed as an extremely promising compound in tissue engineering due to its thermal stability [21]. In their study, Liu Y. and co-investigators fabricated porous scaffolds from poly(glycerol sebacate)/polycaprolactone using the salting-out technique. This experiments demonstrated that articular chondrocytes successfully adhered and proliferated on these scaffolds during short-term culture. Furthermore, bone marrow-derived stem cells differentiated into chondrocyte-like cells on the same scaffolds. This demonstrated that poly(glycerol sebacate)/polycaprolactone scaffolds are promising for cartilage tissue regeneration; however, further in vivo studies are needed [22].

POLY(LACTIC-CO-GLYCOLIC ACID)

Poly(lactic-co-glycolic acid) is a popular biodegradable polymer. Both the Food and Drug Administration and the European Medicines Agency have approved this compound as safe and effective for various medical applications, including orthopedic stabilization. Its hydrolysis produces lactic and glycolic acid monomers, which are then metabolized via the Krebs cycle. Consequently, it is characterized by extremely low toxicity [23].

Poly(lactic-co-glycolic acid) has many advantages for cartilage tissue engineering. These include controlled biodegradability and a near-complete lack of immunogenicity. This polymer supports cell differentiation and viability, thus offering potential as a scaffold material for the regeneration of cartilage pathologies [24]. A study led by Morille demonstrated that poly(lactic-co-glycolic acid)-based scaffolds can provide an optimal environment for mesenchymal stem cell differentiation into chondrocytes [25]. Furthermore, Toyokawe and co-investigators demonstrated, using a rabbit model, that a cannulated poly(lactic-co-glycolic acid) scaffold can regenerate and repair full-thickness osteochondral defects, thus demonstrating excellent predisposition for regenerating damaged cartilage [26].

COMMERCIALIZED BIOMIMETIC SCAFFOLDS

Commercialized biomimetic scaffolds include MaioRegen, Agili-C, and TruFit. These scaffolds were developed to promote cartilage regeneration and have shown promising results, but are not yet widely used for this purpose. Currently, these biomaterials require further and more extensive research due to discrepancies in radiological findings and the low quality of available studies [7].

MAIOREGEN

MaioRegen (Finceramica, Italy) is the most thoroughly studied biomimetic multilayer scaffold designed for in situ cartilage regeneration. This nanostructured implant consists of varying proportions of collagen and hydroxyapatite arranged in three distinct layers. The first layer, which recreates smooth cartilage, is composed entirely of type 1 collagen, the intermediate layer is composed of 3/5 type 1 collagen and 2/5 hydroxyapatite, and the deepest layer is composed of 30% type 1 collagen and 70% hydroxyapatite [27].

In their study, Kon and co-investigators examined 100 active athletes with symptomatic changes in the cartilage and subchondral layer of the knee joint. Some patients were treated with MaioRegen, while others received microfracture. After a two-year follow-up period, therapy using the biomimetic multilayer MaioRegen scaffold yielded significantly better results in the treatment of osteochondral lesions [28]. Furthermore, the simultaneous use of MaioRegen and bone marrow stimulation results in the scaffolds being filled with cytokines and stem cells from the patient's own bone marrow, stimulating cartilage regeneration directly at the site of injury [29].

AGILI-C

Agili-C (CartiHeal, Israel) is an acellular aragonite scaffold. It was designed to replicate the natural structure

and function of joints. Its action aims to stimulate cartilage and subchondral regeneration and operates through a dual mechanism. The first mechanism involves facilitating the adhesion and differentiation of bone marrow stem cells into chondrocytes. The second mechanism involves stimulating chondrocyte migration and proliferation from surrounding cartilage tissue and their deposition into the extracellular matrix [27].

Chubinskaya conducted a study demonstrating that Agili-C scaffolds supported cartilage regeneration and repair in human knee and ankle joints. The most important finding of the study was that acellular Agili-C scaffolds effectively attracted host chondrocytes and increased their cartilage potential [30].

TRUFIT

The TruFit insert (Smith & Nephew, USA) is an acellular synthetic scaffold composed of polylactide and co-glycolide [27]. Cartilage regeneration using the commercialized biomimetic TruFit scaffold was proposed to involve the infiltration of growth factors and bone marrow-derived cells into the insert, thereby facilitating integration and repair of damaged cartilage [31]. Recent studies recommended discontinuing the use of the TruFit insert due to poor graft integration and lack of significant clinical improvement [27]. TruFit was withdrawn from sale due to its low efficacy compared to other standard treatments for cartilage defects [32].

DISCUSSION

Despite medical advances, treating cartilage damage remains a significant challenge. There is a constant need to develop new methods that can effectively and fully regenerate cartilage. More and more research is being conducted in this direction, and biomaterials and cartilage tissue engineering are proving to be innovative.

Natural biomaterials offer several advantages over synthetic biomaterials in tissue engineering. They include mechanical adaptability, bioactivity that allows them to mimic the naturally occurring extracellular matrix, and numerous active sites [33]. However, their use also presents significant limitations. Challenges that must be considered when using natural biomaterials include their temperature sensitivity, difficult processing, and sometimes very complex chemical structure [34]. Among the most important natural biomaterials are gelatin and silk fibroin [6]. In their study, Maihemuti and colleagues developed gelatin scaffolds from cold-water fish skin, providing a biocompatible, low-immunogenic alternative to porcine gelatin. Using a 3D printer, they fabricated various types of scaffolds, which they used to effectively regenerate cartilage defects in the knee joint in a mouse model [23]. In their study, Li and colleagues developed a hydrogel composed of silk fibroin and carboxymethyl chitosan, which they tested in rabbit and mouse models. They demonstrated that the hydrogel supported chondrogenesis in rabbit joints while not triggering an immune response in mice [35].

The advantage of synthetic biomaterials over natural ones is that they can be modified to achieve a wider range of mechanical and chemical properties. Because they are produced under controlled laboratory conditions, we can predict their mechanical and physical properties and control material contamination. However, their greatest limitation in the context of tissue engineering is their limited biocompatibility [36]. In their study, Liang R. and co-investigators grafted polylactic acid chains of varying lengths onto lignin. They obtained copolymers that differed in the proportions of polylactic acid to lignin and their molecular weight. Using the resulting copolymers, they created nanofibrous scaffolds that served as a platform supporting cell growth and mimicking the environment of the cartilage matrix for cartilage regeneration. Ultimately, it was found that scaffolds containing lignin-polylactic acid 40 have a positive effect on the regeneration of damaged cartilage and may support the maintenance of balanced expression of the Col10al gene, which is responsible for the late phase of chondrogenesis [20]. Liu Y., in turn, conducted studies in which combining poly(glycerol sebacate) with polycaprolactone resulted in scaffolds with longer degradation times and increased stiffness. Furthermore, poly(glycerol sebacate)/polycaprolactone scaffolds demonstrated very good cytocompatibility with both bone marrow-derived stem cells and joint chondrocytes in vitro. In the study, bone marrow-derived stem cells demonstrated chondrogenic potential comparable to joint chondrocytes [22]. Toyokawa and co-investigators conducted a study demonstrating that poly(lactic-co-glycolic acid) scaffolds effectively repaired osteochondral defects measuring 5 mm in diameter in a rabbit model. Their study included a treatment group whose defects were treated with a cylindrical, cannulated poly(lactic-co-glycolic acid) scaffold and a control group (i.e., an untreated group). In the study group, fibrous tissue appeared on the scaffold surface as early as the second week after the procedure. Cartilage gradually formed on the joint surface, and bone was rebuilt in the subchondral layer. The regenerated cartilage remained intact until 24 weeks after surgery. In the control group, the untreated defects filled with hematoma as early as the second week, followed by cartilage and bone formation. However, the regenerated cartilage in the untreated defects failed to prop-

erly organize and exhibited an uneven joint surface. Histological studies showed that the groups treated with poly(lactic-co-glycolic acid) scaffolds achieved significantly better results than the control group at 12 and 24 weeks after surgery [26].

Commercialized biomimetic scaffolds designed for cartilage regeneration include MaioRegen, Agili-C, and TruFit [7]. They are relatively easy to use and offer advantages, such as a single-step procedure. However, to be widely used, these scaffolds require further research and more thorough evaluation of their efficacy [37]. Brix M conducted a study evaluating MaioRegen's ability to regenerate single osteochondral lesions ≥1.5 cm^2 in diameter on the femoral condyle. He enrolled eight patients in his prospective study. He assessed the repair capacity of the MaioRegen scaffold at intervals of 6, 12, 18, and 24 months using magnetic resonance imaging and semi-quantitative morphological analyses. Initially, his study demonstrated that the MaioRegen scaffold effectively filled the osteochondral defect. In seven of eight patients, complete integration of the scaffold at the junction was observed. However, 18 months after surgery, reduced quality of the repaired cartilage tissue was observed [38]. A study by Chubinskaya S et al. confirmed that the Agili-C scaffold supports cartilage regeneration and may provide a single-stage solution for the treatment of full-thickness cartilage defects. The study involved harvesting fresh human cartilage tissue from cadavers of different sexes and ages and then culturing it for 60 days with the Agili-C scaffold. The researchers found that chondrocytes migrated from a post-mortem cartilage explant into the porous scaffold, filling its entire volume with a newly formed extracellular matrix rich in type II collagen and aggrecan [30]. Regarding the effectiveness of the TruFit scaffold for cartilage repair, the available evidence is inconsistent. TruFit scaffolds were examined by MRI by Bedi et al., who analyzed 26 cases over 6 to 39 months. The consistent pattern of integration was observed among them. Initially, MRI results deteriorated between 6 and 12 months, but then improved with longer follow-up. In 90% of cases, TruFit scaffold integration was almost complete after 16 months. Barbar and Dockery, using computed tomography, analyzed 9 cases of TruFit scaffold use and concluded that the scaffold did not integrate successfully in any of the cases. Similarly, Dhollander and colleagues concluded that TruFit scaffold implantation was incomplete after 1 year, suggesting the need for a longer follow-up period [39]. Due to equivocal clinical results and lower efficacy compared to other treatments, TruFit was withdrawn from the market [32].

CONCLUSIONS

Further research is needed to improve the treatment of cartilage injuries and diseases, as well as to optimize the biomaterials used in cartilage tissue engineering. Increasing the number of long-term studies seems particularly important. This will enable the assessment of efficacy, durability, and safety, as well as the identification of the best therapeutic options for patients. Collaboration between clinicians, scientists, and industry representatives is crucial here. By deepening our knowledge of cartilage biology and tissue engineering, we can improve treatment and enhance the quality of life of patients with cartilage disorders.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Marta Żerebiec
Student Scientific Association,
Department of Rehabilitation, Medical University of Lublin
Lublin, Poland
e-mail: zerebiecm22@gmail.com

ORCID AND CONTRIBUTIONSHIP

Marta Żerebiec: 0009-0003-7438-238X A B D
Weronika Woźnica: 0009-0007-1549-7290 D
Natalia Kołodyńska: 0009-0002-2943-4315 B D
Zuzanna Kołodyńska: 0009-0000-0017-8317 B D
Natasza Jankowska: 0009-0009-0491-3716 B D
Aleksandra Bełżek: 0000-0001-5543-877X B D
Vivek Vasudevan: 0009-0009-8597-3867 B D
Karolina Turżańska: 0000-0001-7359-9622 E F
Katarzyna Jóźwik: 0000-0002-6499-8688 B D
Małgorzata Drelich: 0000-0001-6709-0440 E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

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