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BIOLOGICAL APPROACH TO THE ROTATOR CUFF REPAIR. FROM THE LAB TO THE PATIENT

Joanna Wałecka
Department of Orthopaedics, Traumatology and Hand Surgery, Poznan University of Medical Sciences, Poland
Rehasport Clinic, Poznan, Poland

SUMMARY
Shoulder pain is the second most frequent reason for patients' musculoskeletal complaints, the most common cause of pain being rotator cuff tendon tear (Matsen 2008). Although conservative treatment is widely suggested in the initial period of disease, the surgical treatment is basic. This procedure commonly involves restoration of the continuity of the tendon to the bone. The development of arthroscopic surgery and implant technology allows for a minimally invasive stabilization of the tendon attachment to the bone. In the course of the development of the techniques for rotator cuff (RC) tendon repair both biomechanical and biological aspects have been highlighted (Gerber *et al.* 1994; Apreleva *et al.* 2002). However, despite the improvement in tendon fixation methods, the problem of healing tendon disorders still remains crucial and unresolved. The goal of study is outlining the possible use of growth factors, scaffolds and stem cells therapy during rotator cuff repair, which might be instrumental in improving tendon-to-bone healing.

Keywords: rotator cuff injury, tendon-to-bone healing, growth factors, cell therapy, scaffolds

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PODEJŚCIE BIOLOGICZNE DO LECZENIA ZESPOŁU STOŻKA ROTATORÓW

Joanna Wałecka
Katedra Traumatologii, Ortopedii i Chirurgii Ręki, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu
Rehasport Clinic, Poznań

STRESZCZENIE
Ból barku jest jest drugą, najczęstszą przyczyną dolegliwości w układzie mięśniowo-szkieletowym. Najczęstsze przyczyny bólu mają miejsce po uszkodzeniu stożka rotatorów (Matsen 2008). Często jako wstępne leczenie zachowawcze w początkowym okresie choroby. Jednak leczenie operacyjne jest metodą podstawową. Procedura ta zwykle obejmuje przywrócenie ciągłości ścięgno-kości. Rozwój artroskopii i konstrukcji implantów umożliwia stabilizację z zachowaniem minimalnej inwazyjności. W trakcie rozwoju technik leczenia uszkodzenia pierścienia rotatorów uwzględniono i podkreślano zarówno udział aspektów biomechanicznych jak i biologicznych (Gerber i wsp. 1994; Apreleva i wsp. 2002). Jednak pomimo innowacji metod mocowania ścięgna, problem zaburzeń gojenia ścięgien jest nadal ważny i nierozwiązany. Celem tego doniesienia jest przedstawienie możliwości wykorzystania czynników wzrostu, rusztowań i komórek macierzystych w terapii podczas naprawy uszkodzonego pierścienia rotatorów.

Słowa kluczowe: uszkodzenie stożka rotatorów, leczenie ścięgno-do-kości, czynniki wzrostu, terapia komórkowa, rusztowania

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Introduction

Shoulder pain resulting from rotator cuff (RC) tear is one of the most common reasons for the patient's visit to an orthopaedic clinic (Matsen 2008). Many patients require surgical treatment, which is currently performed by shoulder arthroscopy aimed to restore the tendon-to-bone attachment, however, the structure of the rotator cuff tendon and the healing process in adults do not allow for the restoration of the normal tendon-to-bone attachment. According to researches, the risk of post-operative retear or tendon non-union ranges from 11% to 94% (Takahashi *et al.* 2002) and is especially high in chronic and massive RC tears. Study of Lubiatowski *et al.* (2013) showed the 13% risk of complete re-rupture or lack of healing of the RC tendons. Experimental studies and clinical observation reported that the main reason of failures treatment is biological. That is why it is necessary to further probe into this aspect, focusing on tendon structure and its healing processes.

Aim

The aim of the paper is to review the use of growth factors, scaffolds and stem cells therapy during rotator cuff repair, which might be instrumental in improving tendon-to-bone healing.

Clinical problem

It is important to consider tendon tear ethology when deciding on appropriate biological treatment. RC tear can occur as the result of acute injury but it most frequently arise from gradual tendon and tendon-to-bone attachment degeneration related to, for example, increasing age, repeated overload or impingement (Valentin *et al.* 2006; Fabiś *et al.* 2014).

Tendon-to-bone attachment is composed of several layers: tendons, fibrocartilage and calcified bone. Individual biomechanical characteristics of each layer are responsible for tensile strength of the tendon-to-bone attachment and they are resistant to compression and multidirectional forces. The structure of the tendon is hipovascular that is blood flow to the tendon is dynamic: it decreases in the extension phase (muscle contraction) and increases in the diastole phase. The most vulnerable part of the tendon is the critical zone of the supraspinatus tendon (SST), located about 1 cm from the tendon attachment, due to impaired blood flow in this area. Numerous factors contribute to gradual degeneration of the tendon, which usually progresses slowly. It results in chronic inflammation and degenerative changes, which can lead to partial or total damage of the tendon when blood supply is impaired. These include microtrauma, trauma, aging and apoptosis. To conclude, the tendon heals relatively more slowly than other connective tissues though both usually undergo similar stages during healing.

Microfracture

Therapeutic use of musculoskeletal growth factors (GFs) is a promising strategy to enhance tendon healing and decrease scar tissue while maintaining biomechanical strength. GFs are a group of cytokines that induce mitosis, extracellular matrix production, neovascularization, cell maturation and differentiation. An easy and cheap method to deliver GFs is performing microfracture to the greater tuberosity, laterally to the site of RC repair (Snyder and Burns 2009). The clot functions as a temporary scaffolding material with GFs reservoir (McCormack *et al.* 2014).

Bone marrow stem cells (*BMSCs*)

Bone marrow is the most commonly used source for stem cells, usually aspirated from the iliac crest or the humeral head (Beitzel *et al.* 2013a; Beitzel *et al.* 2013b). Alternative techniques for obtaining BMSCs are micro or nanofractures to the greater tuberosity, which safely expose tendon footprint. BMSCs probably pass through the holes and improve RC tendon healing. Milano *et al.* (2013) demonstrated that perform-

ing microfracture results in better healing of massive RC tears. In a 12-month follow up MRI analysis, Ellera Gomes *et al.* (2012) showed tendon integrity in all cases where BMSCs were injected to the RC repaired tendon.

Adipose-derived stem cells (*ADSCs*)
ADSCs are harvested from the fat tissue, which is a reproducible source of stem cells. In the literature one study is available in which Oh *et al.* (2014) improved fatty degeneration and RC healing in a rabbit model. The authors claim that local administration of ADSCs might bring about possible improvement in tendon healing.

Platelet rich plasma (*PRP*)
Platelet rich plasma consisting of autologous platelets and growth factors is widely used in RC repair. Baksh *et al.* (2013) underlined that the application of PRP enhanced the process of cell rebuilding, growth factors expression, vascularisation of RC tendons and fibrin reconstruction. Available reports vary as to the effectiveness of PRP on the healing tendon, which can manifest itself in a clinical trial as a reduction of pain shortly after surgery and an improvement of patient satisfaction (Randelli *et al.* 2011). On the other hand, some randomized control trials on PRP showed no effect on RC repair (Castricini *et al.* 2011; Rodeo *et al.* 2012). Studies on PRP application during RC repair differ in respect to PRP preparation, application methods and, also, in results. Barber 2013 (Barber 2013) suggest that the optimal combination of platelets and leukocytes is unknown. What is more, leukocyte level might be crucial to tendon healing.

Scaffolds in RC repair
The ideal scaffold should have appropriate mechanical properties to prevent or limit tendon retear after RC reconstruction. There are two types of scaffolds: biological and synthetic. Biological scaffolds can be classified depending on cell type (small intestine sub mucosa, dermis, pericardium and fascia lata) and source (human, animal). Synthetic scaffolds are manufactured from chemical components and consist of polymers (including polyester, polypropylene, polyacrylamide, Dacron, carbon, silicone, nylon). Thanks to their mechanical structure (host cell integration with three-dimensional protein microstructure and natural porosity), biological scaffolds allow for cell attachment, proliferation, migration and new tissue formation. On the other hand, synthetic scaffolds are thought to have little impact on the tendon-to-bone healing process, however, their ability to maintain mechanical characteristics over time may stabilize the RC tendon repair (Encalada-Diaz *et al.* 2013). Reports on the use of biological scaffolds have shown mixed results for RC repair outcomes and complications rates (Sclamberg *et al.* 2004; Badhe *et al.* 2008; Rotini *et al.* 2011; Peterson *et al.* 2015). To conclude, the available data do not allow definitely to conclude about the successful application of scaffolds. Further research is required in order to reliably evaluate the use of scaffolds (Longo *et al.* 2012; Ricchetti *et al.* 2012; McCormack *et al.* 2014).

Conclusions
The discussed biological aspects and the development of implants may improve the tendon healing. Each biological approach technique has its advantages, but their combination can effectively result in improving tendon-to-bone healing. However, more clinical trials are needed to confirm the efficacy and safety of those procedures in everyday practise of a shoulder surgeon.

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Author responsible for correspondence:
Joanna Wałecka
Department of Traumatology, Orthopaedics and Hand Surgery
University of Medical Sciences
28 Czerwca 1956 No 135/147
61-545 Poznan, Poland
walecka.j@gmail.com

Autor odpowiedzialny za korespondencję:
Joanna Wałecka
Katedra Traumatologii, Ortopedii i Chirurgii Ręki
Uniwersytet Medyczny w Poznaniu
Ul. 28 Czerwca 1956 Nr 135/147
61-545 Poznań, Polska
walecka.j@gmail.com