The Integrity™ Implant: Healing Response to a Hyaluronic Acid-Based Synthetic Scaffold for Tendon Augmentation

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Abstract

Rotator cuff injuries are challenging to repair and have a high incidence of retear. Attempts to augment cuff repair have included the use of synthetic and naturally occurring biomaterials. No perfect biomaterial or implant has been discovered, and each material has its pros and cons.

The desired design of an implant intended to facilitate and augment tendon healing would have both mechanical strength and promote the healing process.

Anika's Integrity Implant is a composite of Hyaff® and polyethelene terephthalate (PET). Hyaff is a benzyl ester derivative form of hyaluronic acid (HA) that exhibits superior stability and strength as well as a slower rate of degradation compared to unmodified HA.

The Integrity Implant was evaluated in a head-to-head study versus REGENETEN (a bovine collagen-based implant) in an established ovine model of infraspinatus tendon injury. After 26 weeks, Integrity exhibited nearly 3 times greater thickness, superior cellular infiltration, greater tissue formation and integration with the native tendon.

Background

Tendon injuries requiring surgical repair can be challenging, and those injuries involving the rotator cuff are perhaps most difficult due to the anatomical convergence of four separate tendons, the confined space mandated by the superior acromial rim and the required range of motion of the glenohumeral joint. Cuff injuries can be traumatic in origin as in the case of joint dislocation or degenerative as is often seen with overuse conditions. Primary repairs have a high incidence of recurrence, especially when two or three of the cuff tendons are involved. Attempts to augment cuff repair have included the use of synthetic and naturally occurring biomaterials, each of which has their pros and cons, and there is no consensus as to the best options. It should be noted that there is no perfect biomaterial/implant for all patients.

Success of such surgical augmentation efforts logically depends upon the patient response to the biomaterial from which the augmentation device is composed, the mechanical properties of the device, the degradation profile of the material over time, and of course patient compliance with the postoperative rehabilitation protocol. As a general rule, naturally occurring materials are more biocompatible than synthetic materials but tend to be less strong and typically have a rapid degradation profile,[1] which is associated with an earlier postsurgical loss of mechanical strength than synthetic materials.

Alternatively, synthetic materials have superior mechanical strength but tend to elicit a more aggressive tissue inflammatory response[1] and excessive scar tissue formation compared to naturally occurring biomaterials. Table 1 provides a list of commonly used medical devices for rotator cuff repair.

Product	Company	Source
Integrity™*	**Anika**	**Hyaluronic acid w/ PET**
REGENETEN™	Smith & Nephew	Bovine collagen
BioBrace®	CONMED	Bovine collagen w/ PLLA
Tapestry®	Zimmer Biomet	Bovine collagen w/ PDLLA
ROTIUM®	Atreon Orthopedics	PLCL and PGA
ArthroFLEX®	Arthrex	Acellular human dermis
GraftJacket™	Stryker	Acellular human dermis
DermaSpan™	Zimmer Biomet	Acellular human dermis

Table 1. Commonly used devices for rotator cuff repair.

*Launched 2024

The Healing Process Following Tendon Injury

The fundamental structure and function of tendons have a direct effect upon the healing process following injury. Mature tendons are comprised of aligned dense mature collagen, relatively low vascularity, and a cell population consisting primarily of fibroblasts. The resident cells secrete collagen which composes the majority of the extracellular matrix (ECM), along with other structural and functional matrix molecules. The ECM is responsible for transmitting the mechanical forces imposed upon the tendon to the embedded resident cells, which in turn modify their secretome accordingly, a process aptly termed "dynamic reciprocity".[2] Greater forces (within limits) translate to stronger tendons.

Disruption of tendon structure following injury initiates the classic acute and chronic inflammatory response, specifically, the almost immediate extravasation of cellular and acellular blood elements (i.e., hemorrhage) including erythrocytes, platelets, neutrophils and macrophages. Their released inflammatory cytokines and chemokines represent the initiation of the healing response. This acute phase is followed by the degradation and resorption of blood elements, an angiogenic response, infiltration of macrophages and fibroblasts from surrounding tissue, and subsequent alignment of the fibroblastic cells in response to mechanical loading. This infiltration of cells is orchestrated in large part by signaling molecules released from the inflammatory cell population and matrix metalloproteinase (MMP)-mediated degradation of the native tendon ECM. The scavenging of cellular debris

is managed by cells such as proinflammatory macrophages which, following transition to an anti-inflammatory/regulatory phenotype, also plays a major role in the resolution of the inflammatory process. Macrophages are the primary orchestrators of tendon healing following injury. Clinical outcomes, such as return to a healthy functional state, persistent inflammation or excessive scar tissue, are largely a consequence of the phenotypic state of the local macrophage population, which in turn is a function of the signaling molecules within the local tissue milieu.

Part of the return to a normal functional state is the required mechanical loading (i.e., physical rehabilitation) that signals the amount and alignment of fibroblasts, secreted collagen fibers, and integration with adjacent normal tendon tissue.

This response to mechanical loading is referred to as Davis's Law, similar to Wolff's Law in bone. Tendon remodeling is therefore characterized by both the synthesis and degradation of collagen and associated matrix molecules.[3]

At the molecular level, all phases of the healing process following injury are mediated by signaling molecules that are produced by the local cell population and those present within the microenvironment, such as TGF-β, FGF, and VEGF and bi-functional molecules such as hyaluronic acid (HA) that have both structural and functional roles. The net influence of proinflammatory vs. anti-inflammatory/prohealing signaling molecules dictates the clinical outcome of the tendon healing process. The use of purified growth factors for tendon repair in attempts to alter the microenvironmental milieu and promote an improved outcome has yielded mixed results. The use of bi-functional molecules that have both structural and functional effects for tendon repair, such as HA, has yet to be evaluated in depth.

The Role of Hyaluronic Acid in Wound Healing

Hyaluronic acid is a naturally occurring component of the extracellular matrix, specifically a glycosaminoglycan (GAG) composed of repeating units of 2 sugars, N-acetyl-D-glucosamine and D-glucuronic acid. The amount of HA varies from tissue to tissue but is particularly important in anatomic locations where lubrication and cushioning are important such as synovial joints, the vitreous, the dermis and the placenta/umbilical cord (Figure 1).

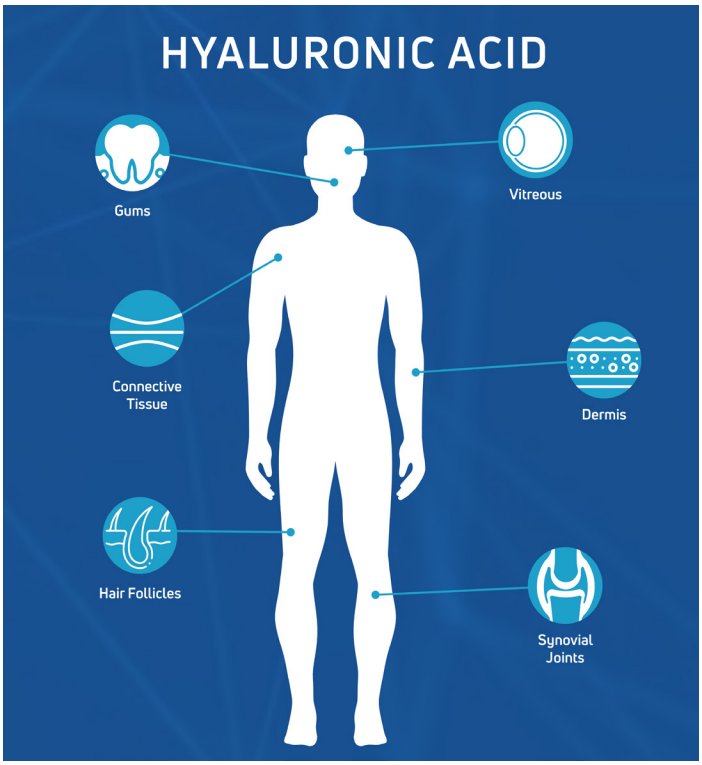

Figure 1. Hyaluronic acid is found in many areas around the body.

The lubricating effect is due to its high viscosity and the ability of HA to bind water which also contributes to its cushioning effects. HA is rapidly degraded with a half-life ranging from minutes within the blood, to hours within the skin and several weeks within cartilage. As much as one third of total body HA is replenished in normal tissues on a daily basis, an indication of its dynamic role in everyday physiologic processes. Stated differently, HA is an integral and dynamic component of native tissues with many mechanical and biologic effects, some of which are described below.

The mechanical effects of HA are mentioned briefly above and include its ability to serve as a "shock absorber" and lubricating agent which explains its prominence in load bearing joints. However, the biologic effects of endogenous HA may be even more important than its physical properties when considering HA in therapeutic applications. At the molecular level, HA serves as a binding site for numerous pro-healing cytokines and chemokines that mediate critical cell functions and biologic processes such as migration, proliferation and differentiation, angiogenesis and immunomodulation. The ability of HA to scavenge free radicals and provide an antioxidant effect has been associated with its anti-inflammatory properties.

At the macroscopic and clinical level, HA is more abundant in fetal tissue than in adult tissue, and its presence has been associated with the lack of scarring and tissue contraction. It has been shown that HA grafts decrease the average wound closure time by 85% compared to the control group and reduce TGF-β1 expression, thus reducing scar tissue formation.[4] The use of HA in both its native form and as a partial benzyl ester in dermatology is well recognized and includes its ability to promote healing of diabetic foot lesions and as a dermal filler in aesthetic dermatology. These HA-mediated pro-healing effects, including the potential to mitigate scar tissue formation, can be particularly useful in orthopedic soft tissue applications such as tendon repair. In summary, HA is a naturally occurring, endogenous molecule with the ability to be formulated for a variety of clinical applications with a high safety profile.

Hyaff®: Anika's Proprietary Technology

Naturally occurring HA degrades rapidly within the body,[5] thus in order to expand its clinical use, it was necessary to determine a way to increase its residence time *in situ*. A breakthrough in medical science was the introduction of a chemically-modified HA derivative, known as Hyaff-11®, a benzyl ester of hyaluronic acid.

Anika's proprietary Hyaff technology involves the chemical modification of HA to alter its liquid gel form and manufacture it into a solid form, producing a more versatile derivative of HA. This chemical modification (esterification with benzyl alcohol) makes it water-insoluble, meaning it can be processed into a variety of different fully resorbable solid-form configurations including fibers, films, granules, textiles, and more.[6]

The uniqueness of Hyaff lies in its prolonged residence time in situ compared to native HA, and that upon degradation, Hyaff's main by-product is the parental HA molecule, providing a biocompatibility profile that leads to an HA-enriched natural healing environment at the implant site.[6,7]

Hyaff has been used globally for more than 20 years, with excellent safety and efficacy results.[8] Clinical studies have demonstrated that as Hyaff fibers degrade, hyaluronic acid is released, creating an HA-rich embryonic-like environment favorable to tissue regeneration and healing.[9]

The Use of Hyaluronic Acid as a Tendon Repair Device – The Integrity Implant

The design of an implant intended to facilitate and augment tendon healing would preferably have both adequate mechanical strength and compliance to withstand the loads placed upon the tendon in vivo and biologic properties that not only mitigate inflammation and scarring but promote and accelerate a functional healing process. Ideally, this device would integrate with adjacent native tendon and substantially degrade and remodel with time, such that any residual material is associated with an acceptable tissue response that does not adversely affect a functional healing outcome.

The Integrity Implant is a composite of 80% Hyaff®-11 and 20% polyethylene terephthalate (PET). Hyaff-11 is a benzyl ester derivative form of HA, that exhibits superior stability and strength as well as a slower rate of degradation compared to unmodified HA. Polyethylene terephthalate (PET) is a nondegradable synthetic material with superior mechanical strength but lacks the favorable biologic properties of HA. PET has been used in sutures since the 1950's and is well known for its biostability, promotion of tissue ingrowth, and long history of human implantation. Both of these materials have a proven effective and safe history of use in humans for a variety of surgical applications. The complementary favorable properties of these two materials satisfy the requirements for a safe and effective tendon repair implant.

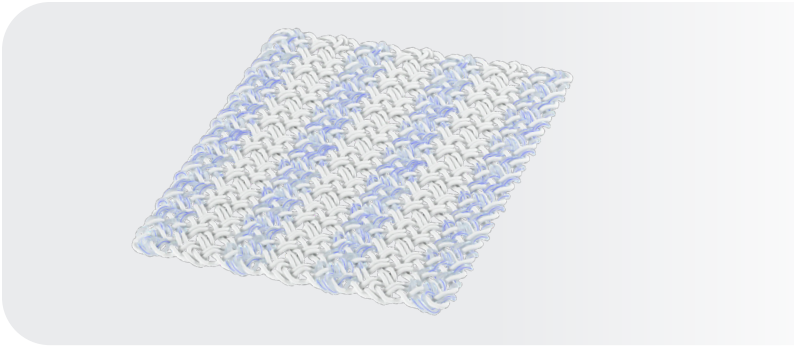

Figure 2. The Anika Integrity Implant.

The Integrity Implant is a knitted scaffold with large pores, laser cut edges, and blue stripes for intraoperative visibility (Figure 2). It is available in commonly used configurations, such as 20x25mm and 25x30mm. The Integrity Implant exhibits greater tensile strength, tear resistance, suture retention strength and reduced stiffness when compared to collagen-based devices, such as REGENETEN, even when wet. (Figure 3)

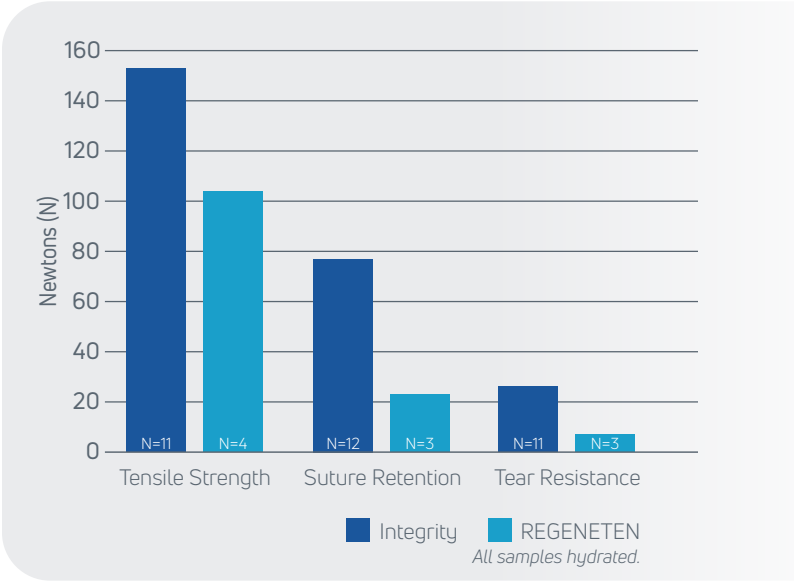

Figure 3. Integrity provides higher tensile strength, suture retention, and tear resistance as compared to REGENETEN.[8]

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Preclinical Study of the Integrity Implant for Rotator Cuff Repair in an Ovine Model

The *in vivo* response to the Integrity Implant was evaluated in a head-to-head study versus REGENETEN[10] in an established ovine model of infraspinatus tendon injury (Figure 4). Each implant was sutured in place over the injured tendon and its ability to augment tendon healing was evaluated over 6, 12 and 26 weeks.

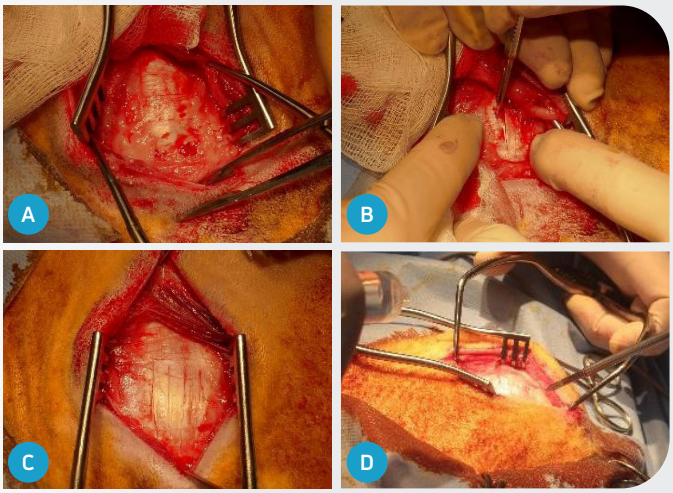

Figure 4. A: A small incision was made over the deltoid muscle which was retracted to expose the infraspinatus tendon.
B & C: The infraspinatus tendon had full thickness slits introduced parallel to the long axis of the tendon with the use of a #15 scalpel blade.
D: Two 3.5mm drill holes were made distal to the insertion of infraspinatus tendon. The device was placed and sutured to the superior aspect of the infraspinatus tendon with non-resorbable interrupted sutures (2-0).

Results as documented by histology and MRI signaling showed a robust infiltration of mononuclear cells, primarily macrophages, into the Integrity Implant that diminished in number over time. This macrophage infiltration was associated with gradual and progressive implant degradation, further infiltration of fibroblasts, and deposition of organized and aligned neocollagen that continued for the entire 26 weeks of the study. The PET component within the remodeled tissue showed the persistent presence of fibers surrounded by dense collagenous tissue and a small number of mononuclear cells. There was no evidence for infection, tissue necrosis, or other adverse effects associated with implant placement at the site of tendon injury.

In summary, the surgical implantation of the Integrity Implant showed the material to be safe, have a prolonged degradation profile, and promote the deposition of dense, organized connective tissue that integrated with the underlying infraspinatus tendon. (Figure 5)

Conclusion

Rotator cuff repairs often fail to heal properly after surgery and have a high incidence of retearing within a couple years. Attempts to augment cuff repair over the past twenty years using biologic or synthetic implants have exhibited only marginal improvements to these metrics. The Integrity Implant combines the healing benefits of hyaluronic acid with the strength and biocompatibility of PET in a single partially resorbable scaffold. Bench testing has demonstrated the superior handling and mechanical properties of the Integrity Implant. In an *in vivo* ovine implantation study at 26 weeks, within the resorbing Integrity structure, new collagenous tissue infiltration forming a new network of tendon tissue had occurred. This resulted in Integrity being nearly 3 times greater in thickness versus REGENETEN, demonstrating robust cellular infiltration, greater tissue formation and excellent integration with the native tendon.

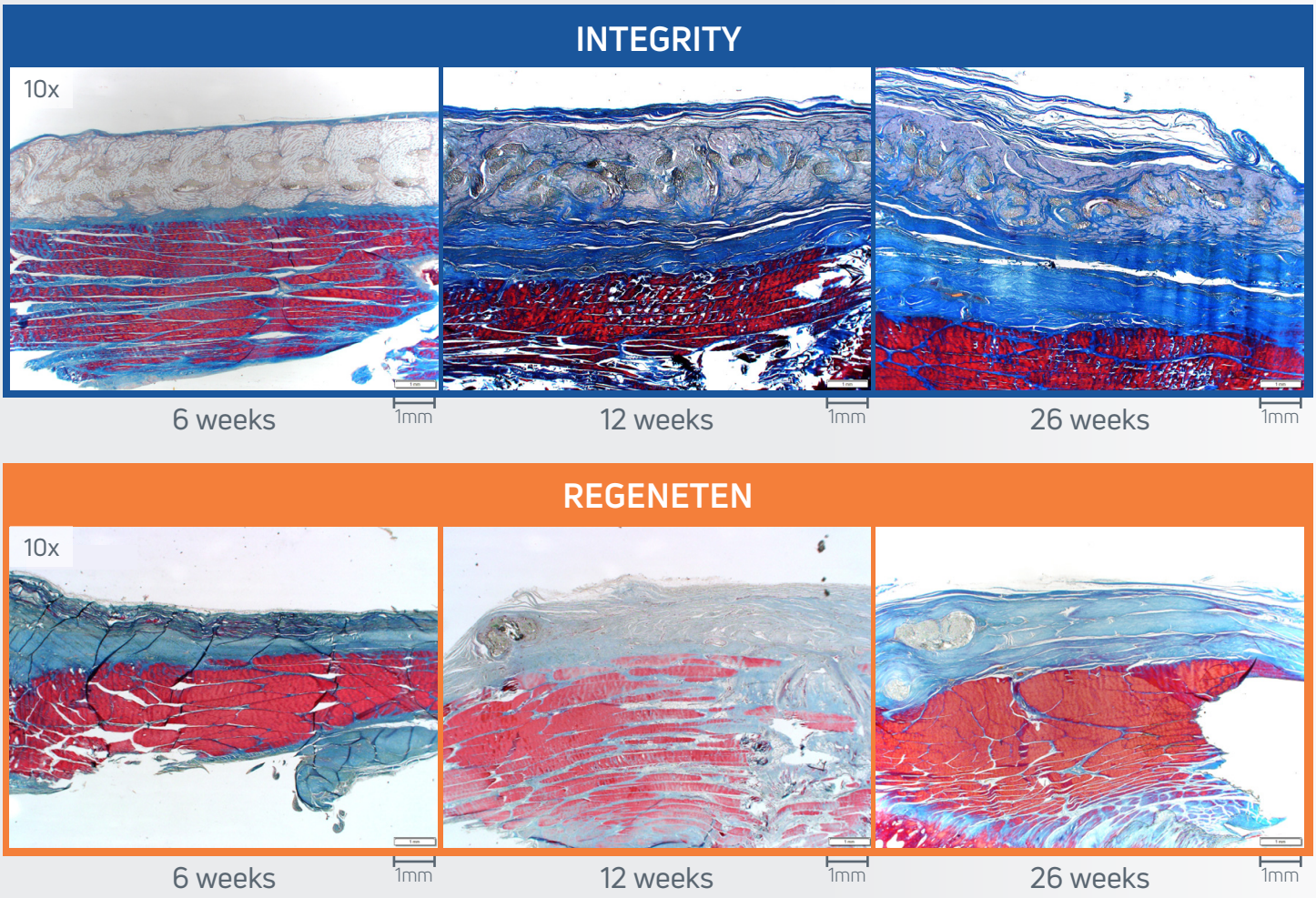

Figure 5. Masson's trichrome stain shows Integrity's increased tendon thickness, nearly 3 times greater than REGENETEN at 26 weeks.

TETRACHROME STAIN	
Blue: Collagen	Pink: Cytoplasm
Red: Muscle	Brown: Nuclei

References

1. de Moraes Porto, Isabel Cristina Celerino. "Polymer biocompatibility." Polymerization (2012): 47-63.
2. Bissell, Mina J., et al. "How does the extracellular matrix direct gene expression?." Journal of theoretical biology 99.1 (1982): 31-68.
3. Davis, Henry Gassett. Conservative surgery. Appleton, 1867.
4. Hu, Min, et al. "Three dimensional hyaluronic acid grafts promote healing and reduce scar formation in skin incision wounds." J. Biomed. Mater. Res., 67.1 (2003): 586-592.
5. Laurent, U. B. G. & Reed, R. K. Turnover of hyaluronan in the tissues. Adv. Drug Deliv. Rev. 7, 237–256 (1991).
6. Milella, E., et al. "Physico-chemical properties and degradability of non-woven hyaluronan benzylic esters as tissue engineering scaffolds." Biomaterials. 23.4 (2002): 1053-1063.
7. Longaker, M. T. et al. Studies in fetal wound healing, VII. Fetal wound healing may be modulated by hyaluronic acid stimulating activity in amniotic fluid. J. Pediatr. Surg. 25, 430–433 (1990).
8. Data on file, Anika Therapeutics, Inc.
9. Bauer C., Niculescu-Morzsa E., Jeyakumar V., et al. Chondroprotective effect of high-molecular-weight hyaluronic acid on osteoarthritic chondrocytes in a co-cultivation inflammation model with M1 macrophages. J Inflamm (Lond). 2016 Sep 13;13(1).
10. Van Kampen, C., et al. "Tissue-engineered augmentation of a rotator cuff tendon using a reconstituted collagen scaffold: a histological evaluation in sheep." Muscles, ligaments and tendons journal 3.3 (2013): 229.

All Data On File, Anika Therapeutics, Inc. Test report date 18 Nov 2022.

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