ПЯТЫЙ ЮБИЛЕЙНЫЙ

ЕВРАЗИЙСКИЙ ОРТОПЕДИЧЕСКИЙ ФОРУМ

EURASIAN ORTHOPEDIC FORUM

USE OF A BIO-INDUCTIVE MULTIFRACTIONAL HYALURONIC ACID IN TENDINOPATHIES IN SPORTS PATIENTS. THERAPEUTIC EVIDENCE AND NEW APPROACHES

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This clinical study is the result of almost

2 years of rehabilitation work on patients suffering from tendinopathies,

including post-traumatic or overuse ones,

that we presented at SIMFER 2024.

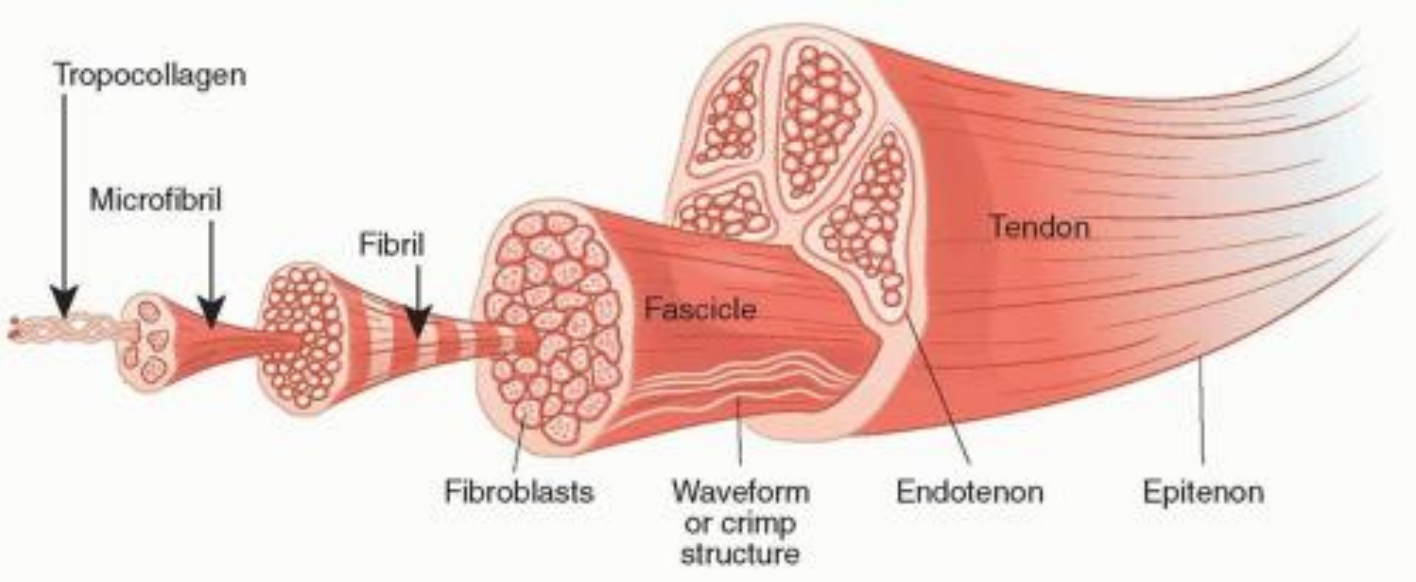
SIMFER

SOCIETÀ ITALIANA DI MEDICINA FISICA E RIABILITATIVA

The Italian Society of Physical and Rehabilitative Medicine

MOVEMENT IS AT THE HEART OF LIFE

TENDON MORPHOLOGY AND PHYSIOLOGY



Healthy tendons are strong bands of bright white, fibroelastic tissue that connect muscles to bones, enabling anatomical skeletal alignment and transmission of tensile forces with great resistance to applied mechanical loads, while providing connective flexibility, which enables body locomotion and joint stability/movement.

TENDINOPATHY, TENDINITIS & TENDINOSIS

- TENDINOPATHY, as a degenerative state of tendon or ligamentous tissue, includes tendinitis and tendinosis.
- TENDINITIS is associated with an acute event accompanied by inflammation and pain.
- TENDINOSIS is rather a chronic tendon degeneration without inflammation, but is also accompanied by pain

TENDINOPATHY PATHOGENESIS

Factors that play a role in tendinopathy development

Tendinopathies are said to result from a variety of disease processes that lead to loss of tissue integrity and partial or total tissue breakdown (Riley, 2005).

Tendons shielded from stress (fully unloaded) show decreases in the mechanical integrity of the tendon tissue and typical changes in terms of cells and ECM are seen histologically (Ohno et al., 1993).

EXTRINSIC FACTORS:

- high mechanical load obtained through sports activities
- drug abuse
- environmental conditions such as road surfaces or footwear that lead to local hyperthermia
- leading to local hyperthermia, hypoxia, oxidative stress and/or apoptosis
- complete absence of load modifies the tendon matrix in a manner similar to that found for overload.

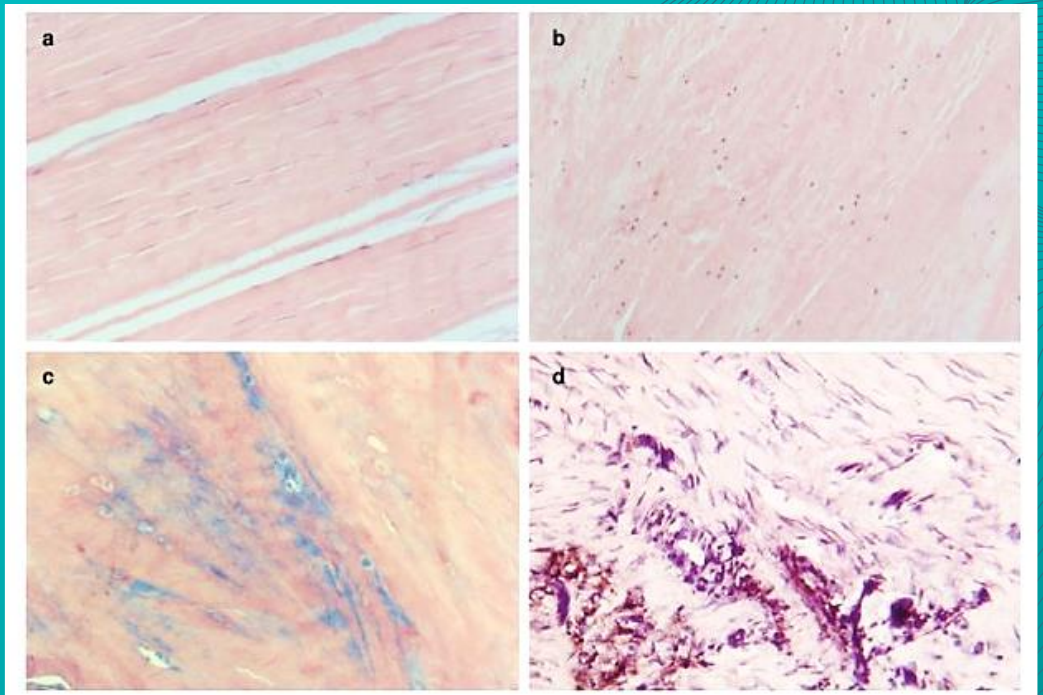
INTRINSIC FACTORS:

- age
- sex
- body weight
- anatomical variants
- systemic diseases (Magnan et al., 2014)
- genetics (Mokone et al., 2006; September et al., 2006) and blood group (Jozsa et al., 1989) also play a non-negligible role in the generation of tendinopathy.

TENDINOPATHY CONCEPTION INCLUDES …

(a) intact tendon

(b) tendon rupture



Histopathology of tendinopathy

Expert Reviews in Molecular Medicine ©2005 Cambridge University Press (parts a, b and d only)

(c) mucoid degeneration

(d) angiofibroblastic changes in tendinopathy

- degenerative tendinopathy with hypoxic, hyaline, or mucoid degeneration of the tissue
- angiofibroblastic hyperplasia, which refers to a transitional state of damaged tendon tissue during the healing process - and in the case of chronic tendinopathy, is referred to as "failed healing" (Clancy, 1989). In addition, Cook and Purdam (2009) proposed and presented a continuum of tendon pathology

Riley GP. Chronic tendon pathology: Molecular basis and therapeutic implications. Expert Reviews in Molecular Medicine 7(5):1-25

REACTIVE TENDINOPATHY

"Reactive tendinopathy" is characterized by:

- increased cell proliferation in the matrix, however, without inflammation. This occurs as a response to acute traction or compression overload and results in short-term thickening of the tendon at a specific location in order to reduce stress at that site. Compared with normal adaptation of the tendon to tensile loading, in which the tendon stiffens without thickening, short-term thickening as a reaction of acute overload appears to be reversible.
- This rapid adaptation goes hand in hand with a turn of the cells toward a more chondroid morphology and increased production of large proteoglycans such as aggrecan, and glycoproteins such as hyaluronic acid (Scott et al., 2007).
- Typically, the increase in these molecules occurs within minutes to a few days, in contrast to the increase in small proteoglycans found primarily in healthy tendons (Samiric et al., 2004).

CHRONIC TENDINOPATHY

At the molecular level, chronic tendinopathy includes an increase (mRNA) in:

- collagen type I and III
- fibronectin (Tillander et al., 2002)
- tenascin-C
- aggrecan
- biglycan (Corps et al., 2006).

While upregulation of collagen and fibronectin mRNAs as well as tenascin-C (Riley et al., 1996) are associated with a healing response (Riley, 2005), increased expression of aggrecan and biglicane is consistent with a mechanobiological response to compression and shear (Corps et al., 2006).

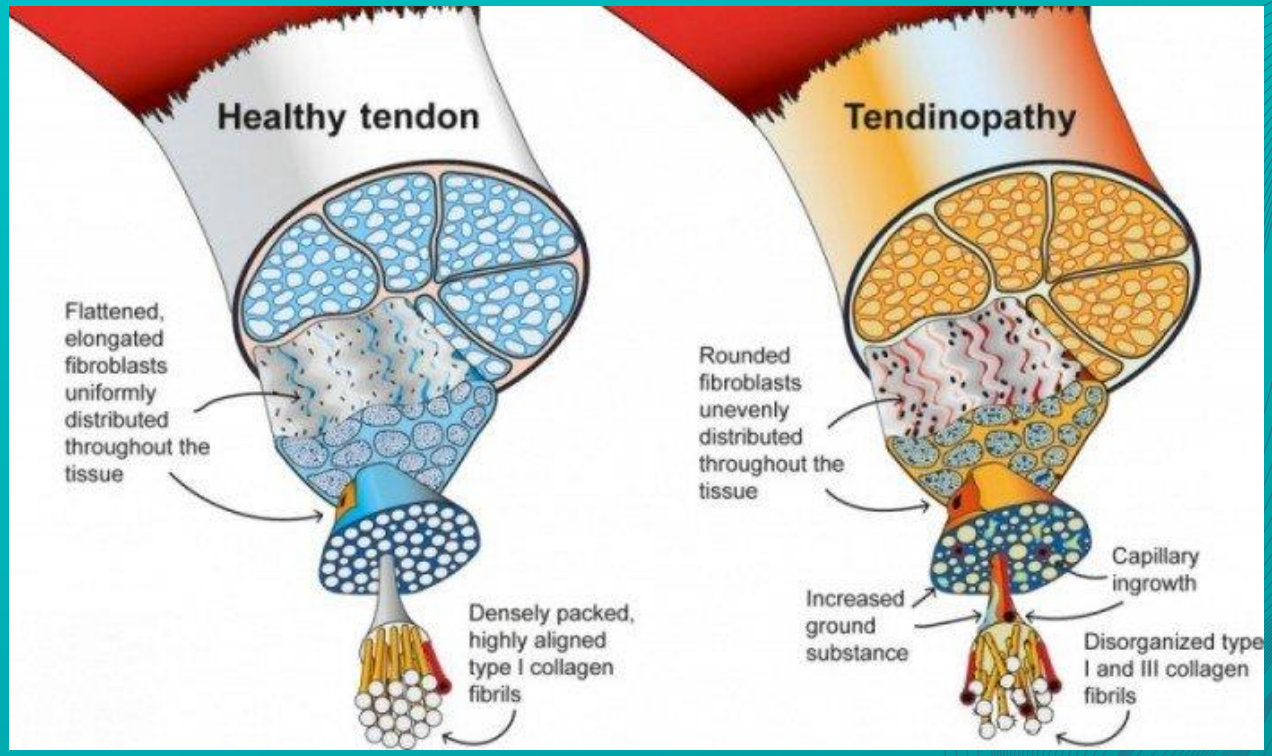
CHRONIC TENDINOPATHY

- Metalloproteinase expressions and activities are also affected in chronic tendinopathy (Riley, 2008; Xu and Murrell, 2008); there is an increase in
- MMP-1 (collagenase),
- MMP-2 (gelatinase) and
- MMP-23
- decrease in
- MMP-3 (stromelysin),
- MMP-10,
- MMP-12 and
- MMP-27.
- The levels of tissue inhibitors of metalloproteinases (TIMPs) are also consistent with ongoing proteolytic activity in tendinopathic tissue. In addition, increased expression of a disintegrin and metalloproteinase (ADAM) and ADAMTS (ADAM with thromospondin motifs), have been associated with painful tendons: increased ADAM12, ADAMTS2 and ADAMTS3 - where ADAM12 has been reported to be involved in cell type change (myogenesis and lipidogenesis; Guo et al., 2005).

WHAT GENERATES ALL THIS?

- INFLAMMATION
- PAIN
- DECREASED MOVEMENT
- TENDON DEGENERATION
- RISK AND/OR RUPTURE OF TENDON
- SURGICAL INTERVENTION
- JOINT ADAPTATION TO MOVEMENT
- REDUCTION IN PATIENT'S QUALITY OF LIFE

WHAT NEEDS?



- REDUCTION OF PAIN AND THEREFORE AN INFLAMMATION
- RECOVERY OF MOVEMENT
- AVOID WORSENING AND REDUCE THE RISK OF IMMOBILIZATION AND SURGERY
- IMPROVEMENT OF QUALITY OF LIFE

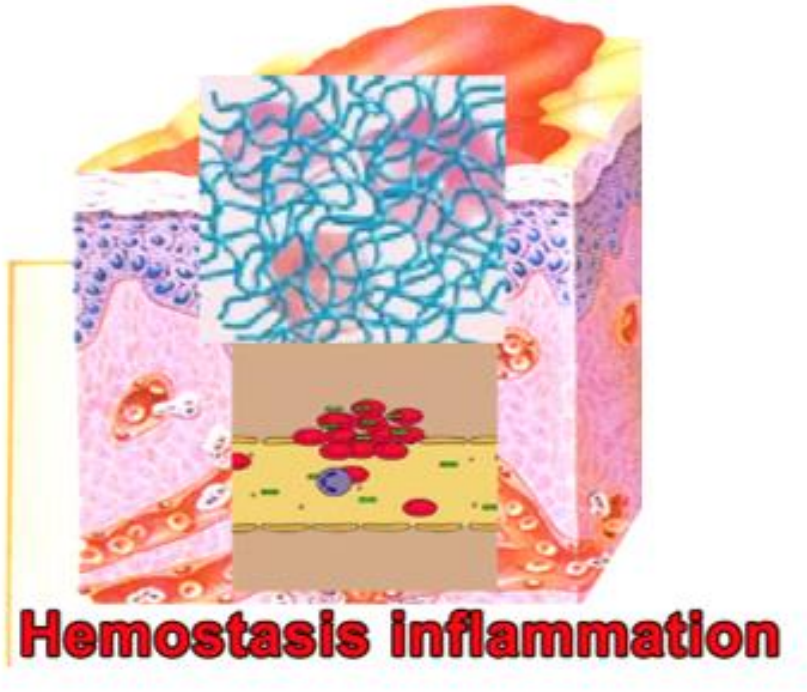
https://www.simphysio.com.au/blog/what-is-a-tendinopathy

WE NEED TO PROMOTE TENDON SELF-REPAIR MECHANISM

1

CONGESTIVE PHASE

PDGF EGF FGF

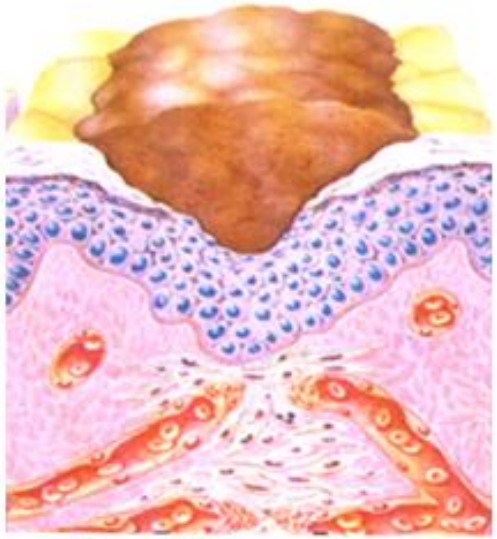


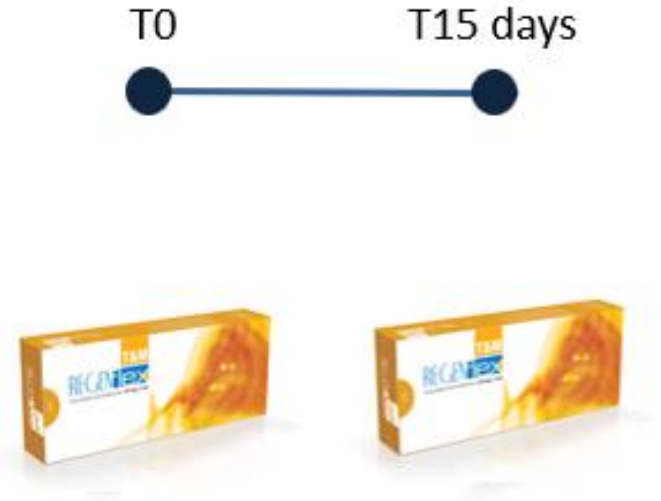
WE NEED TO PROMOTE TENDON SELF-REPAIR MECHANISM

2

PROLIFERATIVE PHASE

PDGF TGF-beta TGF-alfa



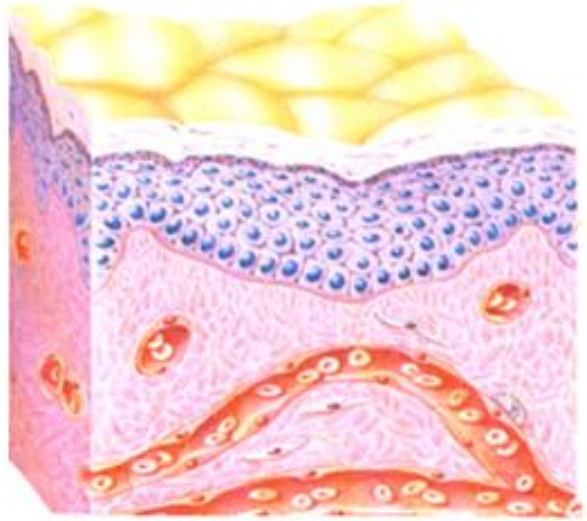


WE NEED TO PROMOTE TENDON SELF-REPAIR MECHANISM

3

REMODELLING PHASE

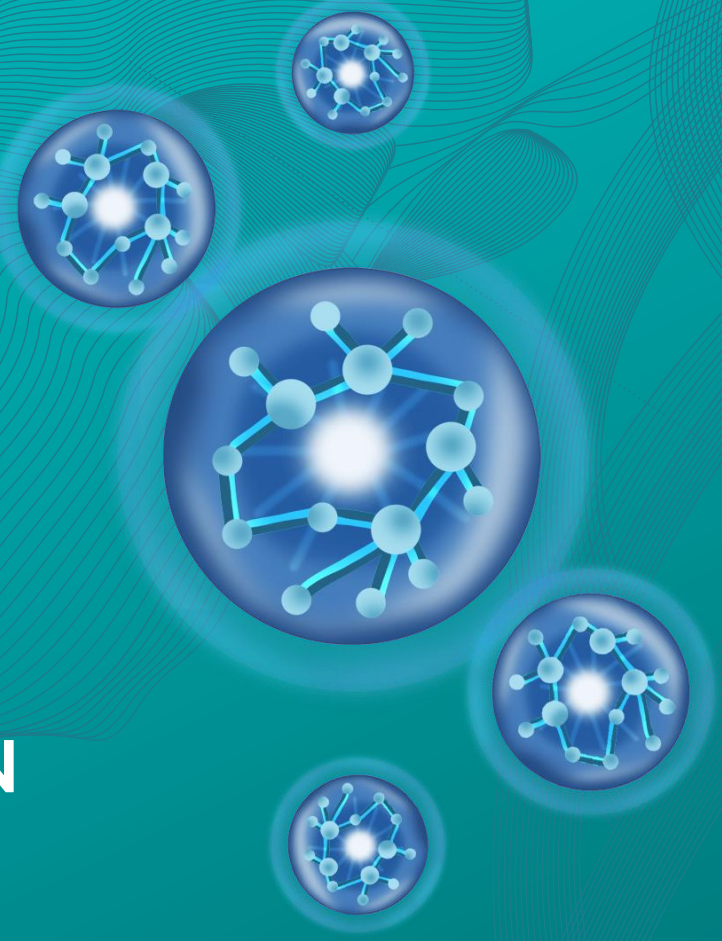
T. 30 days



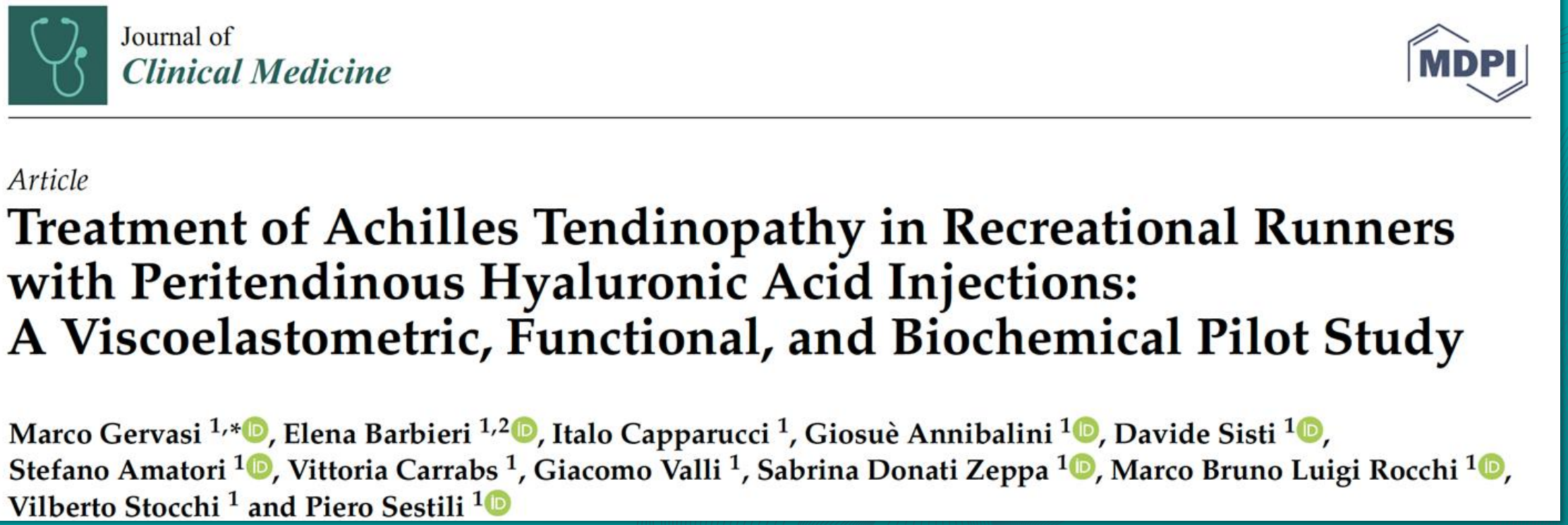
Remodeling & Restoring Phase

WE NEED THE HYALORONIC ACID THAT IS

- SPECIFIC
- BIO-INDUCTIVE
- MULTIFRACTIONAL
- ALLOWS IMMEDIATE REDUCTION OF PAIN AND INFLAMMATION
- ALLOWS SELF-REPAIR OF THE TENDON
- ALLOWS IMMEDIATE RECOVERY OF MOVEMENT



CLINICAL TRIAL



Journal of *Clinical Medicine*

MDPI

Article

Treatment of Achilles Tendinopathy in Recreational Runners with Peritendinous Hyaluronic Acid Injections: A Viscoelastometric, Functional, and Biochemical Pilot Study

Marco Gervasi [1,*], Elena Barbieri [1,2], Italo Capparucci [1], Giosuè Annibalini [1], Davide Sisti [1], Stefano Amatori [1], Vittoria Carrabs [1], Giacomo Valli [1], Sabrina Donati Zeppa [1], Marco Bruno Luigi Rocchi [1], Vilberto Stocchi [1] and Piero Sestili [1]

1. Wu PT, Kuo LC, Su FC, Chen SY, Hsu TI, Li CY, et al. High-molecular-weight hyaluronic acid attenuated matrix metalloproteinase-1 and -3 expression via CD44 in tendinopathy. Scienti-c reports. 2017; 7:40840).

2. Longo UG, Ronga M, Maffulli N. Achilles tendinopathy. Sports medicine and arthroscopy review. 2009;17(2):112-26.

3. McAuliffe S, Tabuena A, McCreesh K, O'Keeffe M, Hurley J, Comyns T, et al. Altered Strength Pro-le in Achilles Tendinopathy: A Systematic Review and Meta-Analysis. Journal of athletic training. 2019;54(8):889-900

THERAPY WAS BASED ON A BIO-INDUCTIVE MULTIFRACTIONAL HA

REGENFLEX T&M
for TENDONS and MUSCLES

RECONDITIONING OF THE TENDON BIOINDUCTION

HA TO SUBSTITUTE THE SYNOVIAL FLUID OF THE TENDON

MOLECULAR WEIGHT	MOLECULAR WEIGHT	MOLECULAR WEIGHT	MOLECULAR WEIGHT	MOLECULAR WEIGHT
2 KDA	100 KDA	200 KDA	500 KDA	1 MDA

MIXED MOLECULAR WEIGHT

MATERIALS AND METHODS

- 130 professional athletes (usually subjected to intensive training of more than 30 hours/week)
- 92 males and 38 females, average age 38 years
- average weight 85 kg in males and 65 kg in females (in both groups with less than 15% body fat)
- with clinical symptoms of severe tendinopathy, with pain and functional limitation with inability to perform activities of daily living or to play sports at usual levels: subjects with severe tendinopathy
- not induced by chronic disease or chronic treatment with tendon-damaging drugs
- confirmed by ultrasound and physical examination based on the Royal London Hospital Test, were selected.

TREATMENT SCHEME

Ultrasound-guided peritendinous injections

- with 4 cm needles
- were administered every 15 days, T0 – T15 – T30,
- as is indicated in IFU of Regenflex T&M.

The therapeutic dose was 2 ml of multifractional hyaluronic acid with a concentration of 1.6%,

- with specific indication in IFU on tendons and ligaments
- (5 free fractions of hyaluronic acid with progressive molecular weight: 2 -100 - 200 -500 thousand - 1 million Daltons).

MATERIALS AND METHODS

A muscle-tendon ultrasound was performed at the beginning and end of the infiltration cycle,

- repeated subsequently at 3 and 9 months.

We evaluated the patients clinically, using:

- V.A.S. scale of pain at rest and in motion,
- measuring active and passive R.O.M. with the S.F.T.R. method.

The inflammation reduction was assessed by measuring specific markers such as:

- MMP-3 (matrix metalloproteinase-3) and IL-1 (interleukin-1) by urine analysis at each infiltration,
- an evaluation also repeated at 3 and 12 months after the end of the infiltration cycle.

RESULTS

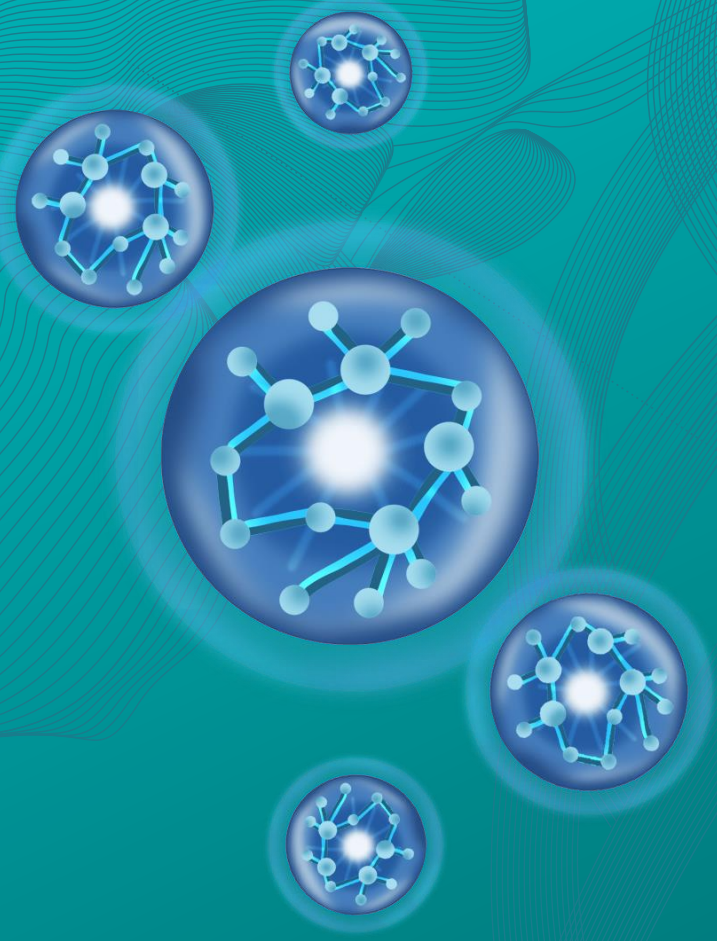
Rapid improvement, starting from T1, of all instrumental and clinical parameters,

- with a significant and rapid reduction in inflammatory status (-23% at T15 days and -70% one year after the end of the infiltrative cycle)
- and pain (-48% at T15 days and - 90% one year after the end of the infiltrative cycle),
- demonstrated both clinically and instrumentally (measured with ultrasound the axial and sagittal thickness of the tendon and the degree of neovascularization),
- as well as an increase in movement capacity and a rapid functional recovery, fundamental in the professional athlete (+47% at T15 days and +70% one year after the end of the infiltrative cycle).

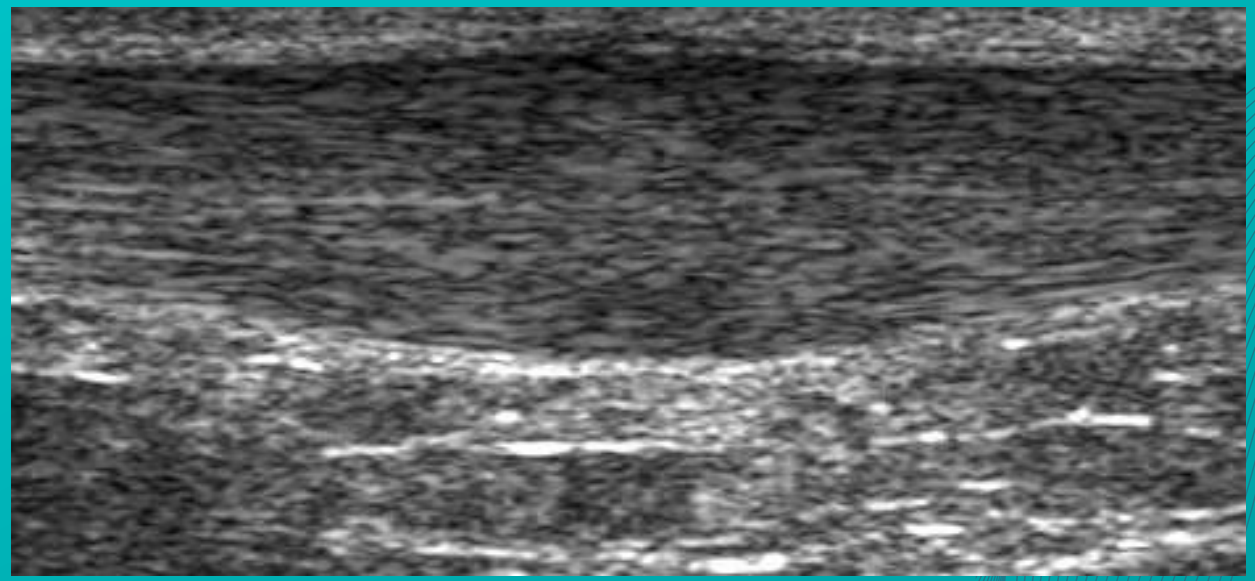
RESULTS

- The result remains stable over time, demonstrated for at least up to 12 months.

- The synchronized reduction of specific biomarkers (MMP-3 and IL-1) demonstrated for the first time that this multifractional hyaluronic acid formulation contributes to the tendon's biological self-healing process as an important support to the tendon's biological self-healing process, based on the analysis of specific biomarkers.

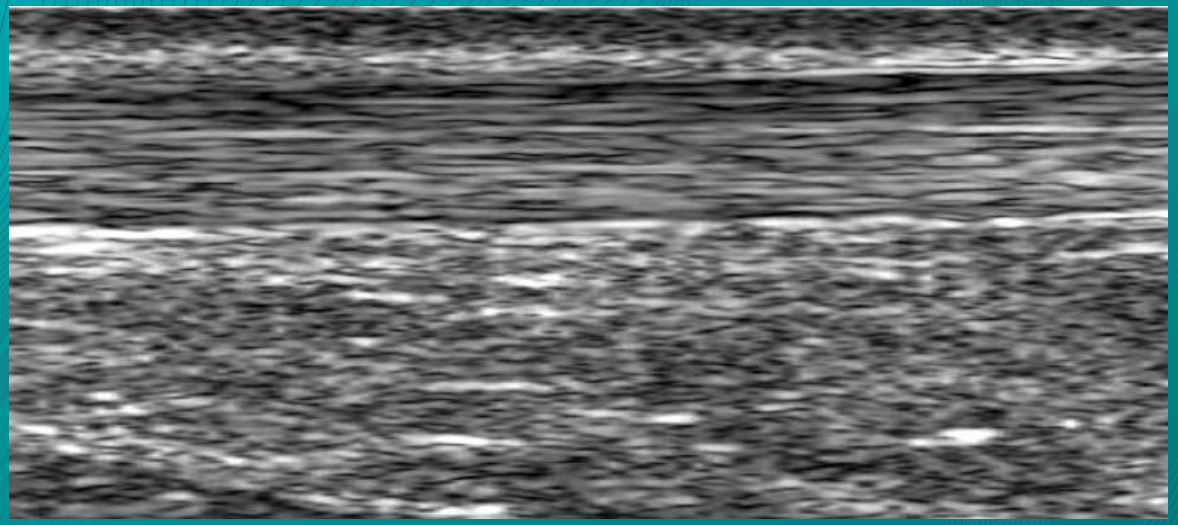


ULTRASONOGRAPHY OF ACHILLES TENDINITIS



T 0
swelling and fiber impairment

T 4
good compaction of the interrupted fiber



BIOCHEMICAL RESPONSE

We also studied the correlation between clinical and biochemical response.

We can see how the decrease in pain and increase in movement capacity are synergistic with the decrease in inflammatory markers.

CONCLUSION

Clinical results indicate that

- the treatment of tendinopathies with bioinductive, multifractional hyaluronic acid with a molecular weight between 2 - 1.000 kDalton (Regenflex T&M, Regenyal Laboratories)
- promotes the tendon's self-repair mechanism,
- ensuring a sudden reduction in pain and a rapid recovery of normal function and physiological structure of the tendon.
- The demonstrated benefit is maintained over time by supporting even intense and pain-free movement capacity.

THANK YOU
FOR YOUR ATTENTION !