GUNA COLLAGEN MEDICAL DEVICES

Bioscaffold of extra-cellular matrix

Characteristics and clinical applications in Orthopedics, Physical Rehabilitation Medicine, Sports Medicine and Rheumatology

GUNA
medical device

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SCIENTIFIC DOCUMENTATION FOR THE EXCLUSIVE USE OF QUALIFIED STAFF

INDEX

CLASSIFICATION

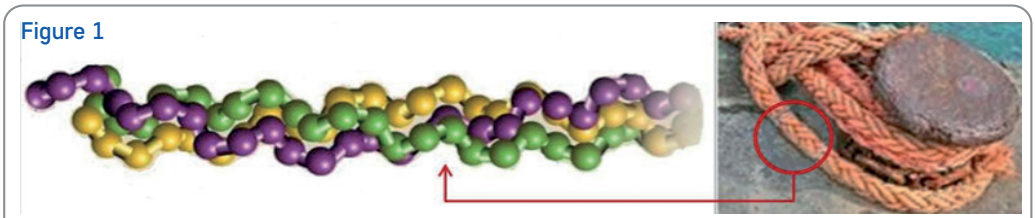
Guna Collagen Medical Devices are Class III injectable collagen-based medical devices, classified and marketed in accordance with Directive 93/42/EEC on Medical Devices.
Guna Collagen Medical Devices are CE-marked (company with Quality Management System UNI CEI EN ISO 13485:2016).

MAIN CHARACTERISTICS

COLLAGEN
Collagen represents 5-6% of body weight and it is the most abundant protein in mammals. Collagen is the main component of ligaments, tendons, bones, cartilage, muscles, skin, and extracellular matrix (ECM) (Boot-Handford and Tuckwell, 2003).

The smallest subunit of collagen is tropocollagen, formed by sequential glucose/galactose units and by 4 amino acids (Proline, Hydroxyproline, Glycine and Lysine). *Figure 1*

Figure 1



The triple helix (three alpha chains) of tropocollagen is the basic unit of mature collagen.

Structure: chain of glucose and galactose + 4 aminoacids:
HYL, GLY, PRO, HYP

At present, 28 types of collagen (21 in mammals) have been identified, composed of 46 distinct polypeptide chains differently combined with each other so to ensure the characteristics necessary for a specific tissue. All types of collagen show a characteristic triple-helix structure. The length of the helix and the size and nature of the non-helical portion vary according to the type of collagen (Silvipriya et al, 2015). Type I collagen is the most common. It can be isolated from skin, bones, teeth and tendons and is suitable for medical applications (Todhunter et al, 1994; Silvipriya et al, 2015).
Collagen is obtained by extraction and hydrolysis from various animal sources. Common sources of collagen for tissue engineering applications include bovine skin and tendons, porcine dermis, and horse tendons and dermis.

TYPE I COLLAGEN OF PORCINE ORIGIN

The collagen contained in Guna Collagen Medical Devices is type I collagen of porcine origin. It is preferred compared to bovine collagen as it is structurally more similar to human collagen. On a genetic level, the similarities between the two mammals *Sus scrofa domesticus* and *Homo sapiens* are remarkable: the two species have a very similar genome and gene sequences. Nucleotide sequences, gene location, length and number of coding regions, non-coding parts of DNA are some of the common genetic aspects between swine and human species.

Porcine collagen guarantees a high level of safety due to its extremely low immunogenicity. This makes collagen a material of choice for many applications, for instance in the aesthetic medicine field, including bio-scaffolds and dermo-cosmetic fillers.

The glycoprotein sequences of the $\alpha 1$ chain and $\alpha 2$ chain of type I collagen of man and swine have a homology of 97% and 94% respectively.

Each vial of Guna Collagen Medical Device (2 ml) contains 100 µg of collagen.

The range of Guna Collagen Medical Devices includes 13 different products, each one containing collagen and, additionally, specific, selected auxiliary substances of plant, mineral or vitamin origin, different for each individual Guna Collagen Medical Device. The aim is to encourage the prevalent mechanical action of collagen.
Figure 2

Figure 2

MD-NECK — CERVICAL TRACT OF THE VERTEBRAL SPINE

Improve mobility of the cervical region of the spine, promote cervical muscle stretching, help to support cervical muscle tissue, help to support cervical muscle tissue in bad posture disorders, soothe cervical column pain due to movement. Contains Collagen of porcine origin and Silica.

MD-THORACIC — THORACIC TRACT OF THE VERTEBRAL SPINE

Improve mobility of the thoracic tract of the spine, help muscle stretching, help to support muscle tissue in bad posture disorders, soothe local pain and pain due to movement and bad posture. Contains Collagen of porcine origin and Cimicifuga.

MD-LUMBAR — LUMBOSACRAL AREA OF THE SPINE

Help lumbar region mobility, help muscle stretching of the lumbosacral area, help to support the lumbar muscle tissue, soothe local pain, pain at rest or caused by movement and bad posture. Contains Collagen of porcine origin and Hamamelis.

MD-ISCHIAL — NERVOUS TISSUES (ISCHIATIC NERVE)

Improve leg mobility, help leg muscle stretching, help to support leg muscle tissue, soothe leg pain while starting to move legs after a long inactivity period. Contains Collagen of porcine origin and Rhododendron.

MD-SHOULDER — SHOULDER JOINT

Improve mobility of the shoulder joint and of the upper limb, help muscle stretching, help to support the muscle tissue, soothe local pain and pain due to movement. Contains Collagen of porcine origin and Iris.

MD-SMALL JOINTS

SMALL JOINTS OF HAND AND FOOT

Improve mobility of the small joints of hand, foot and ankle, help muscle stretching, help to support muscle tissue, soothe local pain and pain due to movement. Contains Collagen of porcine origin and Viola.

MD-HIP

HIP JOINT

Improve mobility of the hip joint, help muscle stretching in the hip region, help to support peri-articular muscle tissue, soothe pain at rest or pain due to joint movement or bad posture. Contains Collagen of porcine origin and Calcium phosphate.

MD-KNEE

KNEE JOINT

Improve knee mobility, help muscle stretching, soothe knee pain during movement. Contains Collagen of porcine origin and Arnica.

MD-MUSCLE

MUSCULAR TISSUES

Enhance muscle relaxation and functioning, help to support the muscle tissue in bad posture disorders, improve mobility, soothe local pain or pain due to movement or bad posture. Contains Collagen of porcine origin and Hypericum.

MD-NEURAL

PERIPHERICAL NERVOUS TISSUES

Improve movement by limiting physiological degeneration of joints and tissues, soothe pain, strengthen the connective tissue layer. Contains Collagen of porcine origin and Colocynthis.

MD-POLY

VERTEBRAL SPINE

Improve joint mobility, help muscle stretching, help to support the muscle tissue in bad posture disorders, soothe local pain and pain due to joint movement or bad posture. Contains Collagen of porcine origin and Drosera.

MD-TISSUE

SOFT TISSUES

Act as a defensive barrier against free radicals, counterbalance the physiological aging of the connective tissue, soothe local pain caused by movement. Contains Collagen of porcine origin, Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin and Thiamine hydrochloride.

MD-MATRIX

EXTRACELLULAR MATRIX OF CONNECTIVE TISSUE

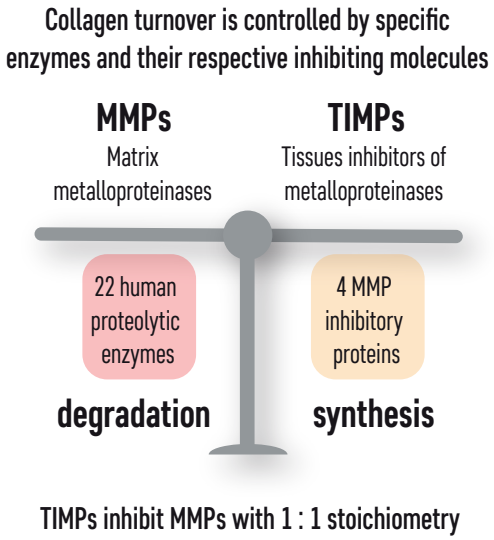
Strengthen extracellular matrix tissues where the collagen is located, act as a defensive barrier against free radicals. Contains Collagen of porcine origin, Citric acid and Nicotinamide.

COLLAGEN METABOLISM

Like all proteins, collagen undergoes synthesis processes and degradation processes. The balance between the degradation and synthesis phases guarantees optimum collagen turnover, which varies in qualitative and quantitative terms and with regard to the duration of the cycle depending on the type of tissue considered. The cyclical collagen synthesis and degradation mechanisms are governed by two fundamental groups of molecules: matrix metalloproteinase (MMP) lithic enzymes, which break down collagen, and the corresponding inhibitory TIMPs (*Tissue Inhibitors of Metalloproteinases*), which downregulate its activity. A correct balance between the activities of these enzymes guarantees the physiological turnover of collagen: if the stoichiometric ratio between specific MMPs and their corresponding TIMPs is 1:1, the collagen degradation and neosynthesis cycle remains within homeostatic parameters; conversely, the prevalence of metalloproteinases over the TIMPs results in a pathological condition in which the collagen degradation phase prevails.

It is interesting to note that MMP activity is mediated by pro-inflammatory cytokines and ROS (reactive oxygen species), whereas TIMP activity is governed by anti-inflammatory cytokines; consequently, in the presence of a persistent prevalently inflammatory cytokine profile (*Low Grade Chronic Systemic Inflammation -LGCSI-*) generated, for example, by overload, ageing or injury, the lithic activity of the MMPs will outweigh the inhibitory action of the TIMPs and will lead to the onset of a pathological degeneration of the collagen structures. *Figure 3*

Figure 3



Cell growth (fibroblasts), cell morphology, cell migration (associated with wound healing mechanisms) and the synthesis and degradation of the collagen matrix mediated by the MMPs and TIMPs are associated with the mechanotransduction mechanism secondary to the anisotropic conditions of the tissue's extracellular matrix. *Figure 4*

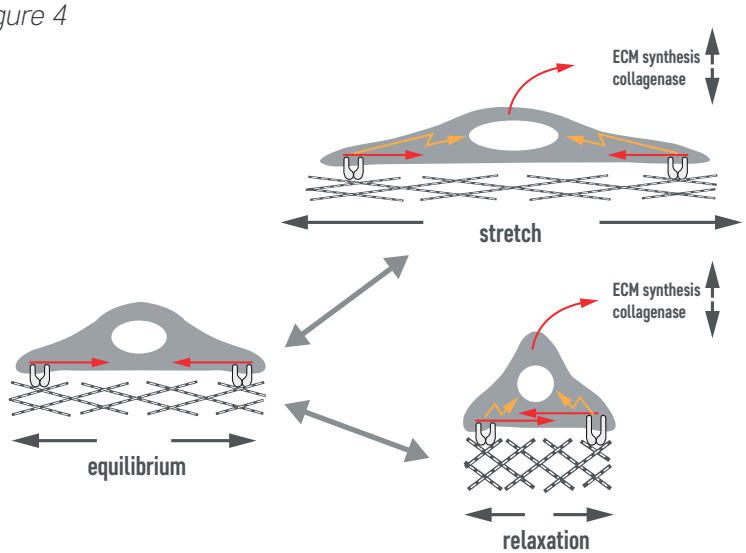


Figure 4

BIOMECHANICAL PROPERTIES OF COLLAGEN: ANISOTROPY

Anisotropy is one of collagen's mechanical properties and describes its fibres' ability to propagate the tensile forces they are subject to in a single preferential direction.

This property, which is fundamental for many biological functions, is gradually lost when the collagen fibres are damaged by ageing, wear and injury processes. More specifically, changes occur in the hydrogen bonds between the collagen fibres, which are fundamental for their orientation.

Collagen fibre anisotropy is essential for ensuring that, thanks to the orientation of the collagen fibres in a single direction (hydrogen bridge bonds are established between the fibres), the extracellular matrix "scaffold" is able to provide the mechanical support that is fundamental for the correct functioning, for example, of the osteoarticular compartment.

Optimum collagen fibre formation and distribution is not only essential for integrity and structural functioning, it also plays a key role in the transmission of tensile forces to the fibroblasts dispersed in the matrix (through interaction with specific transmembrane receptors known as integrins) that are responsible for collagen deposition.

Two aspects are fundamental for the correct fibroblast function:

- The ability to polarise within the extracellular matrix;
- The ability to respond to tensile forces in a "biological" manner.

INTEGRINS are specific receptors present on the surface of fibroblasts that protrude into the extracellular matrix and are able to "capture" a tensile force and translate it into intracellular signalling; in other words, they transform a mechanical force into a biochemical and structural response. *Figure 5*

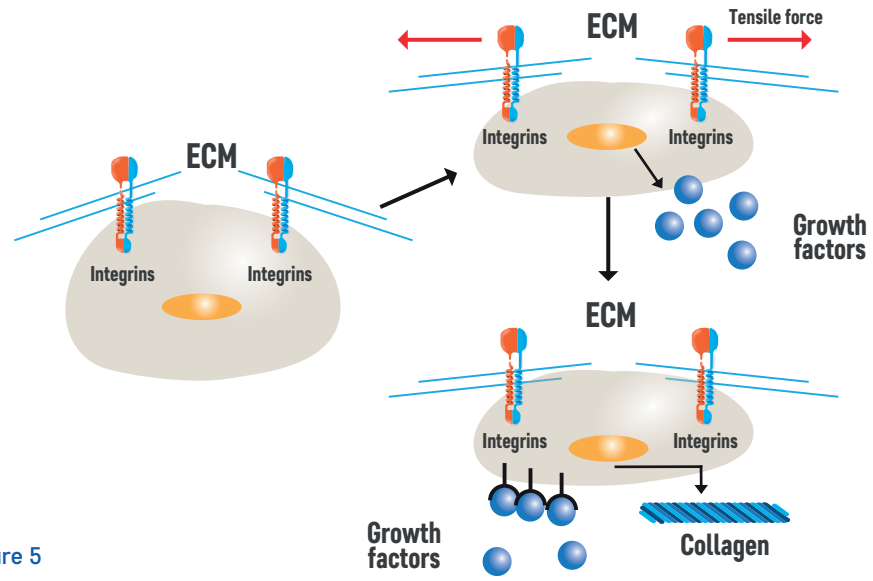


Figure 5

The reduction in collagen fibre anisotropy secondary to an injury, overload, overuse or ageing brings to a reduction in the capacity to transmit tensile forces.

This causes a loss of the two-way communication between the fibroblasts and their surrounding environment; in biological terms, this leads to a reduction in collagen deposition activity, which ultimately results in impaired tissue repair.

MECHANISM OF ACTION OF GUNA COLLAGEN MEDICAL DEVICES

The collagen present in Guna Collagen Medical Devices acts as a bioscaffold of extracellular matrix by means of the deposition of fibrils of collagen in the damaged region, following the locoregional injection of Guna Collagen Medical Devices.

The collagen of **Guna Collagen Medical Devices** is injected locally in order to **replace**, **reinforce**, **give structure to and protect** (adhesion barrier) the tissues of the musculoskeletal system, thereby improving the anatomical and functional structure of the collagen fibres and the tissues containing them and, at the same time, providing mechanical support to the areas involved.

Collagen deposition produces a significant improvement in the mechanical qualities of the damaged tissues; especially when the tissues' **anisotropic** characteristics are restored.

Restoring collagen fibre anisotropy by means of local injections of Guna Collagen Medical Devices effectively induces the same biological response that is obtained with the eccentric work typical of the phases of functional recovery after a tendon lesion and therefore, through the signalling induced by integrin stimulation, it induces the cascade of growth factors (TGF-beta 1, CTGF, IGF-1) required for the production of new collagen by the fibroblast. *Figure 6*

This is a sophisticated biological mechanism that, by means of the local injection of collagen, mechanically reactivates the fibroblast's ability to synthesise new collagen, thus inducing the autologous repair and remodelling mechanisms of the affected connective tissue. Furthermore, the fibroblasts are able to generate, as well as assimilate, tensile forces; these fibroblast contraction forces are essential for wound healing processes.

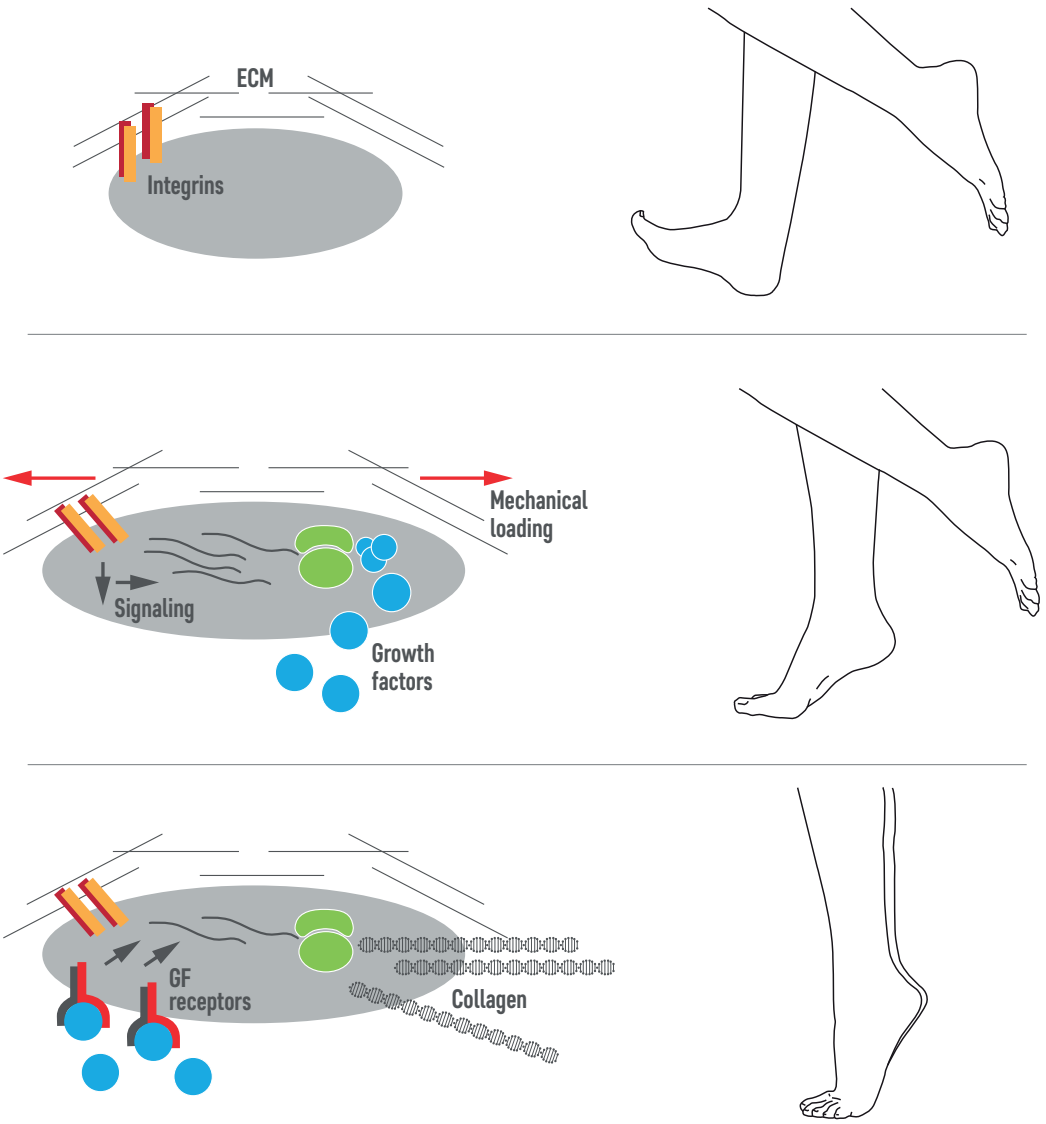


Figure 6

SAFETY AND TOLERABILITY

COLLAGEN IMMUNOGENICITY AND BIOCOMPATIBILITY

In order to support the biomedical applications of type I collagen, a review of the scientific literature was conducted to evaluate, in particular, the general immunogenicity and the biocompatibility of the collagens, their origin and interspecies homology (focusing on human and porcine collagen), the therapeutic applications of collagen and the safety of the medical applications of type I collagen of porcine origin.

Type I collagen is suitable for implantation due to its high bioavailability and low immunogenicity. The high biocompatibility and intrinsic biodegradability of endogenous collagenases make exogenous collagen ideal for biomedical applications (Chattopadhyay and Raines, 2014; Tang and Saito, 2015; Deshmukh et al, 2016). The analysis of the immunological data regarding the clinical use of collagens did not reveal any evidence of adverse immune responses induced by the collagens, regardless of their origins and the extraction methods used to obtain them (Lynn et al, 2004; Tang and Saito, 2015; Deshmukh et al, 2016).

WADA

Guna Collagen Medical Devices do not contain any substance listed by the World Anti-Doping Agency (WADA). They can be administered to professional athletes without any risk associated with doping tests.

COMBINATION WITH OTHER TREATMENTS

Guna Collagen Medical Devices have no drug interactions and can be administered while the patient is undergoing any pharmacological therapy.

The possibility of combining Guna Collagen Medical Devices with any other systemic or local treatment, physiotherapy or other rehabilitation therapies makes Guna Collagen Medical Devices a useful and versatile tool for the treatment of any patients.

CLINICAL APPLICATIONS

From a clinical point of view, Guna collagen-based medical devices can be considered as extracellular matrix bioscaffolds capable of supporting the repair and regeneration of tissues whose connective component has been impaired by overuse, ageing or injury.

Experience from clinical practice confirms that Guna Collagen Medical Devices have the following functions and characteristics:

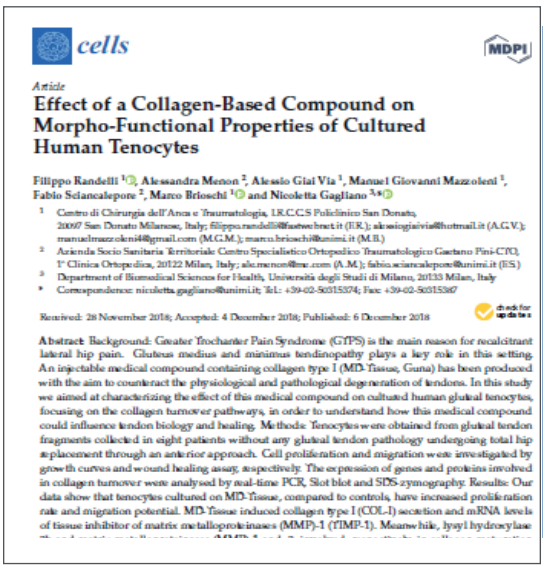
- **Induction of repair and remodelling processes**
- **Increase in the speed of functional recovery**
- **Consolidation and stabilisation of the results achieved with other interventions**
- **Easy to use (intra- and extra-articular injections)**
- **Regenerative and, indirectly, antalgic effect**
- **Excellent tolerability and safety profile**

LITERATURE (ABSTRACTS)

Published data on Guna Collagen Medical Devices and scientific literature on the biomedical use of collagen are available. Preclinical and clinical data on porcine type I collagen for injection support the rationale and confirm the efficacy and safety of its clinical use.

Effect of a Collagen-Based Compound on Morpho-Functional Properties of Cultured Human Tenocytes

- **Randelli F. et al. (2018).**
  This basic research study aimed at characterizing the effect of type I Collagen on collagen turnover using primary human tenocytes. The results obtained suggest that Guna Collagen Medical Devices may induce an anabolic phenotype in the tenocytes by stimulating the proliferation and migration of the tenocytes.



cells

MDPI

Article

Effect of a Collagen-Based Compound on Morpho-Functional Properties of Cultured Human Tenocytes

Filippo Randelli [1]; Alessandra Menon [2], Alessio Giai Via [1], Manuel Giovanni Mazzoleni [1], Fabio Sciancalepore [2], Marco Brioschi [1] and Nicoletta Gagliano [3,*]

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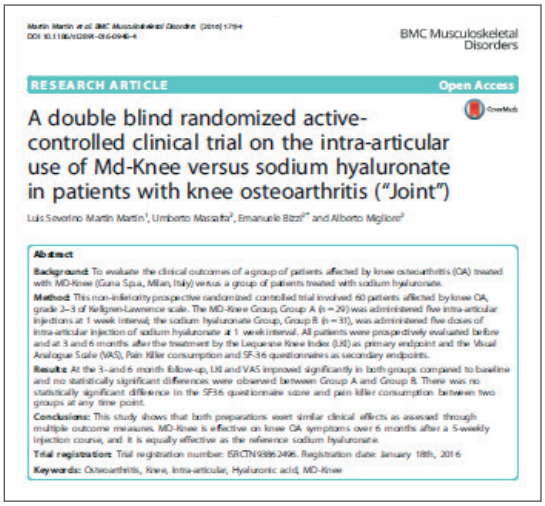
check for updates

Abstract: Background: Greater Trochanter Pain Syndrome (GTPS) is the main reason for recalcitrant lateral hip pain. Gluteus medius and minimus tendinopathy plays a key role in this setting. An injectable medical compound containing collagen type I (MD-Tissue, Guna) has been produced with the aim to counteract the physiological and pathological degeneration of tendons. In this study we aimed at characterizing the effect of this medical compound on cultured human gluteal tenocytes, focusing on the collagen turnover pathways, in order to understand how this medical compound could influence tendon biology and healing. Methods: Tenocytes were obtained from gluteal tendon fragments collected in eight patients without any gluteal tendon pathology undergoing total hip replacement through an anterior approach. Cell proliferation and migration were investigated by growth curves and wound healing assay, respectively. The expression of genes and proteins involved in collagen turnover were analysed by real-time PCR, Slot blot and SDS-zymography. Results: Our data show that tenocytes cultured on MD-Tissue, compared to controls, have increased proliferation rate and migration potential. MD-Tissue induced collagen type I (COL-I) secretion and mRNA levels of tissue inhibitor of matrix metalloproteinases (MMP)-1 (TIMP-1). Meanwhile, lysyl hydroxylase

A double blind randomized active-controlled clinical trial on the intra-articular use of Md-Knee versus sodium hyaluronate in patients with knee osteoarthritis ("Joint")

- **Martin-Martin LS. et al. (2016).**
  This study evaluated the clinical outcomes of a group of patients affected by knee osteoarthritis (OA) treated with MD-Knee, compared to a group of patients treated with sodium hyaluronate. All patients were prospectively evaluated before treatment, and after 3 and 6 months from end of treatment. At the end of the follow-up period, the pain associated with OA was significantly reduced in both groups compared to baseline. No statistically significant differences were observed between group A and group B; both treatments were well tolerated. No systemic adverse events were observed. No joint effusion events were observed during follow-up.


BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

A double blind randomized active-controlled clinical trial on the intra-articular use of Md-Knee versus sodium hyaluronate in patients with knee osteoarthritis ("Joint")

Luis Severino Martin Martin[1], Umberto Massafra[2], Emanuele Bizzi[2*] and Alberto Migliore[2]

Abstract

Background: To evaluate the clinical outcomes of a group of patients affected by knee osteoarthritis (OA) treated with MD-Knee (Guna S.p.a., Milan, Italy) versus a group of patients treated with sodium hyaluronate.

Method: This non-inferiority prospective randomized controlled trial involved 60 patients affected by knee OA, grade 2–3 of Kellgren-Lawrence scale. The MD-Knee Group, Group A (n = 29) was administered five intra-articular injections at 1 week interval; the sodium hyaluronate Group, Group B (n = 31), was administered five doses of intra-articular injection of sodium hyaluronate at 1 week interval. All patients were prospectively evaluated before and at 3 and 6 months after the treatment by the Lequesne Knee Index (LKI) as primary endpoint and the Visual Analogue Scale (VAS), Pain Killer consumption and SF-36 questionnaires as secondary endpoints.

Results: At the 3- and 6 month follow-up, LKI and VAS improved significantly in both groups compared to baseline and no statistically significant differences were observed between Group A and Group B. There was no statistically significant difference in the SF36 questionnaire score and pain killer consumption between two groups at any time point.

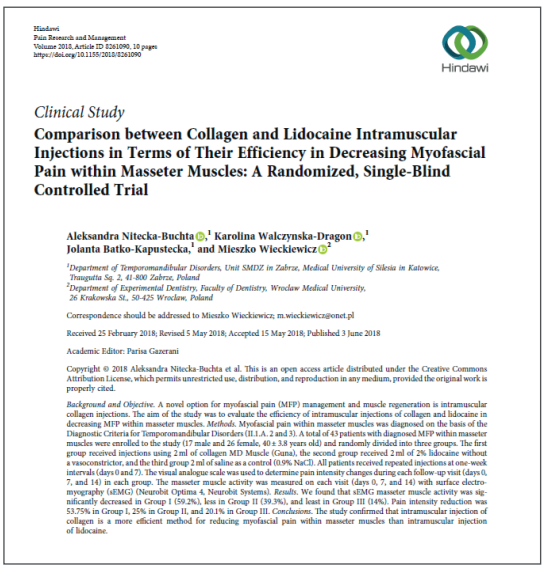
Conclusions: This study shows that both preparations exert similar clinical effects as assessed through multiple outcome measures. MD-Knee is effective on knee OA symptoms over 6 months after a 5-weekly injection course, and it is equally effective as the reference sodium hyaluronate.

Trial registration: Trial registration number: ISRCTN9886 2496. Registration date: January 18th, 2016

Keywords: Osteoarthritis, Knee, Intra-articular, Hyaluronic acid, MD-Knee

Comparison between Collagen and Lidocaine Intramuscular Injections in Terms of Their Efficiency in Decreasing Myofascial Pain within Masseter Muscles: A Randomized, Single-Blind Controlled Trial

- **Nitecka-Buchta A. et al. (2018).**
  This study evaluated the effects of MD-Muscle in myofascial painful syndrome of the masseter muscle. In chronic temporomandibular disorders (TMDs), we observe an alteration in muscle function, which results in a decreased contractile function of the muscle itself. The alteration of myoelectric activity is a marker of this dysfunction. As a result of muscle tissue and connective tissue alterations, painful symptoms occur. The maintenance and the recovery of muscle regenerative capacities, as well as the restoration of ECM turnover, are fundamental for reducing myofascial pain syndrome.
  This randomized, single-blind, controlled clinical trial investigated the effectiveness of the local injection of MD-Muscle compared to lidocaine 2% in controlling pain and promoting muscle relaxation. Evaluation was made at T 7 and T 14. The results of group treated with MD-Muscle show higher efficacy in pain control (VAS) and also in the reduction of masseter muscle myoelectric activity (Electromyography).
  The results also suggest a possible, indirect antalgic effects of intramuscular injections of MD-Muscle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Hindawi

Clinical Study

Comparison between Collagen and Lidocaine Intramuscular Injections in Terms of Their Efficiency in Decreasing Myofascial Pain within Masseter Muscles: A Randomized, Single-Blind Controlled Trial

Aleksandra Nitecka-Buchta,[1] Karolina Walczynska-Dragon,[1] Jolanta Batko-Kapustecka,[1] and Mieszko Wieckiewicz[2]

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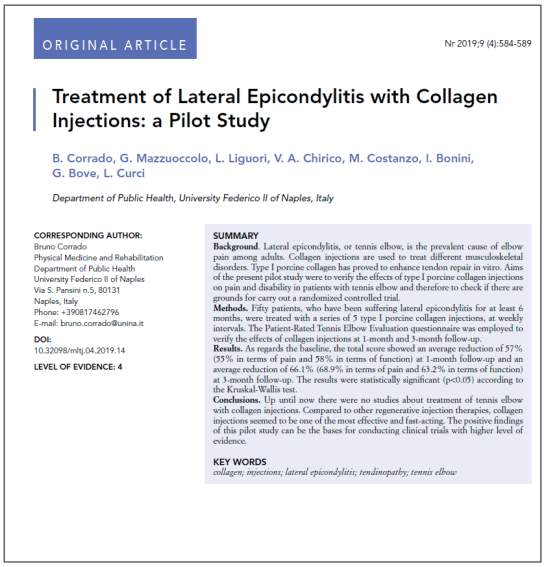
Background and Objective. A novel option for myofascial pain (MFP) management and muscle regeneration is intramuscular collagen injections. The aim of the study was to evaluate the efficiency of intramuscular injections of collagen and lidocaine in decreasing MFP within masseter muscles. *Methods.* Myofascial pain within masseter muscles was diagnosed on the basis of the Diagnostic Criteria for Temporomandibular Disorders (II.1.A, 2 and 3). A total of 43 patients with diagnosed MFP within masseter muscles were enrolled to the study (17 male and 26 female, 40 ± 3.8 years old) and randomly divided into three groups. The first group received injections using 2 ml of collagen MD Muscle (Guna), the second group received 2 ml of 2% lidocaine without a vasoconstrictor, and the third group 2 ml of saline as a control (0.9% NaCl). All patients received repeated injections at one-week intervals (days 0 and 7). The visual analogue scale was used to determine pain intensity changes during each follow-up visit (days 0, 7, and 14) in each group. The masseter muscle activity was measured on each visit (days 0, 7, and 14) with surface electromyography (sEMG) (Neurobit Optima 4, Neurobit Systems). *Results.* We found that sEMG masseter muscle activity was significantly decreased in Group I (59.2%), less in Group II (39.3%), and least in Group III (14%). Pain intensity reduction was 53.75% in Group I, 25% in Group II, and 20.1% in Group III. *Conclusions.* The study confirmed that intramuscular injection of collagen is a more efficient method for reducing myofascial pain within masseter muscles than intramuscular injection of lidocaine.

Treatment of Lateral Epicondylitis with Collagen injection: a Pilot Study



ORIGINAL ARTICLE

Nr 2019;9 (4):584-589

Treatment of Lateral Epicondylitis with Collagen Injections: a Pilot Study

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LEVEL OF EVIDENCE: 4

SUMMARY

Background. Lateral epicondylitis, or tennis elbow, is the prevalent cause of elbow pain among adults. Collagen injections are used to treat different musculoskeletal disorders. Type I porcine collagen has proved to enhance tendon repair in vitro. Aims of the present pilot study were to verify the effects of type I porcine collagen injections on pain and disability in patients with tennis elbow and therefore to check if there are grounds for carry out a randomized controlled trial.

Methods. Fifty patients, who have been suffering lateral epicondylitis for at least 6 months, were treated with a series of 5 type I porcine collagen injections, at weekly intervals. The Patient-Rated Tennis Elbow Evaluation questionnaire was employed to verify the effects of collagen injections at 1-month and 3-month follow-up.

Results. As regards the baseline, the total score showed an average reduction of 57% (55% in terms of pain and 58% in terms of function) at 1-month follow-up and an average reduction of 66.1% (68.9% in terms of pain and 63.2% in terms of function) at 3-month follow-up. The results were statistically significant ($p<0.05$) according to the Kruskal-Wallis test.

Conclusions. Up until now there were no studies about treatment of tennis elbow with collagen injections. Compared to other regenerative injection therapies, collagen injections seemed to be one of the most effective and fast-acting. The positive findings of this pilot study can be the bases for conducting clinical trials with higher level of evidence.

KEY WORDS
collagen; injections; lateral epicondylitis; tendinopathy; tennis elbow

- **Corrado B. et al.(2019).**
  This study assessed the effectiveness of MD-Tissue in reducing pain and disability in patients affected by epicondylitis (also known as tennis elbow syndrome). 50 patients who had been suffering from lateral epicondylitis for at least 6 months, were treated with 5 weekly infiltrations. Evaluation was made by using PRTEE (Patient-Rated Tennis Elbow Evaluation) questionnaire, follow up was performed 1 month and 3 months after treatment. Compared to baseline, results showed a total, average reduction of symptoms by 57% (55% in terms of pain and 58% in terms of function) at 1-month follow-up and an average reduction of 66.1% (68.9% in terms of pain and 63.2% in terms of function) at 3-month follow-up. The results are statistically significant ($p < 0.05$) according to Kruskal-Wallis test.

Efficacy and tolerability of injectable collagen-containing products in comparison to trimecaine in patients with acute lumbar spine pain (Study FUTURE-MD-Back Pain)

Physiol. Res. 68 (Suppl. 1): S000-S000, 2019 *https://doi.org/10.33549/physiolres.934326*

Efficacy and Tolerability of Injectable Collagen-Containing Products in Comparison to Trimecaine in Patients With Acute Lumbar Spine Pain (Study FUTURE-MD-Back Pain)

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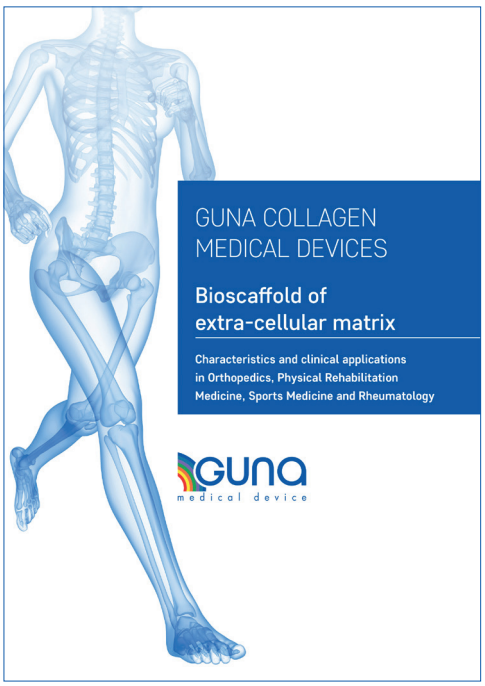
- **Pavelka K. et al. (2019).**
  This study evaluated the efficacy and safety of a combination of MD-Lumbar (2 ml) + MD-Muscle (1 ml) + MD-Neural (1 ml) in patients with chronic Low Back Pain. 97 patients affected by LBP < three months were enrolled and randomized into two groups. One group was administered a combination of Collagen Medical Devices, while the other group was administered 1% trimecaine (4 ml). Both groups underwent subcutaneous paravertebral injections into eight predefined points, with the following scheme: two administrations in the first and second week, one in the third week. Pain intensity, Thomayer's distance, Oswestry Disability Index, Lasègue test, quality of life, consumption of paracetamol as a rescue medication and clinical safety were assessed. Results show a gradual decrease in pain at rest and pain during exercise (VAS) in both groups. Both groups also showed a statistically significant improvement in mobility and quality of life. On the other hand, consumption of paracetamol as a rescue medication was significantly lower in the group treated with collagen.

BIBLIOGRAPHY

- Boot-Handford RP, Tuckwell DS. Fibrillar collagen: the key to vertebrate evolution? A tale of molecular incest. Bioessays. 2003;25(2):142-51.
- Brandão RA, Costa BS, Dellaretti MA, de Carvalho GT, Faria MP, de Sousa AA. Efficacy and safety of a porcine collagen sponge for cranial neurosurgery: a prospective case-control study. World Neurosurg. 2013 Mar-Apr;79(3-4):544-50.
- Catena F, Ansaloni L, Gazzotti F, Gagliardi S, Di Saverio S, D'Alessandro L, Pinna AD. Use of porcine dermal collagen graft (Permacol) for hernia repair in contaminated fields. Hernia. 2007 Feb;11(1):57-60.
- Chattopadhyay S, Raines RT. Review collagen-based biomaterials for wound healing. Biopolymers. 2014;101(8):821-33.
- Christensen B, Dandanell S, Kjaer M, Langberg H. Effect of anti-inflammatory medication on the running-induced rise in patella tendon collagen synthesis in humans. J Appl Physiol (1985). 2011 Jan;110(1):137-41.
- del Nogal M, Luengo A, Olmos G, Lasa M, Rodriguez-Puyol D, Rodriguez-Puyol M, Calleros L. Balance between apoptosis or survival induced by changes in extracellular-matrix composition in human mesangial cells: a key role for ILK-NFκB pathway. Apoptosis. 2012 Dec;17(12):1261-74.
- Deshmukh SN, Dive AM, Moharil R, Munde P. Enigmatic insight into collagen. J Oral Maxillofac Pathol. 2016;20(2):276-83.
- Erdemoglu N, Akkol EK, Yesilada E, Caliş I. Bioassay-guided isolation of anti-inflammatory and antinociceptive principles from a folk remedy, Rhododendron ponticum L. leaves. J Ethnopharmacol. 2008 Sep 2;119(1):172-8.
- Fung DT, Sereysky JB, Basta-Pljakic J, Laudier DM, Huq R, Jepsen KJ, Schaffler MB, Flatow EL. Second harmonic generation imaging and Fourier transform spectral analysis reveal damage in fatigue-loaded tendons. Ann Biomed Eng. 2010 May;38(5):1741-51.
- Friedrichs J, Taubenberger A, Franz CM, Muller DJ. Cellular remodelling of individual collagen fibrils visualized by time-lapse AFM. J Mol Biol. 2007 Sep 21;372(3):594-607.
- Gilani AH, Khan AU, Subhan F, Khan M. Antispasmodic and bronchodilator activities of St John's wort are putatively mediated through dual inhibition of calcium influx and phosphodiesterase. Fundam Clin Pharmacol. 2005 Dec;19(6):695-705.
- Grieve, M., 1994. "A Modern Herbal", Leyel. Tiger Books International, London.
- Henstock JR, Canham LT, Anderson SI. Silicon: the evolution of its use in biomaterials. Acta Biomater. 2015;11:17-26.
- Hussain AI, Rathore HA, Sattar MZ, Chatha SA, Sarker SD, Gilani AH. Citrullus colocynthis (L.) Schrad (bitter apple fruit): a review of its phytochemistry, pharmacology, traditional uses and nutritional potential. J Ethnopharmacol. 2014 Aug 8;155(1):54-66.
- Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell. 2002 Sep 20;110(6):673-87.
- Jurkiewicz A, Ryszka P, Anielska T, Waligórski P, Białońska D, et al. Optimization of culture conditions of Arnica montana L.: effects of mycorrhizal fungi and competing plants. Mycorrhiza. 2010 Jun;20(5):293-306.
- Keil SD, Kiser P, Sullivan JJ, Kong AS, Reddy HL, Avery A, Goodrich RP. Inactivation of Plasmodium spp. in plasma and platelet concentrates using riboflavin and ultraviolet light. Transfusion. 2013 Oct;53(10):2278-86.
- Kook SH, Jang YS, Lee JC. Involvement of JNK-AP-1 and ERK-NF-κB signaling in tension-stimulated expression of type I collagen and MMP-1 in human periodontal ligament fibroblasts. J Appl Physiol (1985). 2011 Dec;111(6):1575-83.
- Krenn L, Beyer G, Pertz HH, Karall E, Kremser M, Galambosi B, Melzig MF. In vitro antispasmodic and anti-inflammatory effects of Drosera rotundifolia. Arzneimittelforschung. 2004;54(7):402-5.

- Linsenmayer, T.F. (1991) Collagen. In: "Cell Biology of the Extracel-Mar Matrix," Hay, E.D. (ed). New York: Plenum Press, pp. 7-44.
- Lynn AK, Yannas IV, Bonfield W. Antigenicity and immunogenicity of collagen. J Biomed Mater Res B Appl Biomater. 2004;71(2):343-54.
- Lyss G, Knorre A, Schmidt TJ, Pahl HL, Merfort I. The anti-inflammatory sesquiterpene lactone helenalin inhibits the transcription factor NF-kappaB by directly targeting p65. J Biol Chem. 1998 Dec 11;273(50):33508-16
- Masaki H. Role of antioxidants in the skin: anti-aging effects. J Dermatol Sci. 2010 May;58(2):85-90.
- Massoud EI. Healing of subcutaneous tendons: Influence of the mechanical environment at the suture line on the healing process. World J Orthop. 2013 Oct 18;4(4):229-40.
- Milani L. A new and refined injectable treatment for musculoskeletal disorder. Bioscaffold properties of collagen and its clinical use. Physiological Regulating Medicine 2010/1; 3-15.
- Nawash O, Shudiefat M, Al-Tabini R, Al-Khalidi K. Ethnobotanical study of medicinal plants commonly used by local Bedouins in the Badia region of Jordan. J Ethnopharmacol. 2013 Jul 30;148(3):921-5.
- Muhammad N, Saeed M, Khan H. Antipyretic, analgesic and anti-inflammatory activity of Viola betonicifolia whole plant. BMC Complement Altern Med. 2012 May 2;12:59.
- Narins RS, Brandt FS, Lorenc ZP, Maas CS, Monheit GD, Smith SR, McIntyre S. A randomized, multicenter study of the safety and efficacy of Dermicol-P35 and non-animal-stabilized hyaluronic acid gel for the correction of nasolabial folds. Dermatol Surg. 2007 Dec;33 Suppl 2:S213-21; discussion S221.
- Ngamphaiboon N, Sweeney R, Wetzler M, Wang ES. Pyridoxine treatment of vincristine-induced cranial polyneuropathy in an adult patient with acute lymphocytic leukemia: Case report and review of the literature. Leuk Res. 2010 Aug;34(8):e194-6.
- Rahman AU, Nasim S, Baig I, Jalil S, Orhan I, et al. Anti-inflammatory isoflavonoids from the rhizomes of Iris germanica. J Ethnopharmacol. 2003 Jun;86(2-3):177-80.
- Sage RJ, Lopiccolo MC, Liu A, Mahmoud BH, Tierney EP, Kouba DJ. Subcuticular incision versus naturally sourced porcine collagen filler for acne scars: a randomized split-face comparison. Dermatol Surg. 2011 Apr;37(4):426-31.
- Schütz C, Quitschau M, Hamburger M, Potterat O. Profiling of isoflavonoids in Iris germanica rhizome extracts by microprobe NMR and HPLC-PDA-MS analysis. Fitoterapia. 2011 Oct;82(7):1021-6.
- Silbernagel KG, Brorsson A, Lundberg M. The majority of patients with Achilles tendinopathy recover fully when treated with exercise alone: a 5-year follow-up. Am J Sports Med. 2011 Mar;39(3):607-13.
- Silvipriya KS, Kumar KK, Bhat AR, Kumar BD, John A, Lakshmanan P. Collagen: Animal Sources and Biomedical Application. Journal of Applied Pharmaceutical Science. 2015;5(03):123-7.
- Solish NJ. Assessment of recovery time for the collagen products Dermicol-P35 27G and 30G. J Am Acad Dermatol. 2010 May;62(5):824-30.
- Tang X, Liu J, Dong W, Li P, Li L, Lin C, Zheng Y, Hou J, Li D. The cardioprotective effects of citric Acid and L-malic Acid on myocardial ischemia/reperfusion injury. Evid Based Complement Alternat Med. 2013;2013:820695.
- Tang J, Saito T. Biocompatibility of Novel Type I Collagen Purified from Tilapia Fish Scale: An In Vitro Comparative Study. Biomed Res Int. 2015;2015:139476.
- Todhunter RJ, Wootton JA, Lust G, Minor RR. Structure of equine type I and type II collagens. Am J Vet Res. 1994;55(3):425-31.
- Trautvetter U, Neef N, Leiterer M, Kiehntopf M, Kratzsch J, et al. Effect of calcium phosphate and vitamin D_3 supplementation on bone remodelling and metabolism of calcium, phosphorus, magnesium and iron. Nutr J. 2014 Jan 17;13:6.
- Tsai KS, Kao SY, Wang CY, Wang YJ, Wang JP, Hung SC. Type I collagen promotes proliferation and osteogenesis of human mesenchymal stem cells via activation of ERK and Akt pathways. J Biomed Mater Res A. 2010 Sep 1;94(3):673-82.
- Turunc Bayrakdar E, Uyanikgil Y, Kanit L, Koylu E, Yalcin A. Nicotinamide treatment reduces the levels of oxidative stress, apoptosis, and PARP-1 activity in Aβ(1-42)-induced rat model of Alzheimer's disease. Free Radic Res. 2014 Feb;48(2):146-58.
- Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. Biofactors. 2009 Jan-Feb;35(1):5-13.



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