GUNA COLLAGEN MEDICAL DEVICES

New scenarios in Dentistry

June 2020

Alessandro Perra – Scientific Director of GUNA S.p.a.

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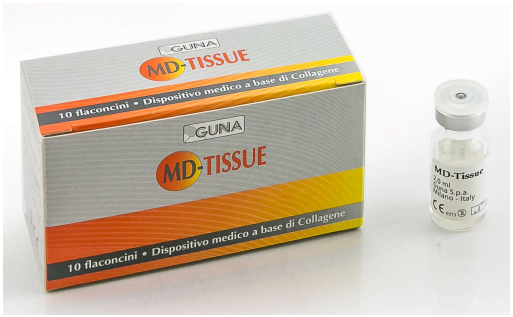
Guna Collagen Medical Devices are a substrate for collagen fibrils reconstitution and act as a

Bio-scaffold of natural collagen



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GUNA MEDICAL DEVICE

- INNOVATION
- EFFICACY
- NATURAL ORIGIN

SWINE COLLAGEN

+

Herbal or mineral substances called “ancillary” or «auxiliary»

MEDICAL DEVICES - CLASS III - INJECTABLE
Directive 93/42 CEE. 1993

‘Medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
-control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means,
-…very important: 93/42/CEE about ancillary substances.

WHY

Collagen Medical Devices?

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An innovative approach to **REGENERATIVE MEDICINE** in Dentistry

An innovative approach to REGENERATIVE MEDICINE in Dentistry

Treatment of tendinopathy, including Greater Trochanter Pain Syndrome and others, remains a

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,*]

promising results have been reported with autologous tenocyte injection [11]. However, there is still little evidence to support the use of biological therapies for treatment of GTPS [12].

An innovative approach to REGENERATIVE MEDICINE in Dentistry

Lengthening contractions or endurance training may

Hindawi
Pain Research and Management
Volume 2018, Article ID 8261090, 10 pages
https://doi.org/10.1155/2018/8261090

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]

number of newly formed microfibers, the fewer the cross-sectional connections and the lower the produced muscle mass [18]. Collagen is strictly needed for proper muscle regeneration. Collagen decreases apoptosis and increases myoblast proliferation [18]. The extracellular matrix is also

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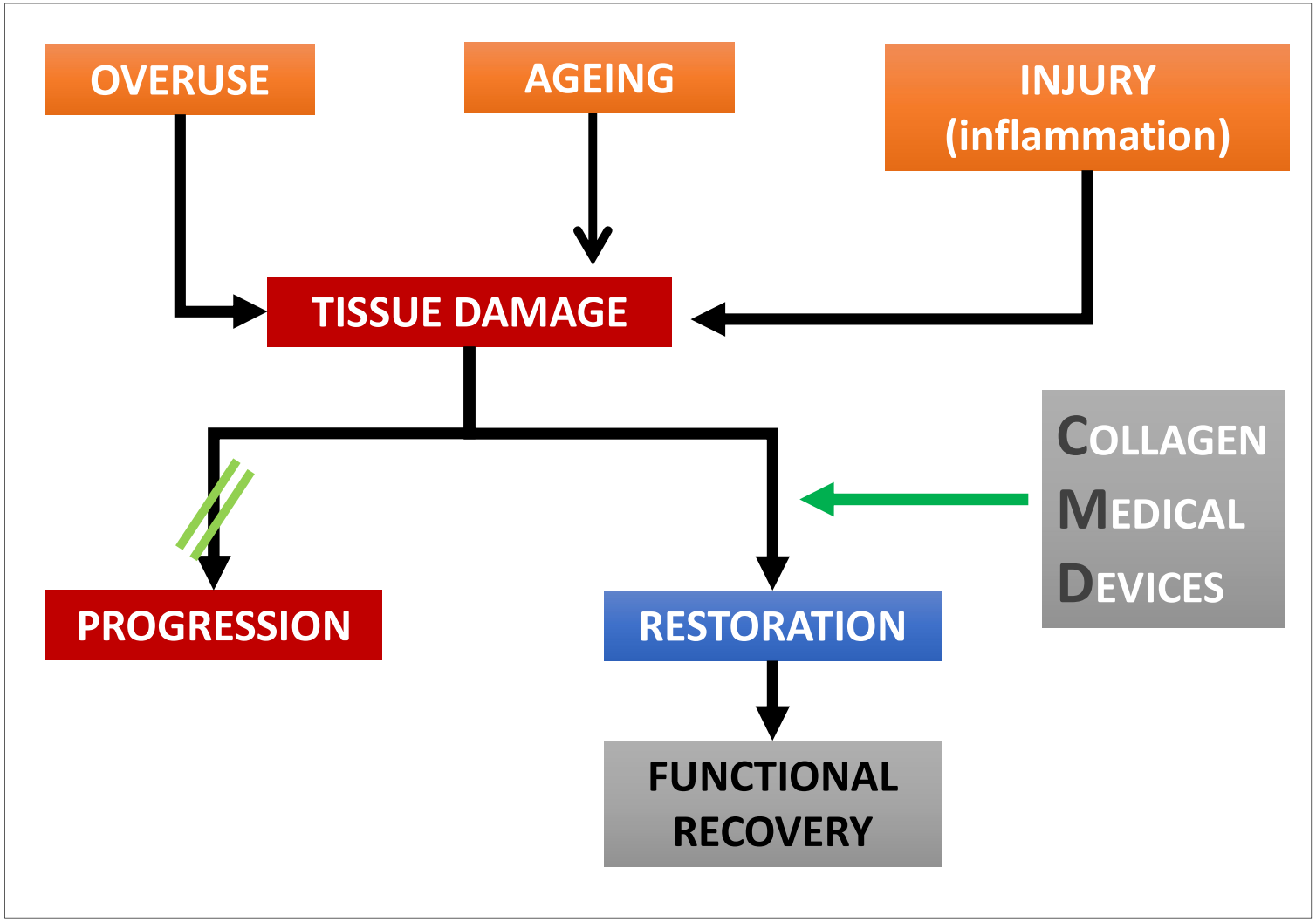
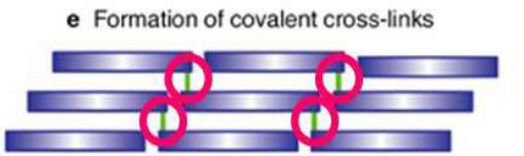
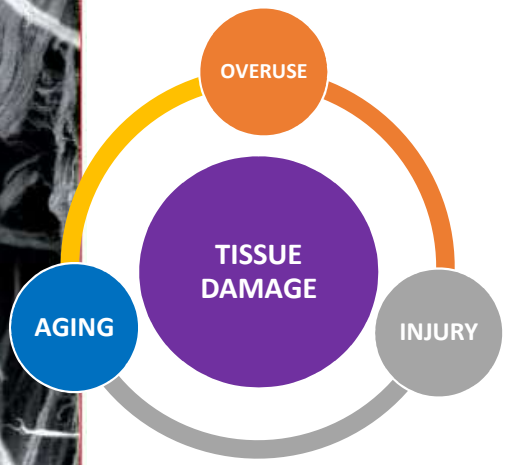
A new concept

Induction of the
inflammation pro-resolution phase
and **tissue repair and regeneration.**







Healthy ligament = Parallel collagen fibers

Damaged ligament = Loss of parallelism of collagen fibers

Hsu *et al. Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology* 2010, **2**:12
http://www.smarttjournal.com/content/2/1/12

SMARTT
SPORTS MEDICINE ARTHROSCOPY
REHABILITATION THERAPY TECHNOLOGY

REVIEW Open Access

Functional tissue engineering of ligament healing

Shan-Ling Hsu[†1,2], Rui Liang[†1] and Savio LY Woo*[1]

Abstract

Ligaments and tendons are dense connective tissues that are important in transmitting forces and facilitate joint articulation in the musculoskeletal system. Their injury frequency is high especially for those that are functional important, like the anterior cruciate ligament (ACL) and medial collateral ligament (MCL) of the knee as well as the glenohumeral ligaments and the rotator cuff tendons of the shoulder. Because the healing responses are different in these ligaments and tendons after injury, the consequences and treatments are tissue- and site-specific. In this review, we will elaborate on the injuries of the knee ligaments as well as using functional tissue engineering (FTE) approaches to improve their healing. Specifically, the ACL of knee has limited capability to heal, and results of non-surgical management of its midsubstance rupture have been poor. Consequently, surgical reconstruction of the ACL is regularly performed to gain knee stability. However, the long-term results are not satisfactory besides the numerous complications accompanied with the surgeries. With the rapid development of FTE, there is a renewed interest in revisiting ACL healing. Approaches such as using growth factors, stem cells and scaffolds have been widely investigated. In this article, the biology of normal and healing ligaments is first reviewed, followed by a discussion on the issues related to the treatment of ACL injuries. Afterwards, current promising FTE methods are presented for the treatment of ligament injuries, including the use of growth factors, gene delivery, and cell therapy with a particular emphasis on the use of ECM bioscaffolds. The challenging areas are listed in the future direction that suggests where collection of energy could be placed in order to restore the injured ligaments and tendons structurally and functionally.

Functional Tissue Engineering
ECM bioscaffolds

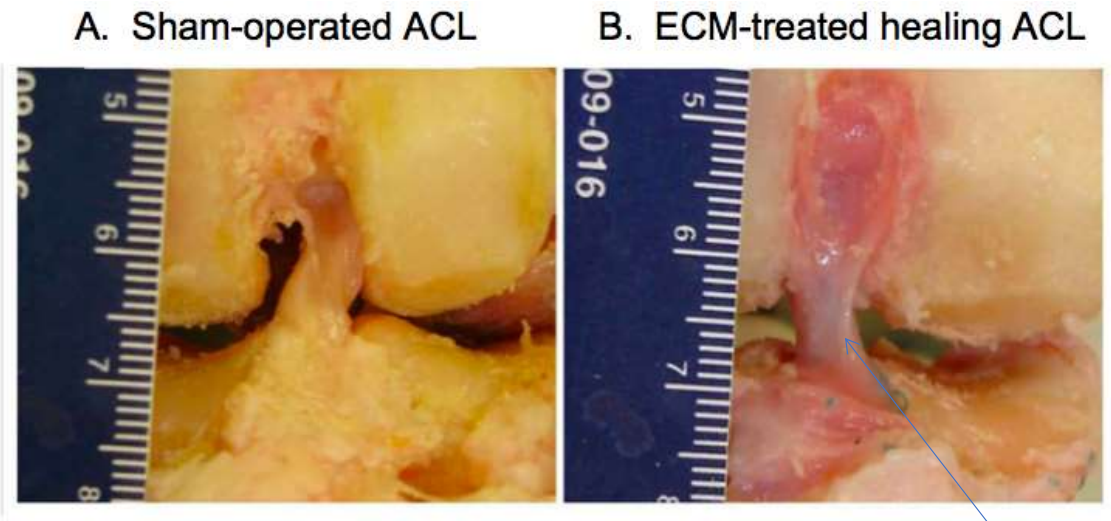


Figure 3 Gross morphology of (A) Sham-operated ACL; and (B) ECM-treated healing ACL at 12 weeks (permission requested from Woo et al. [133]).

Hsu et al., Functional tissue engineering of ligament healing. Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology 2010, 2:12

Brightness due to proteoglicans scaffold

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GUNA MEDICAL DEVICE

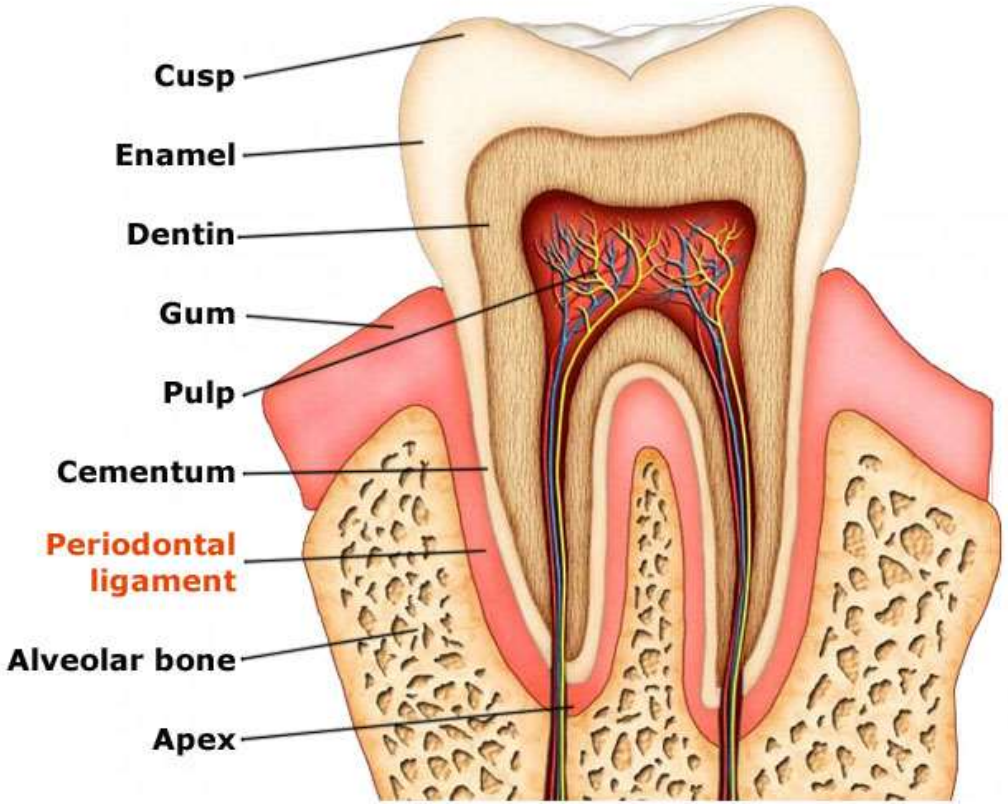
- INNOVATION
- EFFICACY
- NATURAL ORIGIN

Why COLLAGEN?

COLLAGEN

- Collagen **is the most abundant protein** (structural protein – tissue; molecular weight 300KDa) in mammalians' organism – accounting for about **5-6% of an adult's body weight** (Van der Rest et Al., 1991); one third (Trentham et Al., 1977) or one fourth (Lynsenmeyer, 1991) of the whole protein mass of higher animals is composed of collagen: **bones** and **tendons**, **joint capsules** and **muscles**, **ligaments** and **fascia**, teeth and serous membranes, the skin and the extracellular matrix (ECM).

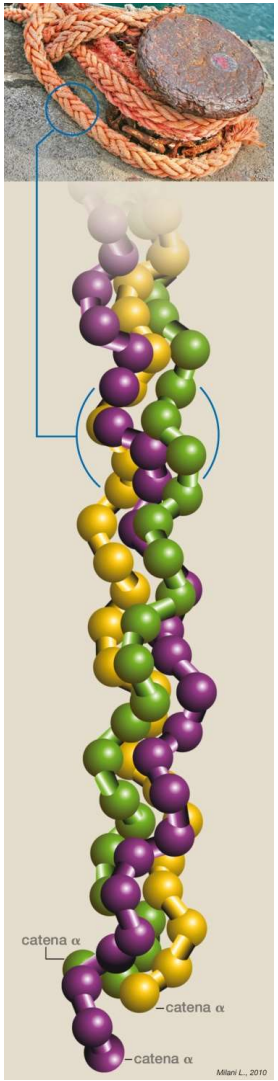
Periodontal ligament


Cusp
Enamel
Dentin
Gum
Pulp
Cementum
Periodontal ligament
Alveolar bone
Apex

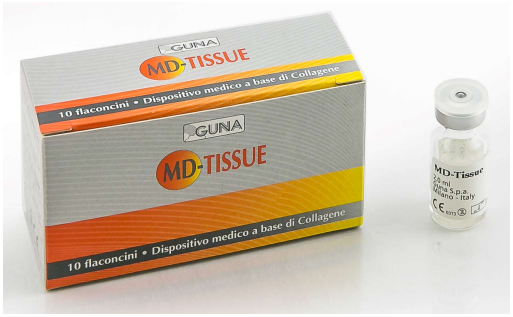
The triple helix (three *alpha* chains) of **tropo-collagen** is the basic unit of mature collagen.

Structure: chains of *glucose and galactose* *+ 4 aminoacids:*

- HYL
- GLY
- PRO
- **HYP**



COLLAGEN Medical Device Characteristics



NUMBERS…

- *Tropocollagen M.W. = 300 kDa*
  - *1 Da = 1.66 X 10^{-27} Kg*
  - *Tropocollagen W ≈ 5 X 10^{-22} Kg*
- *100 µg of Tropocollagen ≈ 2 X 10^{14} Molecules*

- ***One vial content: 2ml /100 µg of Tropocollagen***

Hydrolized collagen (Tropocollagen)/Vial content

≈

2 X 10^{14} Molecules

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GUNA MEDICAL DEVICE

- INNOVATION
- EFFICACY
- NATURAL ORIGIN

Why SWINE Collagen?

The SIMILARITY between the α1-chain collagen type 1 of humans and pigs is 97%, and it is 93% for α2-chain

SAFETY OF PORCINE COLLAGEN MEDICAL USE
Literature -1-

Efficacy and Safety of a Porcine Collagen Sponge for Cranial Neurosurgery: A Prospective Case-Control Study

Rafael Augusto Castro Santiago Brandão, Bruno Silva Costa, Marcos Antonio Dellaretti, Gervásio Teles C. de Carvalho, Marcello Penholate Faria, Atos Alves de Sousa

Key words
- Cerebrospinal fluid leak
- Collagen matrix
- Collagen sponge
- Dural closure
- Dural graft
- Duraplasty

Abbreviations and Acronyms
CSF: Cerebrospinal fluid
CT: Computed tomography
MRI: Magnetic resonance imaging

Department of Neurosurgery, Santa Casa Hospital at Belo Horizonte, Minas Gerais, Brazil

To whom correspondence should be addressed: Rafael Brandão, M.D. [E-mail: rafabrand@gmail.com]

Citation: World Neurosurg. (2013) 79, 3/4:544-550.
DOI: 10.1016/j.wneu.2011.08.015
Journal homepage: www.WORLDNEUROSURGERY.org
Available online: www.sciencedirect.com

OBJECTIVE: The use of dural grafts is very useful when primary dural closure cannot be achieved. Our primary objective was to study the incidence of postoperative cerebrospinal fluid leak, including fistula and pseudomeningocele, and postoperative infection by comparing autologous material and a new collagen graft.

MATERIALS AND METHODS: A prospective nonrandomized study with a new collagen-based product derived from porcine cells (Peridry) was performed. It was used for dural replacement in 50 patients who underwent a variety of neurosurgical procedures requiring the use of a dural graft. These results were compared with a control group of 50 patients who were treated with autologous duraplasty material. The follow-up period was 3 months.

RESULTS: Postoperative overall cerebrospinal fluid fistula occurred in 6% of both groups. No patient in the collagen group developed any sort of infection. One patient in the control developed osteomyelitis in the bone flap.

CONCLUSION: The new collagen-based product derived from porcine cells (Peridry), compared with an autologous tissue, is safe, effective, easy to use, as well as time saving in cranial neurosurgery.

Porcine collagen scaffolds for cranial neurosurgery are safe, effective and easy to use

SAFETY OF PORCINE COLLAGEN MEDICAL USE
Literature -2-

ORIGINAL ARTICLES

Subcuticular Incision Versus Naturally Sourced Porcine Collagen Filler for Acne Scars: A Randomized Split-Face Comparison

Robert J. Sage, MD,* Matteo C. Lopiccolo, MD,* Austin Liu, MD,*
Bassel H. Mahmoud, MD, PhD,* Emily P. Tierney, MD,† and David J. Kouba, MD, PhD*‡

BACKGROUND Subcuticular incision is performed to release fibrotic bands beneath acne scars and to stimulate neocollagenesis. Naturally sourced porcine collagen has been approved for filling moderate to deep facial wrinkles and nasolabial folds. To our knowledge, naturally sourced porcine collagen filler has not yet been tried as a treatment for correcting atrophic acne scars.

OBJECTIVE To objectively assess and directly compare the efficacy and safety of subcuticular incision versus naturally sourced porcine collagen dermal filler in correcting atrophic and rolling acne scars.

MATERIALS AND METHODS We performed a prospective, randomized, split-face, single-blind study to evaluate intermediate long-term efficacy of subcision and collagen dermal filler on 20 unilateral faces. Patients and blinded physicians evaluated results.

RESULTS Patients rated subcision as superior to collagen dermal filler at 3 months ($p = .03$). At 6 months, subcision had a slightly higher rating than collagen dermal filler ($p = .12$). Blinded evaluators leaned toward subcision at 3 months ($p = .12$) and at 6 months showed no preference ($p = .69$).

CONCLUSION Subcuticular incision and naturally sourced porcine collagen dermal filler appear to be efficacious for improving atrophic and rolling acne scars. Patients may prefer subcuticular incision over collagen dermal filler. Blinded evaluators found no significant difference between the treatments.

The authors indicate no significant interest with commercial supporters.

Use of porcine collagen dermal filler in correcting acne scars

Hernia (2007) 11:57–60
DOI 10.1007/s10029-006-0171-6

ORIGINAL ARTICLE

Use of porcine dermal collagen graft (Permacol) for hernia repair in contaminated fields

F. Catena · L. Ansaloni · F. Gazzotti · S. Gagliardi ·
S. Di Saverio · L. D'Alessandro · A. D. Pinna

Abstract

Background Complicated hernias often involve contaminating surgical procedures in which the use of polypropylene meshes can be hazardous. Prostheses made of porcine dermal collagen (PDC) have recently been proposed as a means to offset the disadvantages of polypropylene meshes and have since been used in humans for hernia repairs. The aim of our study was to evaluate the safety and efficacy of incisional hernia repair using PDC as a mesh in complicated cases involving contamination.

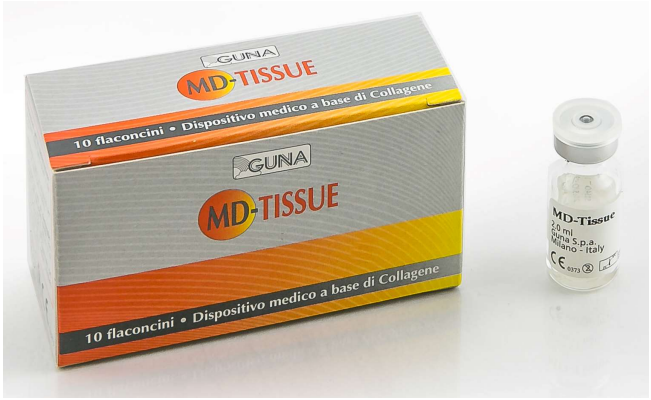
Methods A prospective study of hernia repair of complicated incisional hernias with contamination using PDC grafts was carried out at the Department of General, Emergency and Transplant Surgery of St Orsola-Malpighi University Hospital.

Results From January 2004 up to the writing of this article, seven patients were treated for complicated incisional hernias with a PDC prosthesis. In six out of seven patients a bowel resection was carried out. There were not surgical complications. Morbidity was 14.2%. No recurrences and wound infections were observed.

Conclusions Incisional hernioplasty using PDC grafts is a potentially safe and efficient approach in complicated cases with contamination.

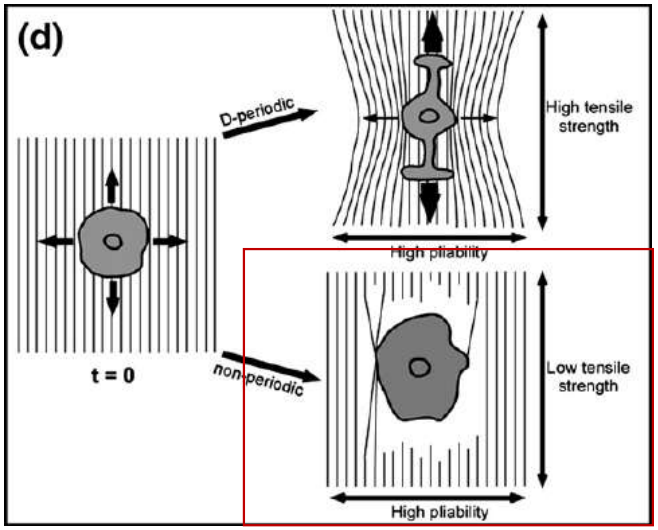
Porcine dermal collagen is safe and effective for hernia repair in contaminated fields

GUNA MDs -
HOW DO THEY ACT?



An important characteristic of collagen fibers

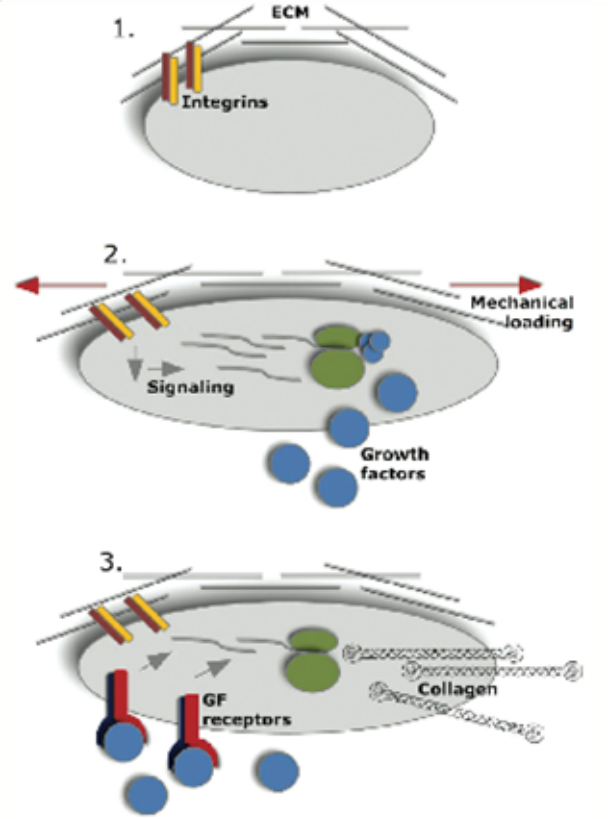
Anisotropy



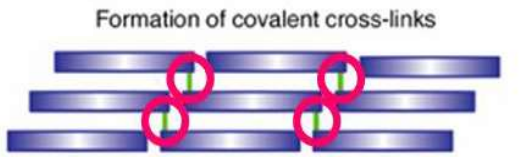
TENSEGRITA'
DIPENDENZA DELLA DIREZIONE
Capacità di un tessuto di indirizzare le forze esercitate su di esso in un'unica direzione

Jens Friedrichs et al. Cellular Remodelling of Individual Collagen Fibrils Visualized by Time-lapse AFM. J. Mol. Biol. 2007

Transformation of a mechanical force into a biochemical and structural response

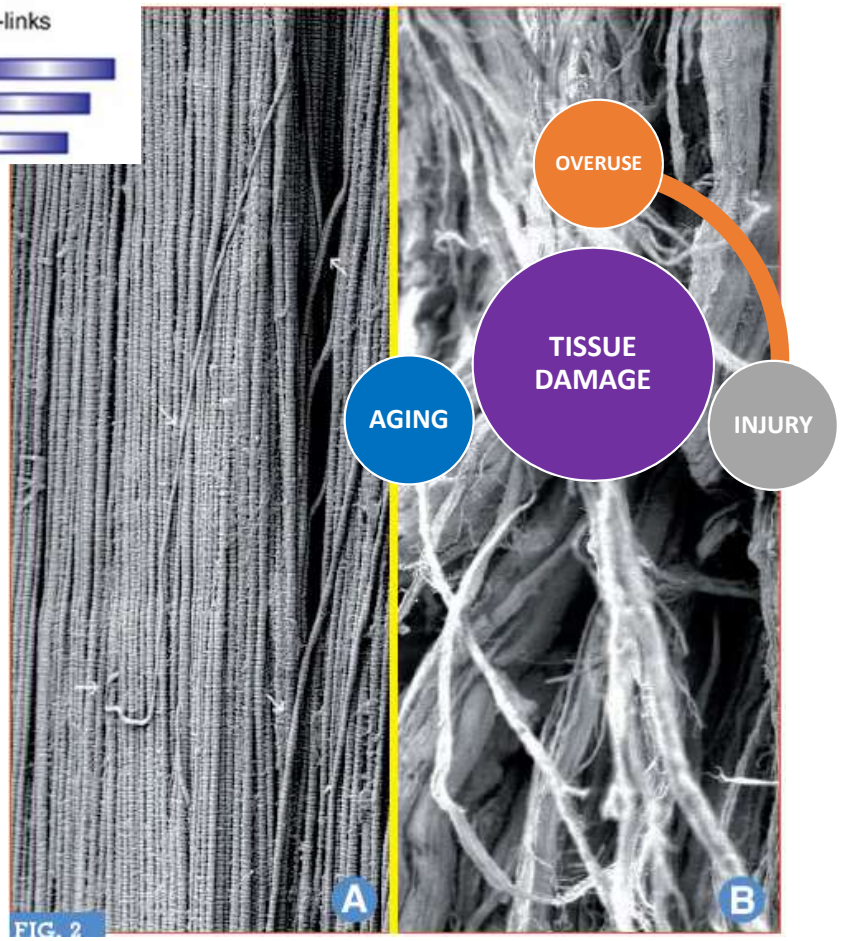


- Transforming growth factor-β-1 (TGF-β-1)
- Connective tissue growth factor (CTGF)
- Insulin like growth factor-I (IGF-I)
- IL-6



Anisotropy conditions are ensured by the proper alignment of collagen fibers into the extra-cellular matrix.

The paralleilism of collagen fibers is ensured by covalent type *cross-link*s.



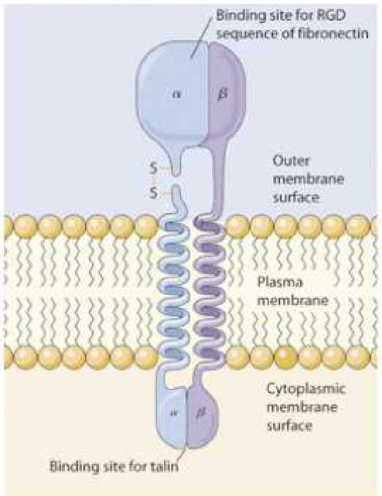
Healthy ligament = Parallel collagen fibers

Damaged ligament = Loss of collagen fibers parallelism

Aging, inflammatory damages, and *mechanical damages* alter the collagen fibers' parallelism reaching to a loss of anisotropy.

The role played by INTEGRINS

- Integrin molecules are major structural components of adhesion complexes at the cell membrane **linking the ECM to the cytoskeleton**.
- Integrins establish a **mechanical continuum** along which forces can be transmitted from the outside to the inside of the cell, and vice versa.
- Integrins together with the cytoskeleton form a **mechanically sensitive organelle**.
- At the myotendinous junction, lack of integrin expression will lead to structural damage during muscle contraction.
- Integrins can **convert mechanical signals to adaptive responses in the cell**.



Integrins consist of two large non-covalently bound transmembrane proteins (alpha and beta subunits). A number of both alpha and beta subunits combine to produce a large variety of heterodimeric integrins. On the outer surface, the subunits interact to form a binding site for the adhesive glycoprotein, the RGD sequence of the ECM glycoprotein. Within the cell, the receptor binds components of the cytoskeleton to enable the ECM to communicate through the plasma membrane to the cytoskeleton.

- Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiol Rev 2004, 84, 649–698.

SIGNAL TRANSDUCTION: ARTICLES

Integrins and Signal Transduction Pathways: The Road Taken

Edwin A. Clark* and Joan S. Brugge†

Adhesive interactions play critical roles in directing the migration, proliferation, and differentiation of cells; aberrations in such interactions can lead to pathological disorders. These adhesive interactions, mediated by cell surface receptors that bind to ligands on adjacent cells or in the extracellular matrix, also regulate intracellular signal transduction pathways that control adhesion-induced changes in cell physiology. Though the extracellular molecular interactions involving many adhesion receptors have been well characterized, the adhesion-dependent intracellular signaling events that regulate these physiological alterations have only begun to be elucidated. This article will focus on recent advances in our understanding of intracellular signal transduction pathways regulated by the integrin family of adhesion receptors.

sary and sufficient to target integrins to focal adhesions in a ligand-independent manner, whereas the α cytoplasmic domains regulate the specificty of the ligand-dependent interactions (9, 10).

Integrins link ECM proteins on the extracellular face of the cell membrane to cytoskeletal proteins and actin filaments on the cytoplasmic face. A model, based on results from in vivo localization and in vitro binding studies of integrin-cytoskeletal protein complexes that are detected in cells cultured on ECM proteins (7–9), is shown in Fig. 1A. However, because the precise molecular interactions involved in these large protein assemblies are difficult to dissect without disturbing the complex, it may not accurately reflect the true binary interactions in vivo.

Actin-binding proteins that co-localize with integrins in focal adhesions include α-actinin, talin, vinculin, and tensin (Ta-

Integrin transmembrane signaling and cytoskeletal control

Kenneth M Yamada and Shingo Miyamoto

National Institute of Dental Research, Bethesda, USA

Integrins are remarkably multifunctional: they mediate cell adhesion and migration, orchestrate organization of the actin-based cytoskeleton, and activate signal transduction pathways. Recent studies have identified a variety of steps and hierarchies in these intracellular cytoskeletal and signaling responses, laying the groundwork for future studies on specificity and coordination with responses to growth factors.

Current Opinion in Cell Biology 1995, 7:681–689

JOURNAL OF CELLULAR PHYSIOLOGY 189:1–13 (2001)

REVIEW ARTICLE

Fibronectin, Integrins, and Growth Control

ERIK H.J. DANEN[1]* AND KENNETH M. YAMADA[2]

[1]Division of Cell Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[2]Craniofacial Developmental Biology and Regeneration Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland

Cell proliferation is controlled not only by soluble mitogens but also by components of the extracellular matrix (ECM) such as fibronectin, to which cells adhere via the integrin family of transmembrane receptors. Input from both growth factor receptors and integrins is required to stimulate progression through the G1 phase of the cell cycle, via induction of G1 cyclins and suppression of inhibitors of the G1 cyclin-dependent kinases. Extensive crosstalk takes place between integrin and growth factor receptor signaling pathways, and mitogenic signaling is weak and transient in the absence of integrin-mediated cell adhesion. In normal untransformed cells, all of the important mitogenic signal transduction cascades, namely those downstream of the Ras and Rho family small GTPases and the phosphoinositide 3-OH kinase-PKB/Akt pathway, are regulated by integrin-mediated cell adhesion. As a result, these cells are anchorage-dependent for growth. In contrast, constitutive activity of each of these pathways has been reported in cancer cells, which not only reduces their mitogen dependence but also allows these cells to grow in an anchorage-independent fashion. J. Cell. Physiol. 189: 1–13, 2001. © 2001 Wiley-Liss, Inc.

historical perspective

Sensing the environment: a historical perspective on integrin signal transduction

Cindy K. Miranti* and Joan S. Brugge†‡

*Van Andel Research Institute, Grand Rapids, MI 49503, USA
†Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA
‡e-mail: joan_brugge@hms.harvard.edu

focus on signalling and adhesion

Cell adhesion mediated by integrin receptors has a critical function in organizing cells in tissues and in guiding haematopoietic cells to their sites of action. However, integrin adhesion receptors have broader functions in regulating cell behaviour through their ability to transduce bi-directional signals into and out of the cell and to engage in reciprocal interactions with other cellular receptors. This historical perspective traces the key findings that have led to our current understanding of these important functions of integrins.

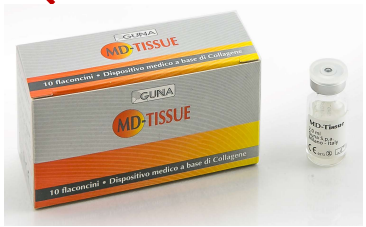
COLLAGEN DECLINE

MMPs^{+++} for

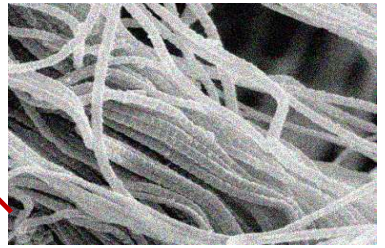
- Infections
- Chronic inflammation
- Oxidative stress
- Traumas

HISTOLOGICAL DECLINE

Damage of collagen fibers

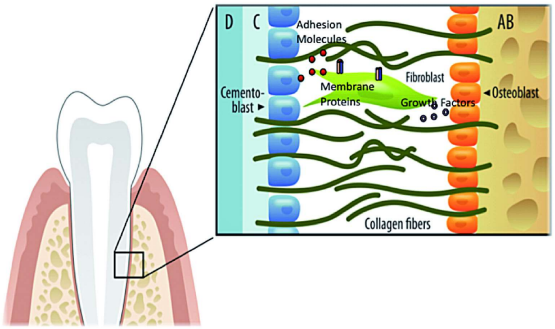


Loss of anisotropy



Insufficient neo-collagen synthesis

PDL molecular biology



The infiltration of hydrolyzed collagen into the extra-cellular matrix has a dual action:

1. Replace, support, reinforce, protect connective tissues

2. Increase the conditions of anisotropy and therefore the tensile forces capable of stimulating fibroblast
for the synthesis of autologous collagen

The evidence from Research

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 Mazzoleni [1], Fabio Sciancalepore [2], Marco Brioschi [1] and Nicoletta Gagliano [3,*]

1 Centro di Chirurgia dell'Anca e Traumatologia, I.R.C.C.S Policlinico San Donato, 20097 San Donato Milanese, Italy; filippo.randelli@fastwebnet.it (F.R.); alessiogiaivia@hotmail.it (A.G.V.); manuelmazzoleni4@gmail.com (M.M.); marco.brioschi@unimi.it (M.B.)

2 Azienda Socio Sanitaria Territoriale Centro Specialistico Ortopedico Traumatologico Gaetano Pini-CTO, 1ˆ Clinica Ortopedica, 20122 Milan, Italy; ale.menon@me.com (A.M.); fabio.sciancalepore@unimi.it (F.S.)

3 Department of Biomedical Sciences for Health, Università degli Studi di Milano, 20133 Milan, Italy

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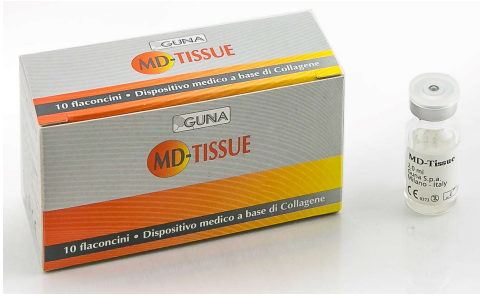
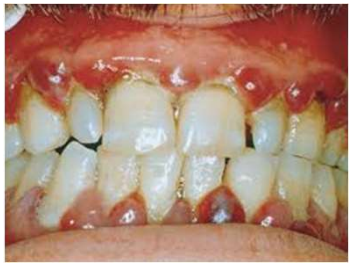
MD-TISSUE





1) COLLAGEN SUPPLEMENTATION

Collagen acts as a bio-scaffold improving anisotropy and tensile strength of dermis connective tissue

2) ANCILLARY SUBSTANCES WITH ANTIOXIDANT ACTIVITY

VITAMIN C; B1; B2

Ascorbic acid (vitamin C) is one of the most important water-soluble biological antioxidant, capable of neutralizing many reactive oxygen species and nitrogen. The Riboflavin (vitamin B2) has antioxidant activity. Thiamin hydrochloride (vitamin B1) has antioxidant, erythropoietic, anti-atherosclerotic and detoxifying activity.

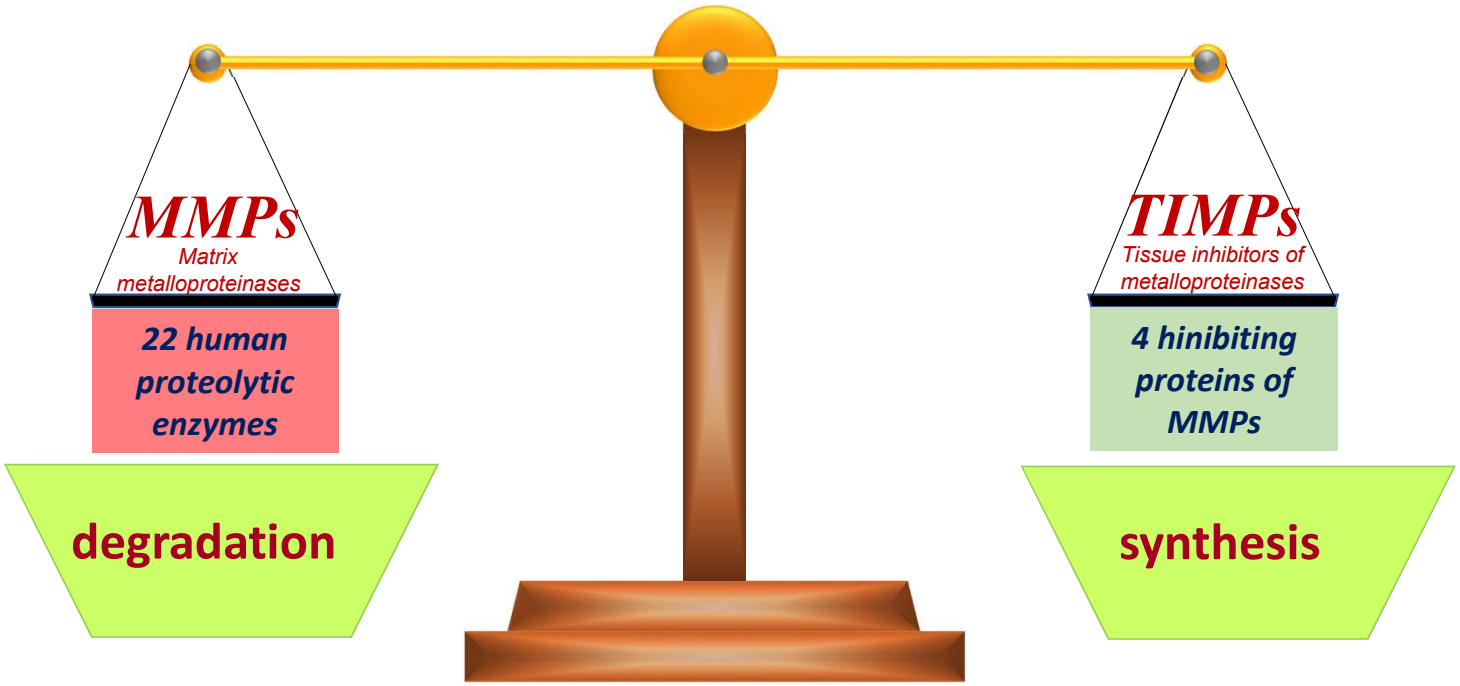
These substances aim to create a defensive barrier against free radicals, counteracting connective tissue aging.

•*Masaki H. Role of antioxidants in the skin: anti-aging effects. J Dermatol Sci.* ***2010*** *May;58(2):85-90.*

•*Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. Biofactors. 2009 Jan-Feb;35(1):5-13.*

•*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*

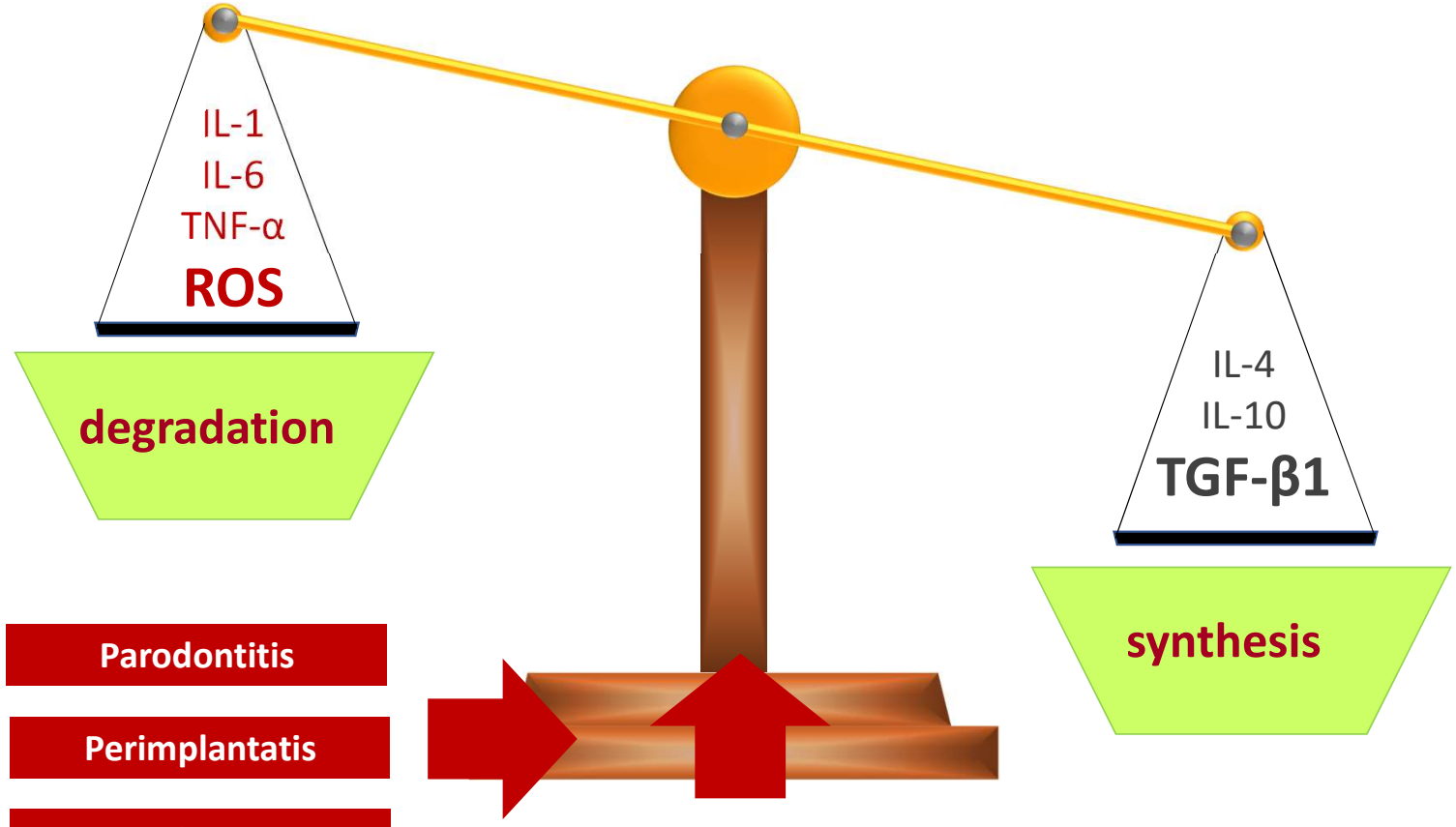
Collagen turnover is controlled by specific enzymes and corresponding inhibitory molecules



TIMPs hinibit MMPs in a ratio of 1:1

Yalcinkaya E, Celik M, Bugan B. Extracellular matrix turnover: a balance between MMPs and their inhibitors. Arq Bras Cardiol. 2014;102(5):519-20.

COLLAGEN TURNOVER



MATERIALS and METHODS

Human tenocytes from gluteus minimus

- n=8 (4M + 4F)
- age 64,8 ± 7,2 years

NC

MD-Tissue (50 µg/ml)

- cell proliferation → growth curves
- gene expression → real time PCR
- protein analysis → slot blot
- cell morphology → immunofluorescence
- collagen degradation → SDS-zymography
- cell migration → wound healing assay

Courtesy from Prof.ssa N. Gagliano

CELL PROLIFERATION

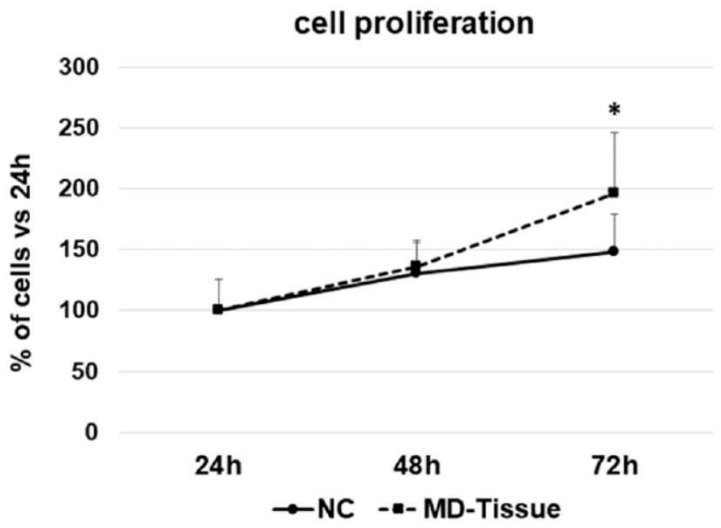


Figure 1. Growth curves of tenocytes grown without (NC) or on MD-Tissue at the indicated time points. Data are expressed as percentages vs. the time point T24 and are mean + SD. * $p < 0.05$ vs. 72 h NC.

COLLAGEN SYNTHESIS

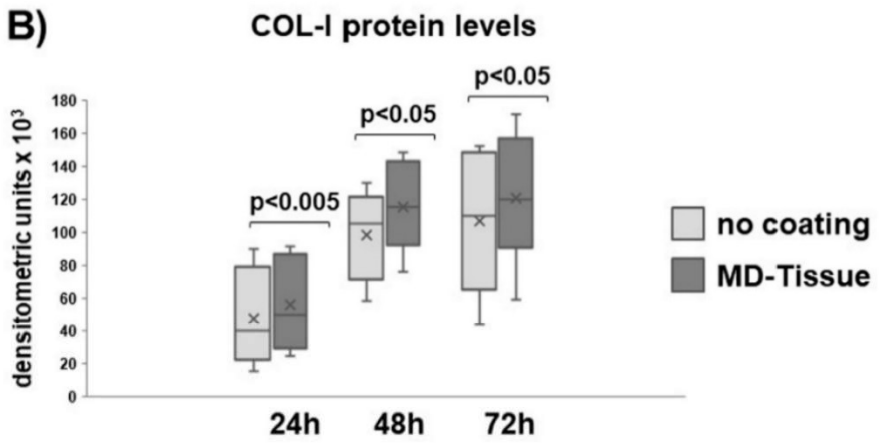
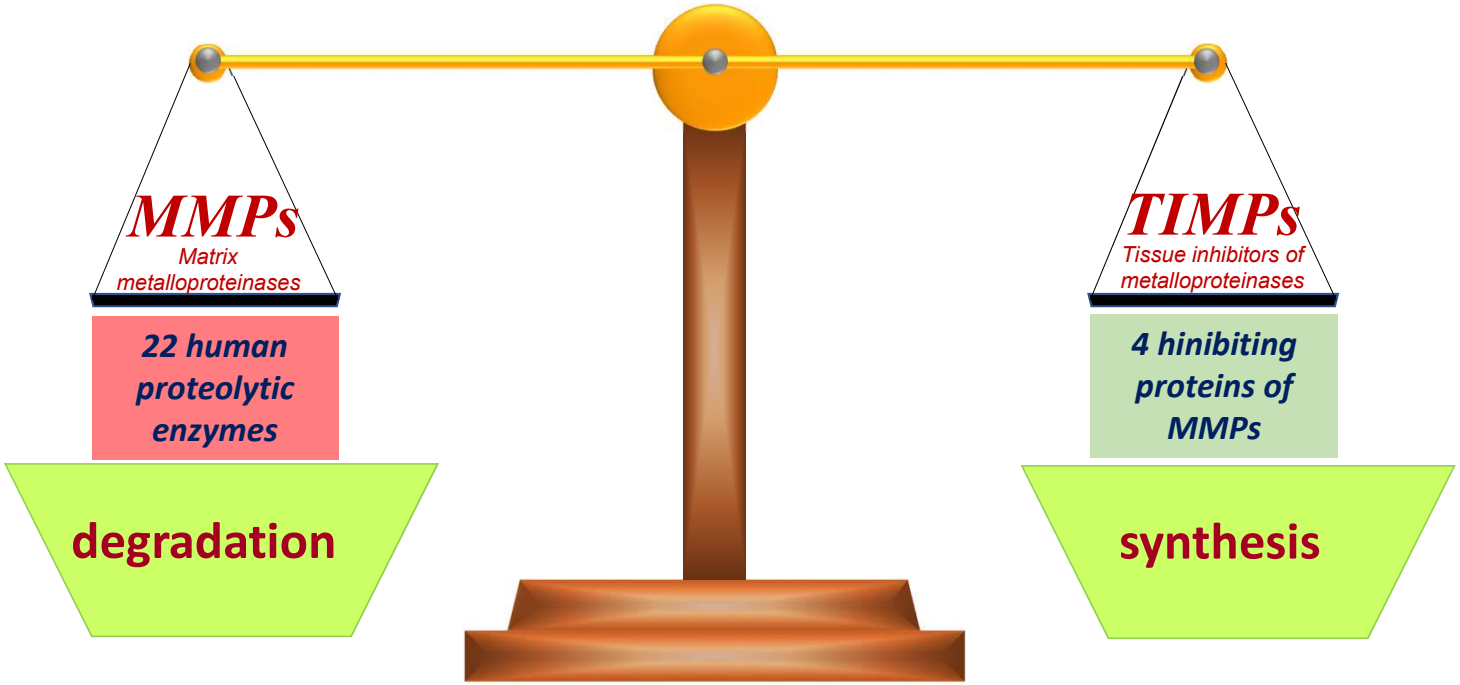


Figure 4. Representative slot blot analysis for collagen type I (COL-I) expression (**A**) expression in cell-culture medium of tenocytes cultured without coating (NC) or on MD-Tissue. Bar graphs displaying COL-I (**B**) protein levels analyzed densitometric scanning of immunoreactive bands in panel A. Data are expressed as mean ± SD for the 8 samples. (**C**) Slot blot analysis for COL-I showing that COL-I expression originates from tenocytes.

COLLAGEN TURNOVER



COLLAGEN TURNOVER MEDIATED BY MMPs and TIMPs

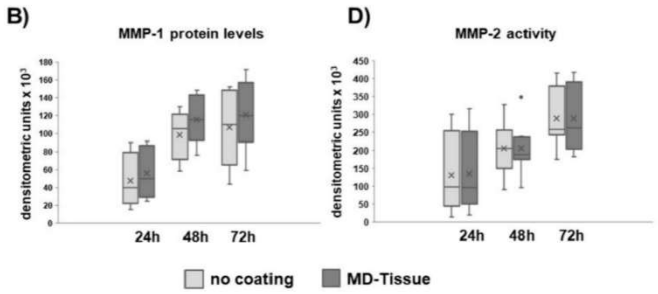


Figure 5. Representative slot blot for matrix metalloproteinase-1 (MMP-1) levels (**A**) and representative SDS-zymography showing MMP-2 activity in serum-free cell supernatants of NC and MD-Tissue tenocytes. Bar graphs showing MMP-1 protein levels (**C**) and MMP-2 activity (**D**) after densitometric analysis of immunoreactive and lytic bands, respectively. Data obtained from the eight samples are expressed as a % of densitometric units vs NC and are ± SD. NC: no coating.

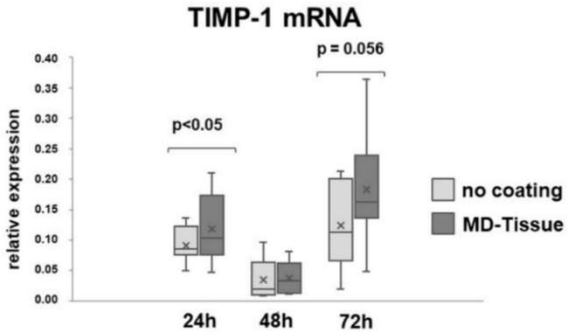


Figure 6. Bar graphs showing tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) gene expression after normalization on GAPDH mRNA levels. Data obtained from the eight samples are expressed as mean ± SD. **NC.** no coating.

CELL MIGRATION

WOUND HEALING ASSAY

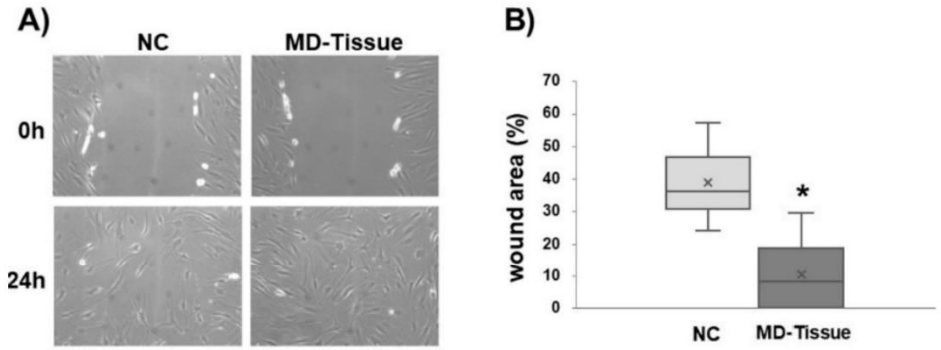


Figure 8. (**A**) Representative micrographs showing wound healing assay in control tenocytes (NC) and tenocytes grown on MD-Tissue at 0 and 24 h after the scratch. Original magnification: 10×. (**B**) Bar graphs showing the area of wound closure, expressed as a % of the area at 0 h, in cultured tenocytes in both experimental conditions 24 h after the scratch. * $p < 0.005$ vs. NC.

CONCLUSIONS

CELL GROWTH

↑ cell proliferation

COLLAGEN TURNOVER

↑ COL-I synthesis

↓ COL-I degradation

MIGRATION

↑ cell migration

- **Tendon healing and repair**
- **Decreased vulnerability to injury**

Courtesy from Prof.ssa N. Gagliano

NOT ONLY ANISOTROPY

The Scientific World Journal
Volume 2012, Article ID 342854, 11 pages
doi:10.1100/2012/342854

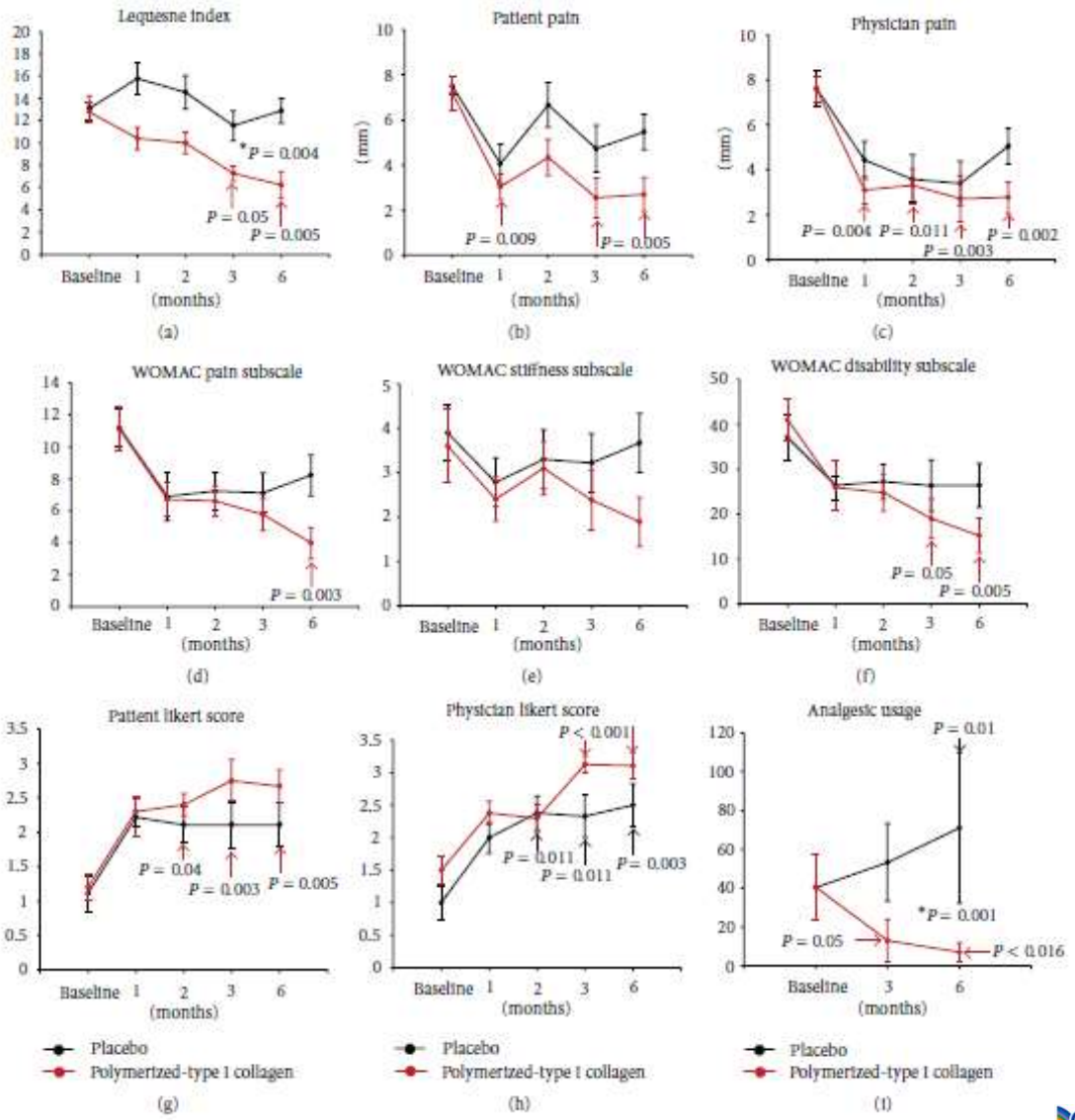
The ScientificWorldJOURNAL

Clinical Study

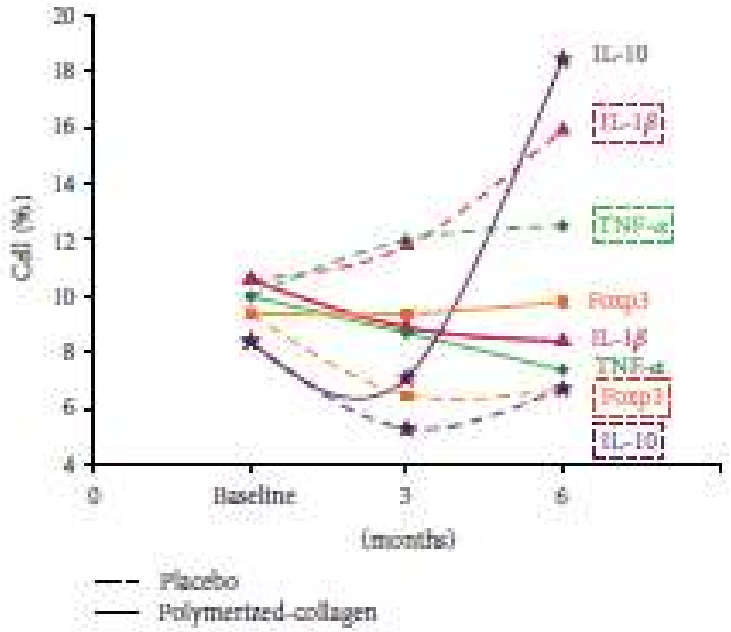
Polymerized-Type I Collagen Downregulates Inflammation and Improves Clinical Outcomes in Patients with Symptomatic Knee Osteoarthritis Following Arthroscopic Lavage: A Randomized, Double-Blind, and Placebo-Controlled Clinical Trial

Janette Furuzawa-Carballeda,[1] Guadalupe Lima,[1] Luis Llorente,[1] Carlos Nuñez-Álvarez,[1] Blanca H. Ruiz-Ordaz,[2] Santiago Echevarría-Zuno,[3] and Virgilio Hernández-Cuevas[3]

[1] *Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga No. 15, Col Sección XVI, 14000 Mexico City, DF, Mexico*
[2] *Department of Molecular Biology and Biotechnology, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Apartado Postal 04510, México City, DF, Mexico*
[3] *Unidad Médica de Alta Especialidad, Hospital de Traumatología y Ortopedia, IMSS, Boulevard Manuel Ávila Camacho s/n, Ex-ejido de Oro, 53120 Naucalpan, MEX, Mexico*



Primary and secondary measures of efficacy. Clinical evaluation was performed at baseline and every month during the study.
The primary endpoints included (a) Lequesne index, (b) patient pain visual analogue scale (VAS), (c) physician pain visual analogue scale (VAS), (d) WOMAC pain subscale, (e) WOMAC stiffness subscale, (f) WOMAC disability subscale, (g) patient's and (h) physician's global assessment of disease activity on a 5-point rating scale, global assessment of change in disease activity at the end of the treatment (Likert
score: 0 = very poor; 1 = poor; 2 = fair; 3 = well; 4 = very well), (i) consumption of NSAIDs tablets per month. Arrows depict the month in which the treatment reached a *P < 0.05 compared to baseline, in black for placebo and in red for polymerized collagen group. Results* represent mean *± SD. P values indicate statistical significant differences between treatment groups.*



Total cytokine- and Foxp3-expressing peripheral cells in patients with symptomatic knee OA under Polymerized-type I collagen or placebo at baseline, 3, and 6 months.

guna.it

STUDIES ON GUNA MEDICAL DEVICES

THE SCIENTIFIC RESEARCH ON COLLAGEN MEDICAL DEVICES

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,*]

1 Centro di Chirurgia dell'Anca e Traumatologia, I.R.C.C.S Policlinico San Donato, 20097 San Donato Milanese, Italy; filippo.randelli@fastwebnet.it (F.R.); alessiogiaivia@hotmail.it (A.G.V.); manuelmazzoleni4@gmail.com (M.G.M.); marco.brioschi@unimi.it (M.B.)
2 Azienda Socio Sanitaria Territoriale Centro Specialistico Ortopedico Traumatologico Gaetano Pini-CTO, 1° Clinica Ortopedica, 20122 Milan, Italy; ale.menon@me.com (A.M.); fabio.sciancalepore@unimi.it (F.S.)
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* Correspondence: nicoletta.gagliano@unimi.it; Tel.: +39-02-50315374; Fax: +39-02-50315387

Martin Martin et al. BMC Musculoskeletal Disorders (2016) 17:94
DOI 10.1186/s12891-016-0948-4

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]

Muscles, Ligaments and Tendons Journal 2019;9 (4)

ORIGINAL ARTICLE

Nr 2019;9 (4):584-589

Treatment of Lateral Epicondylitis with Collagen Injections: a Pilot Study

B. Corrado, G. Mazzuoccolo, L. Liguori, V. A. Chirico, M. Costanzo, I. Bonini, G. Bove, L. Curci

Department of Public Health, University Federico II of Naples, Italy

Hindawi
Pain Research and Management
Volume 2018, Article ID 8261090, 10 pages
https://doi.org/10.1155/2018/8261090

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]

[1]*Department of Temporomandibular Disorders, Unit SMDZ in Zabrze, Medical University of Silesia in Katowice, Traugutta Sq. 2, 41-800 Zabrze, Poland*
[2]*Department of Experimental Dentistry, Faculty of Dentistry, Wroclaw Medical University, 26 Krakowska St., 50-425 Wroclaw, Poland*

ARTYKUŁ ORYGINALNY / ORIGINAL ARTICLE

Ortopedia Traumatologia Rehabilitacja
© MEDSPORTPRESS, 2019; 6(6); Vol. 21, 427-434
DOI: 10.5604/01.3001.0013.7400

Terapia kolagenowa w spondylozie odcinka lędźwiowego kręgosłupa – badanie pilotażowe. Czy droga podania ma znaczenie?

Collagen Therapy in Lumbar Spondylosis – a Pilot Study. Does the Route of Administration Matter?

Piotr Godek

Sutherland Medical Center, Warszawa

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

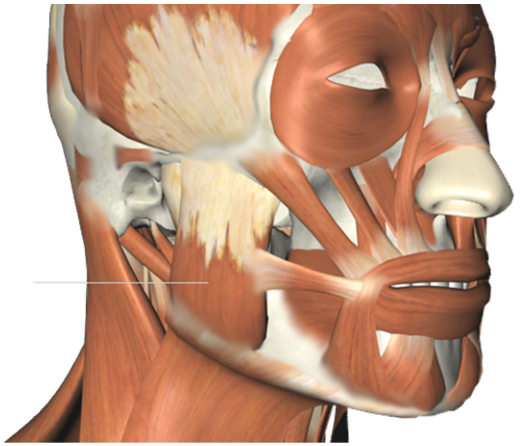
Efficacy and Tolerability of Injectable Collagen-Containing Products in Comparison to Trimecaine in Patients With Acute Lumbar Spine Pain (Study FUTURE-MD-Back Pain)

K. PAVELKA[1], H. JAROSOVA[1], L. MILANI[2,3], Z. PROCHAZKA[4], P. KOSTIUK[4], L. KOTLAROVA[5], A. M. MERONI[6], J. SLIVA[7]

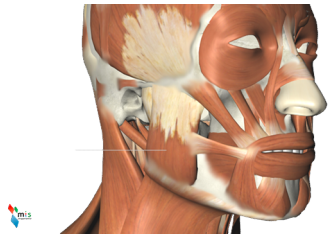
[1]Institute of Rheumatology, Prague, Czech Republic, [2]University Sapienza, Rome, Italy, [3]University of Siena, Italy, [4]Edukafarm, Prague, Czech Republic, [5]Department of Pharmacology, InpharmClinic, Jesenice u Prahy, Czech Republic, [6]Department of Orthopedics and Traumatology, Niguarda Hospital, Milano, Italy, [7]Third Faculty of Medicine, Charles University, Prague, Czech Republic

p.a.

INTRAMUSCULAR INJECTION (IN THE MASSETER AREA)



GUNA-MUSCLE



1) COLLAGEN SUPPLEMENTATION

Collagen acts as a bio-scaffold improving anisotropy and tensile strength of dermis connective tissue

2) ANCILLARY SUBSTANCES WITH ANTIPAIN ACTIVITY

HYPERICUM PERFORATUM

Hindawi
Pain Research and Management
Volume 2018, Article ID 8261090, 10 pages
https://doi.org/10.1155/2018/8261090

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]

[1]*Department of Temporomandibular Disorders, Unit SMDZ in Zabrze, Medical University of Silesia in Katowice, Traugutta Sq. 2, 41-800 Zabrze, Poland*
[2]*Department of Experimental Dentistry, Faculty of Dentistry, Wroclaw Medical University, 26 Krakowska St., 50-425 Wroclaw, Poland*

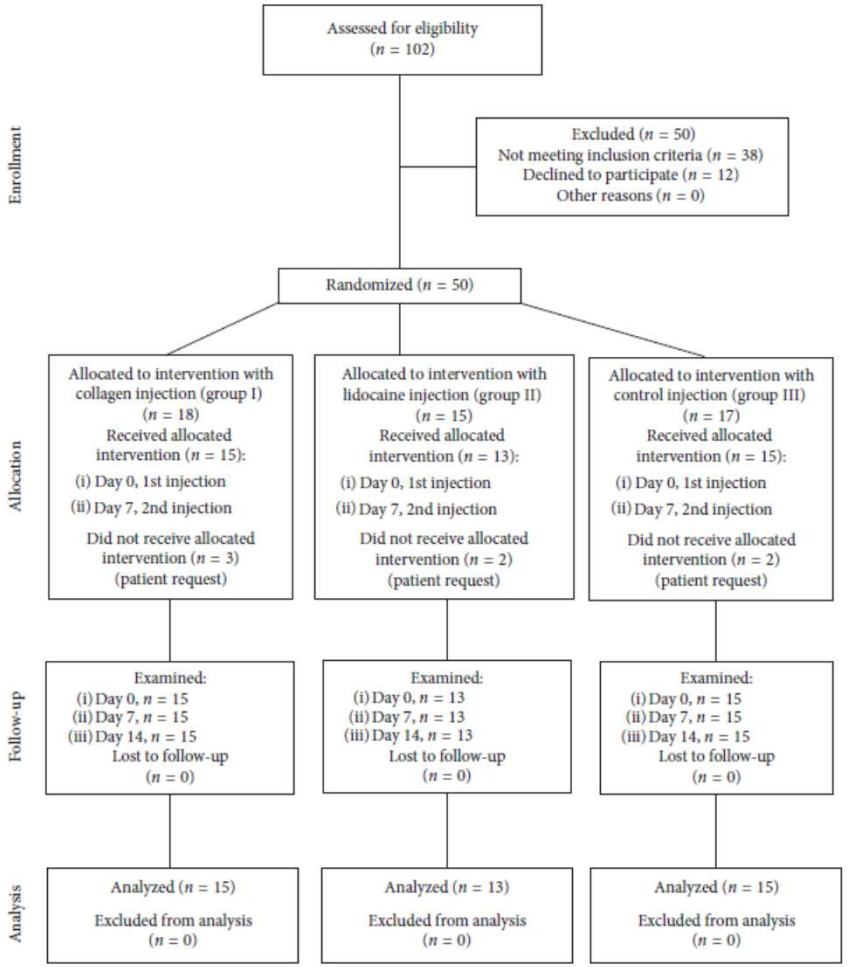
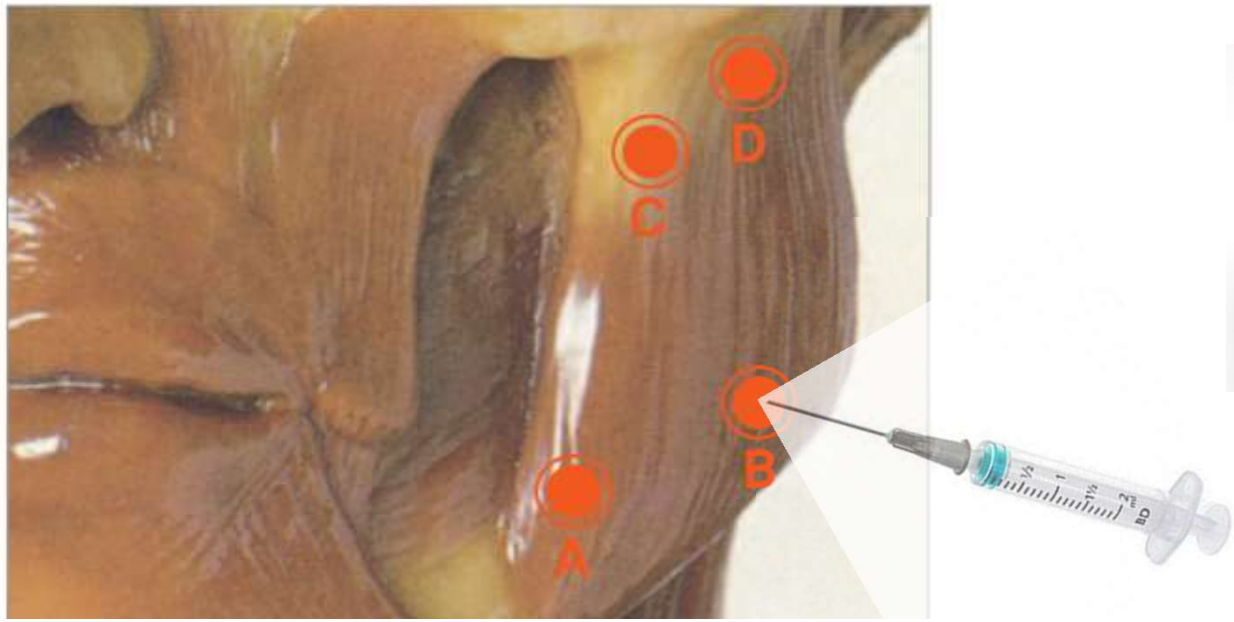


FIGURE 1: CONSORT three-arm diagram showing the flow of participants through each stage of the presented randomized controlled trial.

Table 3: Baseline characteristics of 43 patients with MFP within masseter muscles included in the study.

	Group I	Group II	Group III
Male/female, *n*	5/10	5/8	7/8
Age (years)	37.2 ± 4.97	42.8 ± 0.98	40.3 ± 1.18
Duration of myofascial pain (weeks), mean (SD)	30.2 ± 31.48	34.3 ± 29.26	38.3 ± 26.47
Bilateral involvement of myofascial pain (number of patients)	2	1	0

INFILTRATION IN TRIGGER POINTS



- 2 ml
- 1-1.5 cm deep on the skin surface
- 0.4x19 mm needle

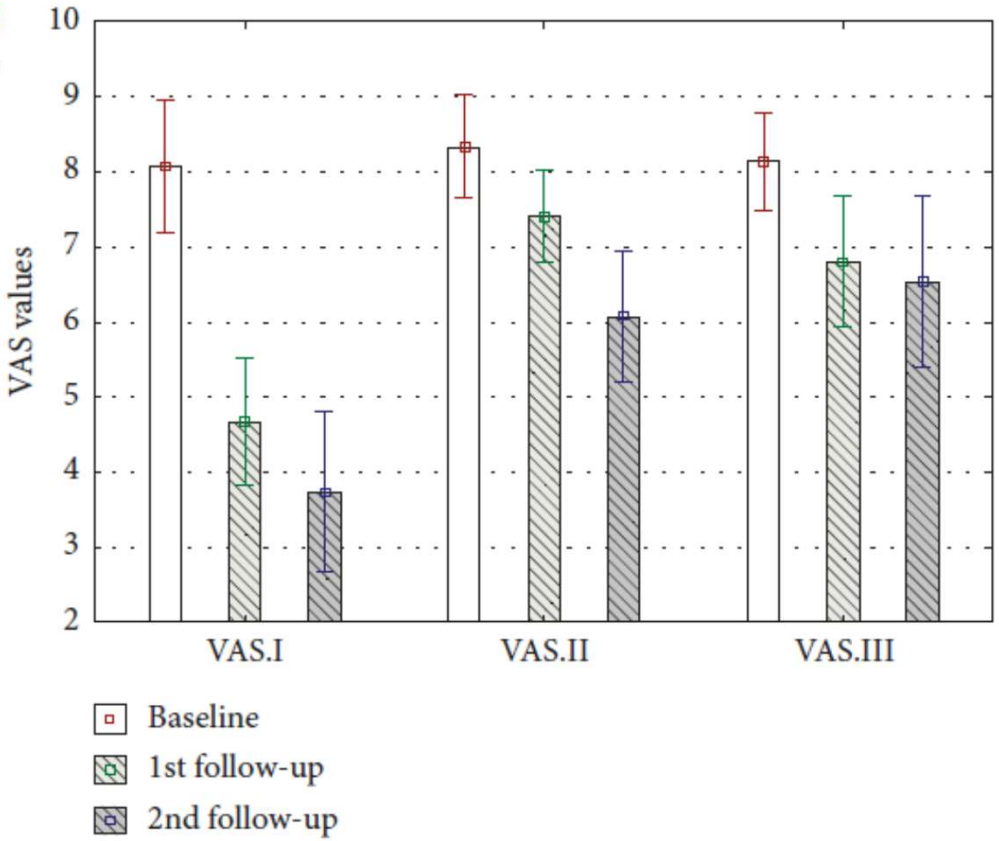


FIGURE 2: VAS mean value changes in Group I, Group II, and Group III during the trial (days 0, 7, and 14).

Pain reduction measured by VAS at the end of follow-up:

- **53.75% (- 4.3 points) in Group I, treated with MD-MUSCLE**
- **25%** (- 2 POINTS) in Group II (**Lidocaine 2%**)
- **20.1%** (- 1.63 points) in Group III (**Saline solution**).

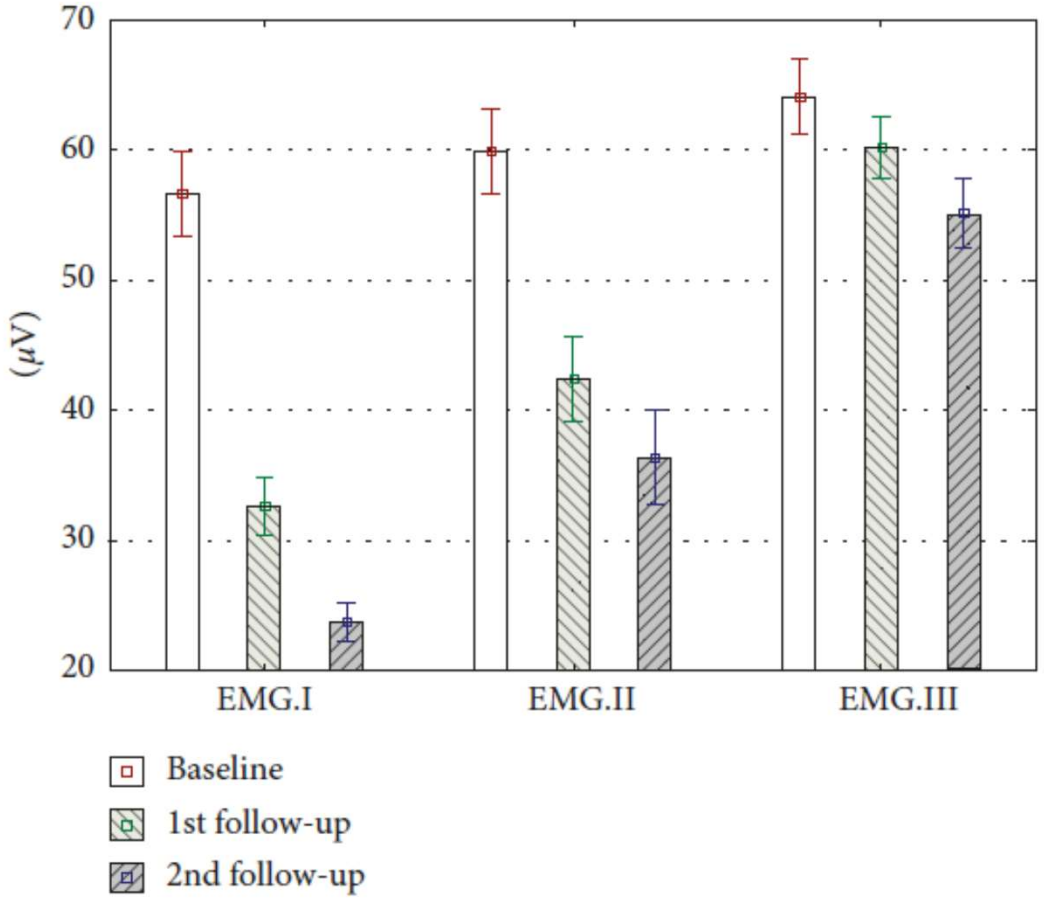
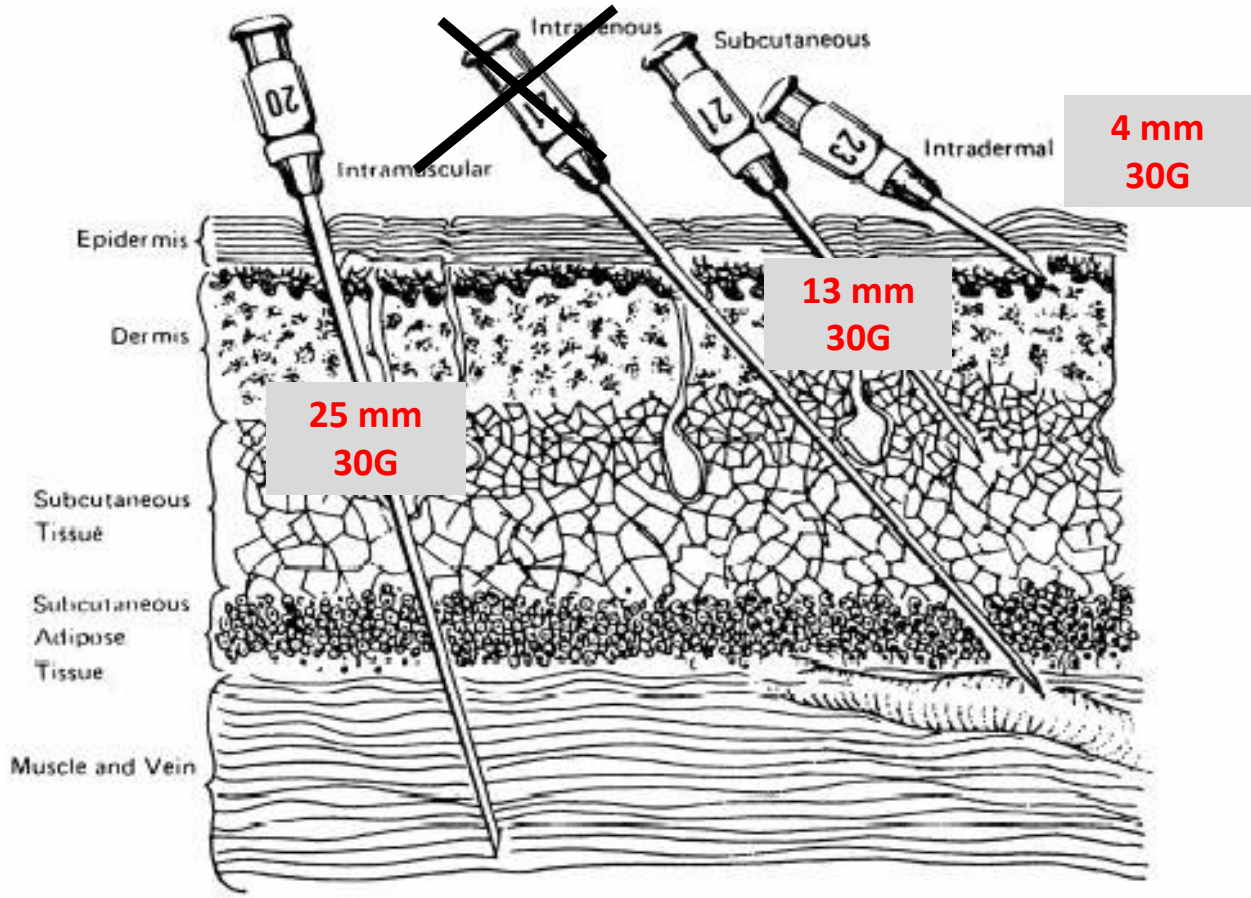


FIGURE 3: Changes in mean values of superficial electromyographic activity of masseter muscles in Group I, Group II, and Group III during the trial (days 0, 7, and 14).

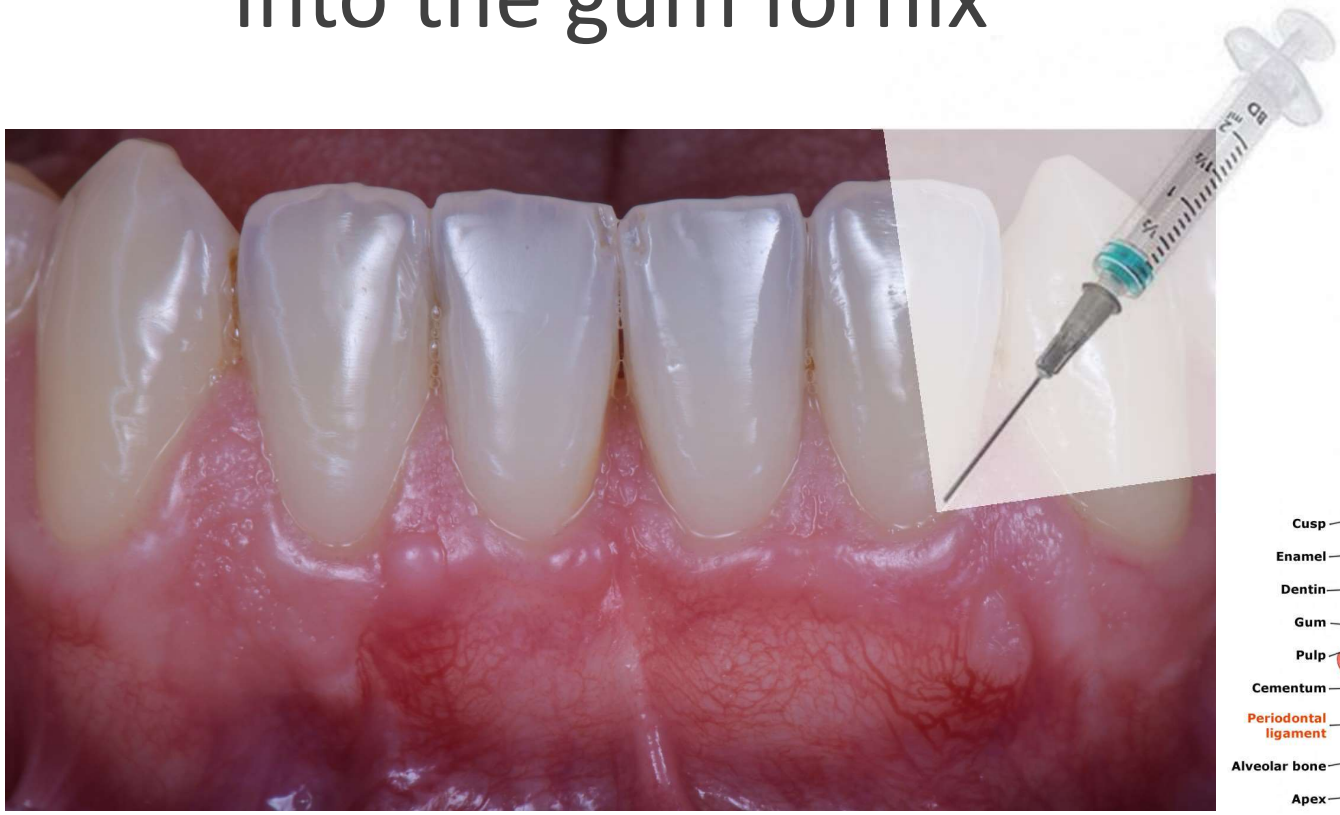
Myoelectric activity of masseter muscle was reduced at the end of follow-up:

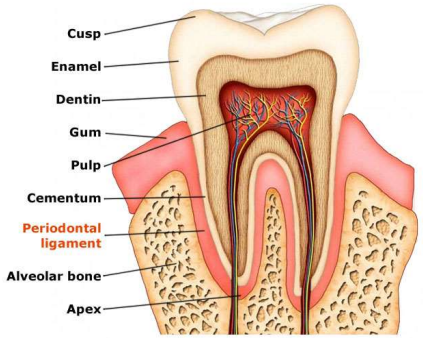
- **59.2% (- 32.9 points) in Group I**
- **39.3% (- 23.5 punti) in Group II**
- **14% (- 8.9 punti %) in Group III.**

DIFFERENT INJECTIONS

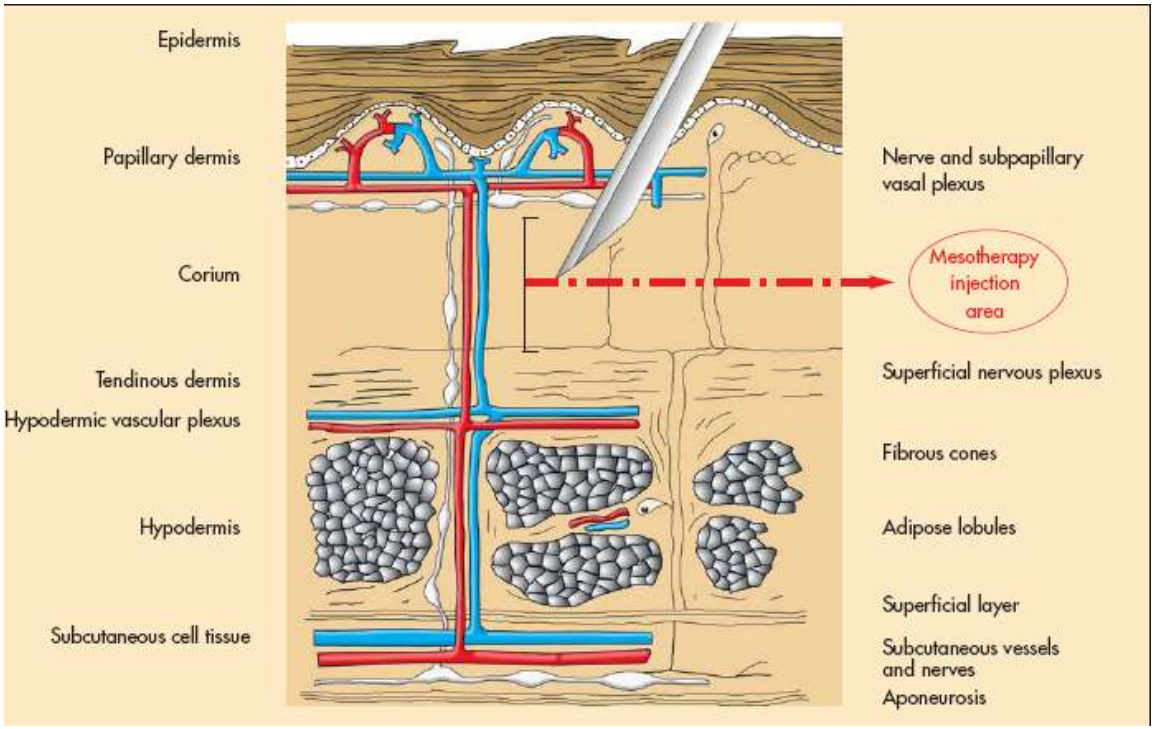


Into the gum fornix

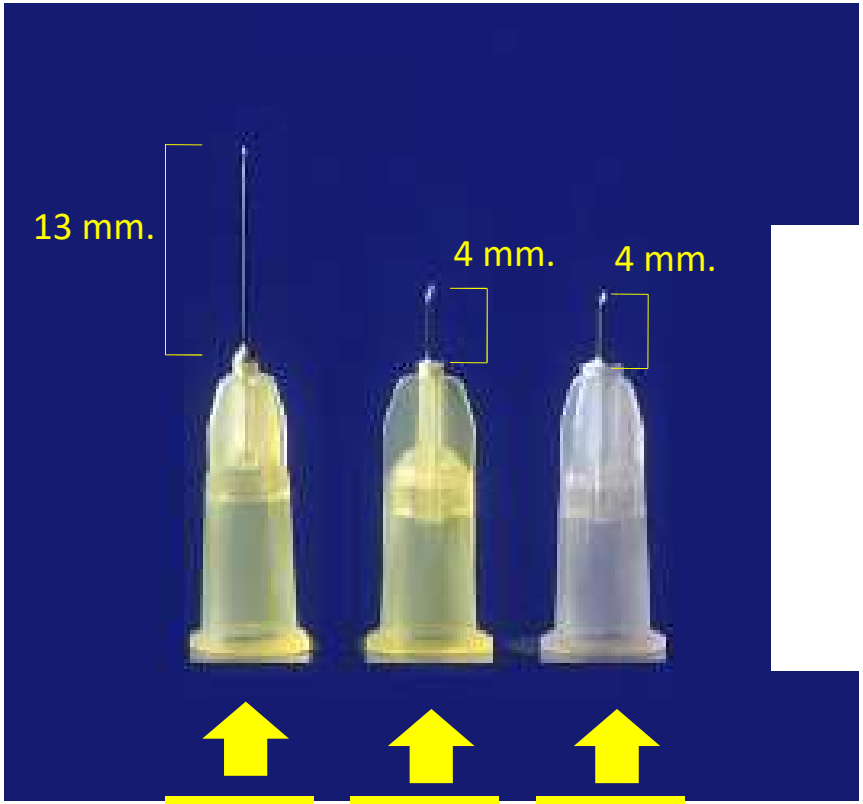




- **WHERE: intradermal or subcutaneous**
- **HOW MANY POINTS: several symptomatic points**
- **HOW MUCH: 0.2-0.3 ml each injection**



NEEDLES



LENGHT

GAUGE

NEEDLES FOR PAIN MANAGEMENT

2,5 ml | 5 ml | 10 ml | 20 ml | INSULIN

- HOW MANY POINTS: several symptomatic points
- HOW MUCH: 0.2-0.3 ml each injection