THERAPEUTICS

A NEW AND Refined INJECTABLE TREATMENT FOR MUSCULOSKELETAL DISORDERS – BIOSCAFFOLD PROPERTIES OF COLLAGEN AND ITS CLINICAL USE

SUMMARY

Connective tissue and collagen in particular – a real protein-tissue – progressively degrade and reveal to be inadequate to perform the functions they are to accomplish in each organism. This is due to aging, sedentarity, intense physical activity or inadequate sports activity, postural alteration, alimentary disequilibrium, and PNEI-axis alteration. Specific injectable Medical Devices (MD) (both distrectual and tissular) represent a new and refined tool in prevention and therapy to treat the ageing of articular structures, as well as periarticular ones and those concerning mesodermic supporting tissues. These MDs replace the lack of collagen, which is always recurrent in the inflammatory and/or degenerative diseases of the locomotor apparatus and other anatomical structures of mesodermic origin; they are natural, free from negative side effects (excellent safety); they can be associated with homotoxicological therapies as well as allopathic ones that are being applied or that will be scheduled; moreover, they can be associated with physical therapies. Non-invasiveness of injections using Guna MDs – which are the first to highlight quality therapeutic results in 7 controlled clinical trials (Registration Dossier c/o Istituto Superiore di Sanità [Italian Superior Health Institute]) – together with other characteristics such as effectiveness, tolerability, absence of allergic reactions and their natural origin make them a valuable tool in standard procedures (both in treatments by specialists or general practitioners) and in processes aimed at improving the patients’ quality of life, which could otherwise worsen or become further chronic.

KEY WORDS

COLLAGEN, MEDICAL DEVICE, ANCILLARY SUBSTANCE, GUNA MEDICAL DEVICE, PAIN, OSTEO-ARTHRO-MYO-FASCIAL PATHOLOGIES

COLLAGEN – COMPOSITION AND ACTION

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).

– According to some hypotheses, the ancestral gene that synthesizes collagen has evolved to its present form due to further mutations starting from one single unit composed of only 54 base pairs of DNA.

– At present the alpha 2 collagen gene is composed of about 38,000 base pairs.

– The basic difference between functional proteins, which are involved in biochemical, enzymatic, immune, membrane and/or transmembrane receptor processes, and structural proteins, which play an important role in building the scaffold of higher organisms (connective tissue in a wider sense and more specifically – fibrous tissue) is not considered so important for collagen.

For example, collagen VI plays an essential role in the processes of cell adhesion, replication and survival through its interaction (cross-talk) with integrins and/or other transmembrane receptors (Pflaf et Al., 1993; Jan et Al., 2004), showing both roles: the genetic absence of Collagen VI causes severe morpho-functional alterations of muscle fibres and apoptosis by acting directly on the mitochondrion (Rizzuto, 2003) due to a failure to regulate cell permeability (last author mentioned).

– Collagen “health” is ultimately the individual’s health: man’s peak of collagen biosynthesis occurs between 45 and 60 years of age (Heine, 2009): after that age there is a rapid decrease of collagen that is also accompanied by a rapid decrease of elastin and proteoglycans (Milani, 2004 a) (FIG. 1).

An insufficient renewal of the ECM brings about a sluggish function of the
Faulty routing of waste will cause the accumulation of toxins usually directed by the cells in the microvessels of the lymphatic system; this impacts oxygenation of tissues, nutrient assimilation and hydration. Fragility and sclerosis are silent symptoms preceding degeneration and possible tissue differentiation (disease evolution according to Reckeweg).

The base unit of collagen is tropocollagen (FIG. 2), a glycoprotein composed of three left-handed helices of polypeptide units carrying glucose and galactose molecules that are attached only to the molecule of the amino acid hydroxylysine (Hyl), one of the only four amino acids that form tropocollagen with Glycine (Gly), Proline (Pro) and 4-Hydroxyproline (Hyp).

Tropocollagen has some interesting structural “anomalies” compared to other proteins:
- In the molecule:
  1) Every triplet of amino acids always starts with Glycine (Gly-A-B);
  2) The amino acid sequence is often represented by the triplet Gly-Pro-Hyp;
  3) These triplets cannot usually be found in other proteins and have to be considered unique and special;
  4) Proline determines the twisting, the “change of direction” along the axis of the protein strand; that’s why it is absolutely absent in globular proteins;
  5) Many residues of Hyp have two sugar residues. Therefore, collagen is a glycoprotein (great amount of protein – small amount of sugar) and not a proteoglycan (PG) (great amount of sugar – small amount of protein);
  6) Axial periodicity (text, see after: FIG. 6), a true metamorphism that is visible only with the electron microscope.

These “anomalies” guarantee a perfect strength and function of the molecule: when the three polypeptide units are intertwined in a tight triple helix, stabilized between hydroxylated amino acids (crosslinks) by weak H+ bonds, they give basic and special characteristics to collagen 2: structural strength and organoleptic rigidity. The spatial configuration of tropocollagen is a cylindrical braid composed of three rods wrapped in an helix. This gives the molecule great resistance and flexibility: to break a 1 mm diameter collagen fiber an 11 kg weight must be applied to each end.

The hydrogen bond is a weak, non-covalent bond: it is the number of atoms that gives it its strength, as it occurs with fibroin, the structural protein of silk.

The hydroxylation of Pro and Hyp and the hydroxylation of Lys and Hyl occur thanks to the cofactor ascorbic acid (Vitamin C) and to the substrate acidum α-ketoglutaricum, one of the three-carboxylic acids of Krebs’ Cycle. A deficit of one of these metabolic boosters will cause severe alterations of the connective tissue which can manifest as scurvy and cancer cachexia. A failed hydroxylation to Hyp and Hyl leads to the formation of a collagen fibril that is structurally and functionally impaired.

According to the different types of collagen involved some severe genetic cases of Osteogenesis imperfecta, Bethlem myopathy, Ulrich’s scleroatonic muscular dystrophy, mitochondrial myopathy may occur, just to mention a few that illustrate the truth behind Garrod’s “old” theory (1902) – “one gene, one enzyme” which still applies today.

The diseases due to an acquired collagen deficiency are also thought to have their pathogenesis in a faulty synthesis and use of collagen (TAB. 1).

- I would like to remind that Lys, precursor of tropocollagen 5-Hyl is an essential amino acid that must be sourced from food and/or from supplementation.
- Collagen biosynthesis is carried out by different cell lines (fibroblasts in the loose and fibrous fibrillar connective tissue, osteoblasts in bones, chondroblasts in cartilage, etc.)

After the amino acids interlock, the globular procollagen is produced at an intracellular level and is pushed outwards through the Golgi apparatus (Olsen, 1983) (FIG. 3). Here, thanks to the shortening of the 2 telomeres (one N-terminal, the other C-terminal), the procollagen turns into protocollagen; as soon as procollagen is being formed, this produces a negative feedback on the collagenous-genetic cell, by inhibiting a further synthesis.

- The procollagen microfibrils are therefore polymerized outside the collagenous-genetic cell.

The single units of procollagen are staggered thanks to Lysyl-oxidase, linearly and in parallel array to gradually form one microfibril, one subfibril, and
one collagen fibril. \textbf{(FIG. 4)}.

Several collagen fibrils constitute a collagen fibre.

- This process is thought to occur, at least partly, via an autocatalytic route (Procko, 2004; Cisneros et al., 2006).

In some rare moments biology by-passes the rigid genetic determinism and the most flexible epigenetic possibilism and shows great adaptability supported by autocatalysis with more flexibility and adaptability (Lima de Faria, 2003).

- The fibrils are characterized by a periodicity: they show small structural units along their own course which repeat every 670 Angstrom \textbf{[FIG. 5 (1, 2)]}. This undermines deeply the Darwinian and post-Darwinian pure evolutionary theory (Milani, 2009).

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Such arrangement of the fibrils in the formation of collagen fibres guarantees a great strength in terms of:

- **RESISTANCE**
- **NON-EXTENSIBILITY**
- **NON-COMPRESSIBILITY,** but also
- **PLASTICITY**
- **FLEXIBILITY**
- **LOAD RESISTANCE**
- **TORSION RESISTANCE**

These characteristics make collagen an extremely versatile “structure” that Nature has been selecting during hundreds of millions of years and upheld as the best means to fulfil its many functions.

Besides these characteristics, collagen is the prerequisite for the activation of the repair process of all the body tissues.

- Before concluding this section, I would like to point out a further characteristic of collagen that is little known, but extraordinary: **piezoelectricity**, an electric charge generated by pressure, traction, torsion (Athenstedt, 1974).

Thanks to its helical structure, collagen, an out-and-out electric dipole, can oscillate thus piloting the growth and the orientation of the neo-fibrils. From this point of view, a special electromagnetic activity is ascribed to the large trabeculations of the connective tissue that are located between the big muscular bundles and their tendons of origin and insertion.

Heine (2009), resuming the work by Bergsmann and Bergsmann (1997), suggests that the large connective trabeculae clearly correspond to the Chinese Acupuncture Meridians.

- In any case, they can be found more frequently between antagonistic muscle groups (Milani, 2004 b), which raises the real possibility to intervene therapeutically with injections of collagen in these points/areas in cases of osteo-arthritis and local myo-fascial interstitial pathologies.
THE ARTICULAR STABILIZATION SYSTEMS
– THE COLLAGEN REIGNS

The restraint and stabilization function of each joint must ensure two principles in apparent opposition: stability and locomotion.
Later we are going to explain how the anatomical alterations that cause changes in one or both of these functions, cause dysfunctions and pathologies of the skeletal muscle, with resulting motor deficit.
The stabilization systems are represented by stabilizing structures that cooperate at different levels for an optimal articular functionality.

1 – EXTRA-ARTICULAR COMPARTMENT
(FIG. 7)

– LIGAMENTS
Intra-articular (only big joints) and extra-articular elements consisting of a parallel system of collagen bundles.
By examining the conditions under which the ligaments are put under tension-traction, it is easy to determine the reason why they can be blocked or prevented from movement.

– INTRA ARTICULAR CAPSULE
The covering element for protection and reinforcement of the joint, is fixed on the two elements of the adjacent bones. In smaller joints, the line of intersection is located along the edge of the articular cartilage. The capsule consists of interwoven heavily and closely staggered bundles of collagen, zones of less dense fibrillar tissue and adipose lobules.
The collagen bundles that form the joint capsule are never arranged longitudinally between the two articular heads, but rather obliquely following the interwoven trajectories thus forming a strong and rigid capsule.

– TENDONS
The long tendons connecting one section with the other of the locomotor system are provided with restraint elements that keep the two sections in contact with the bone axis during the joint movement.
The tendons are strengthened and protected by mucous sheaths, in some cases along the whole stretch of sliding.
Between tendon and sheath there is a lubricant liquid, similar to the synovial fluid, which facilitates the tendon sliding.

– MUSCLES
Also the muscles are involved in the articular resistance through their surface coating bundles (coating aponeurosis), deep fascia, connective tissue which sometimes acts as an individualized lamina, and intermuscular septa.
If the restraining function of the muscles is insufficient, only the capsule and ligaments ensure this function: their resistance is below the threshold of effort, and the joint is exposed to not sustainable risks.
– Many cases of mild to medium severity of hip dysplasia can be controlled by inducing hypertrophy of the surrounding muscles by means of specific physical exercises and nutritional sup-

FIG. 5
1: Sugars linked to collagen (ruthenium red colour). Correlation of sugar (black precipitations) to the periodicity of collagen fibrils (ME 112.000X).
2: Section of a collagen fibril (ME 240.000X). A cycle of 67 nm (670 A) is formed on the basis of collagen molecules each time slipped of one-quarter of their length.

Ultrastructure of the collagen. Native collagen fibril type I (AFM images).
– The most recent ultrastructural measurements show a period of 67 nm (670A) and not of 64 nm, as previously reported by various Authors and frequently even by scientific literature and in medical textbooks.
– Collagen shows a clear and defined "metameric" structure with a simple or elementary recurrent base scaffold.
plementation with MAP-Son Formula (personal observations).
Even after many years the situation of X-ray shows only minimal endoarticular alterations that are compatible with normal mobility and quality of life.

2 – INTRA-ARTICULAR COMPARTMENT

– LIGAMENTS
Intra-articular ligaments of the big joints (FIG. 8).

– ARTICULAR CARTILAGE
The great Italian anatomist R. Amprino (Anatomical Institute, University of Turin), had the merit to carry out the early studies on the mechanical function of the collagen fibrils of the hyaline cartilage in man (Amprino, 1938). The collagen fibrils are arranged in vertical bundles in the fundamental substance of the deep layer while they are arranged tangentially on the surface layer. Overall, the fibrillar arches form a structure similar to a Romanesque arch (FIG. 9); this is an optimal architectural solution for well withstanding the pressure from above and tangential forces exerted during the joint movement.

All extra-and intra-articular structures consist basically of collagen.

– The (rare) genetic-metabolic alterations, mechanical alterations (recurring microtrauma, trauma), abnormal posture, age (chrono-aging) acquired collagenopathies, chronic inflammatory diseases and cancers damage the integrity of collagen fibers and consequently - of the support system as well as the mechanical function of the whole organism.

Some studies carried out by Ozaki et al., (1988) and Riley et al., (1994) show - in autopsy reports - flagrant changes in the composition of collagen in rotator cuff tendinitis and how the body triggers the collagen neosynthesis in an attempt to remodel the micro-damage and repair the tendons involved, also in elderly.

The electron microscope photographs shown in Provenzano et al., (2001) on the ultrastructure of the repair process of medial collateral ligament injuries of the knee, are very exhaustive (FIG. 10).

– Gronemann et al., (2004) show that patients affected with fibromyalgia in non-tender (non-trigger) points have lower levels of Hyp compared with healthy controls and - in general - a lower total concentration of amino acids in collagen.

The amount of total protein and myosin are within normal range.

Electron microscopy shows atrophic muscle fibrils only in cases of fibromyalgia.

The above mentioned Authors conclude that fibromyalgic patients have significantly reduced collagen amount in the muscles and this could lower the threshold for muscle microtrauma (FIG. 11).

The results of these studies confirm those of Yurus et al., (1986), Savolainen et al (1987), and Mackey et al., (2002).

– Xu and Shen (2007) show that the oral administration of collagen reduces the degeneration of articular cartilage and the levels of intracartilage MMP-13, MMP-9, and cathepsin K.


– The effects of collagen administration (of different origin) in the prevention and therapy, are shown in TAB. 2 (author, 2010).

Trentham et al., (1993) report successful results obtained with the administration of collagen in cases of active rheumatoid arthritis in a randomized, double-blind, placebo controlled trial carried out on a high number of cases (among which 4 complete resolutions), as well as the more recent trial by

The use of hydroxyapatite-collagen nanocomposites (implants) has produced interesting results in serious deforming pathologies of the the cervical spine (Itoh et al., 2004).
- However, the method is highly complicated and impractical as it involves fixing and removal interventions.

**GUNA MEDICAL DEVICES FOR THE INJECTIVE TREATMENT OF DYSFUNCTIONAL AND PAINFUL ARTHRO MYOFASCIAL PATHOLOGIES**

A new substantial and refined approach to the painful dysfunctional pathologies of the musculoskeletal system and of the related motor functions is now offered by Guna Medical Devices for use in clinical practice and in specialist facilities.

The 13 Guna Medical Devices (MD) contain collagen and ancillary substances of natural origin (TAB. 3).

The ancillary substances allow a more effective and specific placement of collagen and have the function of conveying and stabilization.

> Eight of these MD are specific of the individual anatomical skeletal areas and of the disorders connected with them: MD-NECK, MD-THORACIC, MD-LUMBAR, MD-SHOULDER, MD-HIP, MD-KNEE, MD-SMALL JOINTS, MD-POLY (multi-articular); one is specific for the sciatic nerve [MD-ISCHIAL], and four others that are specific for tissue diseases, derived predominantly from mesodermal tissue: MD-MUSCLE, MD-NEURAL, MD-MATRIX (Extra Cellular Matrix), MD-TISSUE (soft tissues) (TAB. 3: FIG. 12).

All 13 Guna MD contain, in addition to the carrier excipient (ancillary), collagen of porcine origin.

- The swine tissues have a very high average content of collagen (22.8% =...
Glycine, Proline = 13.8%; Hydroxy-Proline = 13%).
The average content of the other amino acids is only 3% (max Glutamic acid = 9.5%; min Tyrosine = 0.4%); the 50% is then made up of collagen.

Thanks to the particular process of tangential filtration, sterilization and control of molecular weight, a pure product (without contaminants) is obtained, that has the standard chemical and physical characteristics of a good and clinical safety.
The purpose of the local administration of this biomaterial “where it is needed” is structural: to replace, strengthen, structure and protect (adhesion barrier) the cartilage, the tendons, the ligaments, the joint capsules, etc.; to improve the structure of collagen fibers and - consequently - of all anatomical structures in which it is present; to provide mechanical support to the district concerned.

– One of the most important causes of district joint pain is the laxity of the intra-and extra-articular stabilization structures; the loose restraint systems determine joint hypermobility, especially in not physiological directions and angles that wear and tear early the restraint systems themselves and act towards a progressive degeneration of the cartilage.

The mechanical support provided by the collagen is an effective natural support scaffold (bio-scaffold).

The infiltration of collagen and the single ancillary ingredients, is perfectly tolerated by the patient and devoid of adverse reactions. It is physiological, compatible and does not cause microinflammation with subsequent fibrotic retraction, as in prolotherapy, which covers basically the same purpose: the stabilization of periartricular structures.

– The proteoglycans (PGs) of the Extracellular Matrix (ECM) cementing the collagen fibers improve the viscoelastic properties of the endoarticular fluid, which does not happen in prolotherapy.

The loose musculoskeletal components and hypermobile joints stimulate local nociceptors and cause tension and excessive stress to localized areas. By reinforcing these areas, regeneration and analgesic effects occur.

Guna MD improve physiological joint mobility, promote localized muscle distention, relieve localized pain or pain caused by joint movement or faulty posture.

Guna MD are 2ml injectable ampoules for subcutaneous, intradermal, periartricular, intraarticular and intramuscular (local muscles) use.

➤ Guna MD can be used by themselves or along with in different associations (up to 2 ampoules per MD) according to the specific needs of the patient, or mixed with PRM injectable ampoules for Pain Therapy (ex. MD-NECK + MD-MUSCLE + GUNA-NECK + GUNA-MUSCLE) or as a complement to Homotoxicology (ex. Zeel T, Arnica comp.-Heel) or even conventional or local anesthetic injectable treatment.
Guna MD can also be used when the patient is treated with cortisone, NSAIDs and / or chondroprotective drugs without contraindications - and - as already mentioned - if the patient receives - during the treatment - manipulative therapy or other physical therapeutic methods (acupuncture, electroacupuncture, shiatsu, physiokinesitherapy), instrumental methods (magnetic therapy, ultrasound, laser therapy, electrotherapy, etc.) or thermal therapy.

**MAIN INDICATIONS OF GUNA MEDICAL DEVICES**

**MD-NECK**
- Cervical pain secondary to cartilage degeneration of the cervical spine segments (cervical osteoarthritis) (in association with MD-POLY)
- Cervical pain secondary to muscle trigger point (in association with MD-MUSCLE)
- Stiff neck (in association with MD-MUSCLE and MD-NEURAL)
- Muscle tension cervical pain (in association with MD-NEURAL and MD-MUSCLE)
- Whiplash (in association with MD-NEURAL and MD-MUSCLE)
- Cervical pain due to postural defects (in association with MD-NEURAL and MD-MUSCLE)
- Alterations of the cervical axis (articular facet syndrome) (in association with MD-NEURAL)
- Cervical spinal ligaments syndrome (in association with MD-NEURAL and MD-MATRIX)
- Cervical radicular neuritis (in association with MD-NEURAL)

**MD-THORACIC**
- Back pain secondary to degenerative disorders of the cartilage of the dorsal spine segments (spinal osteoarthritis) (in association with MD-POLY)
- Back pain secondary to scoliosis (in association with MD-MUSCLE and MD-NEURAL)
- Back pain secondary to trigger point of the dorsal muscles (in association with MD-MUSCLE)
- Pain secondary to osteophytes of the dorsal spine (in association with MD-NEURAL and MD-MATRIX)
- Back pain secondary to osteoporosis (in association with MD-NEURAL, MD-MUSCLE, and MD-TISSUE)
- Alterations of the dorsal axis (articular spinal costal facet syndrome) (in association with MD-NEURAL and MD-MATRIX)
- Syndrome of spinal dorsal ligaments (in association with MD-NEURAL)
- Radicular neuritis of the dorsal spinal nerves (in association with MD-NEURAL).

**EFFECTS OF COLLAGEN ADMINISTRATION**

<table>
<thead>
<tr>
<th>PREVENTION</th>
<th>Author/s</th>
<th>Chronological order</th>
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<tbody>
<tr>
<td>1 Inhibition of collagenesis</td>
<td>Scufl, 1994</td>
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<td></td>
<td>Walker, 1994</td>
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<td></td>
<td>Wilson-Townsend, 1994</td>
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<td></td>
<td>Kriegal, 1995</td>
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<tr>
<td>2 Inhibition of matrix metalloproteasis (MMPs)</td>
<td>Lee and Langer, 1983</td>
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<td>Lee, 1984</td>
<td></td>
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<td></td>
<td>Moses, 1990</td>
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<td>Moses, 1993</td>
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<tr>
<th>THERAPY</th>
<th>1 Wounds healing</th>
<th>Lansman et Al., 2009</th>
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<tbody>
<tr>
<td>2 Repair of Articular cartilage</td>
<td>Stone et Al., 1997</td>
<td>Cook et Al., 2006</td>
</tr>
<tr>
<td>3 Repair of tendons (acute and chronic pathologies)</td>
<td>Chenet et Al., 2007</td>
<td>Karaoğlu et Al., 2007</td>
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**FIG. 11**
Photomicrographs (ME 3.000X) of muscle tissue of a fibromyalgic patients (left) and normal control (right).

- In the fibromyalgic tissue significant changes in the collagen structure can be observed (moth-eaten).
**MD-LUMBAR**
- Low back pain secondary to lumbar cartilage degeneration (low back pain and lumbar osteoarthritis)
- Osteophytosis of the lumbar spine segments (in association with MD-NEURAL and MD-MATRIX)
- Low back pain secondary to muscle-tendon trigger points (in association with MD-MUSCLE)
- Low back pain from postural defects (in association with MD-NEURAL, MD-MUSCLE, and MD-TISSUE)
- Mechanical alterations of the lumbar and lumbosacral axis (in association with MD-NEURAL)
- Syndrome of lumbar and lumbosacral spinal ligaments (in association with MD-MATRIX)
- Sacroiliac joint syndrome (in association with MD-NEURAL)
- Radicular neuritis of the lumbar and lumbosacral spinal nerves (in association with MD-NEURAL and MD-ISCHIAL).

**MD-SHOULDER**
- Humero-scapular periarthritis (in association with MD-POLY)
- Rotator cuff syndrome (in association with MD-MUSCLE and MD-TISSUE).

**MD-NECK**
- Shoulder-arm syndrome (in association with MD-NEURAL and MD-MUSCLE)
- Frozen shoulder (in association with MD-MUSCLE)
- Shoulder pain secondary to dislocation (pre-therapy and post-reduction, in association with MD-NEURAL)
- Epicondylitis (in association with MD-NEURAL and MD-POLY).

**MD-THORACIC**
- Gastro-oesophageal reflux disease (in association with MD-NEURAL and MD-POLY)
- Intercostal neuritis (in association with MD-NEURAL)
- Kyphosis (in association with MD-NEURAL and MD-MUSCLE).

**MD-MUSCLE**
- Humero-scapular periarthritis (in association with MD-POLY)
- Rotator cuff syndrome (in association with MD-MUSCLE)
- Epicondylitis (in association with MD-NEURAL and MD-ISCHIAL).

**MD-MATRIX**
- Osteoarthritis (in association with MD-MUSCLE and MD-TISSUE)
- Cystic diseases (in association with MD-NEURAL)
- Lymphangioma (in association with MD-NEURAL)
- Dupuytren's contracture (in association with MD-NEURAL).

**MD-TISSUE**
- Knee pain secondary to rheumatoid arthritis or other autoimmune diseases (in association with MD-POLY)
- Acute and chronic arthrosynovitis secondary to trauma, arthrosis and rheumatoid arthritis (in combination with MD-POLY)
- Arthrosynovitis post-traumatic and post-surgical acute and chronic
- Traumatic injuries or collateral ligament of the knee
- Meniscus pain (in association with MD-POLY)
- Preparation of meniscectomy surgery (in association with MD-MUSCLE)
- Maintenance therapy after knee surgery (in association with MD-MUSCLE-NEURAL).

**MD-ISCHIAL**
- Osteoarthritis of the hand fingers
- Rhizoarthrosis of the thumb (Forestier's disease)
- Arthralgia caused bunion
- Carpal tunnel syndrome (in association with MD-MUSCLE and MD-TISSUE).

**MD-KNEE**
- Gonarthrosis (in association with MD-POLY)
- Knee pain secondary to rheumatoid arthritis or other autoimmune diseases (in association with MD-POLY)
- Arthrosynovitis post-traumatic and post-surgical acute and chronic
- Traumatic injuries or collateral ligament of the knee
- Meniscus pain (in association with MD-POLY)
- Preparation of meniscectomy surgery (in association with MD-MUSCLE)
- Maintenance therapy after knee surgery (in association with MD-MUSCLE-NEURAL).

**MD-SMALL JOINTS**
- Osteoarthritis of the hand fingers
- Rhizoarthrosis of the thumb (Forestier's disease)
- Arthralgia caused bunion
- Carpal tunnel syndrome (in association with MD-MUSCLE and MD-TISSUE).

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**GUNA Medical Device**

<table>
<thead>
<tr>
<th>GUNA Medical Device</th>
<th>COMPOSITIONS</th>
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<tbody>
<tr>
<td>MD-NECK</td>
<td>Collagen + Silica</td>
</tr>
<tr>
<td>MD-THORACIC</td>
<td>Collagen + Cimicifuga racemosa</td>
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<tr>
<td>MD-LUMBAR</td>
<td>Collagen + Hamamelis virginiana</td>
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<td>MD-SHOULDER</td>
<td>Collagen + Iris versicolor</td>
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<tr>
<td>MD-HIP</td>
<td>Collagen + Calcium phosphate</td>
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<tr>
<td>MD-KNEE</td>
<td>Collagen + Arnica montana</td>
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<tr>
<td>MD-MUSCLE</td>
<td>Collagen + Viola odorata</td>
</tr>
<tr>
<td>MD-NEURAL</td>
<td>Collagen + Drosera rotundifolia</td>
</tr>
<tr>
<td>MD-NEURAL</td>
<td>Collagen + Hypericum perforatum</td>
</tr>
<tr>
<td>MD-MUSCLE</td>
<td>Collagen + Citrullus colocynthis</td>
</tr>
<tr>
<td>MD-MATRIX</td>
<td>Collagen + Citric Acid, Nicotinamide</td>
</tr>
<tr>
<td>MD-TISSUE</td>
<td>Collagen + Ascorbic Acid, Magnesium Gluconate, Pyridoxine chloride, Riboflavin, Thiamine chloride</td>
</tr>
</tbody>
</table>
• De Quervain’s disease (in association with MD-NEURAL)
• Simple metatarsalgia
• Metatarsalgia associated with Morton’s neuroma (in association with MD-NEURAL)
• Rheumatoid arthritis of the hand and foot (in association with MD-POLY)
• Hand and foot tendinopathy secondary to prolonged immobilization (in association with MD-MATRIX).

MD-ISCHIAL

• Sciatica
• Lumbar-sciatic pain (in association with MD-LUMBAR and MD-NEURAL)
• Lumbar neuralgia (in association with MD-MUSCLE)
• Sciatica after surgery for herniated disc L4-L5, L5-S1 (in association with MD-NEURAL)
• Morton’s neuroma (in association with MD-NEURAL).

MD-POLY

• Nonspecific diffuse pain (in association with MD-NECK or MD-THORACIC or MD-LUMBAR, and MD-NEURAL)
• Costal sternal syndrome (in association with MD-NEURAL)
• Chronic polyarthritis secondary to autoimmune disease (eg, Systemic Lupus Erythematosus) (if the neuralgic symptoms prevail: in association with MD-NEURAL; if muscle symptoms prevail: in association with MD-MUSCLE)
• Syndrome of “the broken bones” (if the neuralgic symptoms prevail: in association with MD-NEURAL; if muscle symptoms prevail: in association with MD-MUSCLE)
• Joint pain secondary to viral disease (in association with other specific Guna MD)
• Joint pain secondary to cancer (eg, chronic leukemia, multiple myeloma) (in association with other specific district Guna MD).

MD-MUSCLE

• Treatment of acute, subacute, chronic myofascial pain
• Treatment of trigger points (in association with MD-NEURAL)
• Treatment of referred pain areas (in association with MD-NEURAL)
• Fibromyalgia (in association with MD-NEURAL and MD-MATRIX)
• Dermatomyositis.

MD-NEURAL

• Brachial nerve neuralgia secondary to cervical entrapment syndrome (in association with MD-NECK)
• Persistent intercostal neuralgia (in association with MD-THORACIC)
• Postherpetic neuralgia (in association with MD-THORACIC or MD-LUMBAR)
• Atypical facial neuralgia (in association with MD-NECK and MD-TISSUE)
• Trigeminal neuralgia (in association with MD-NECK and MD-MATRIX)
• Pain of the temporomandibular joint (in association with MD-NECK)
• Radicular neuritis of the cervical dorsal, lumbar, sacral spinal nerves, (respectively in association with MD-NECK, MD-THORACIC, MD-LUMBAR, and MD-ISCHIAL).

MD-MATRIX

MD-MATRIX can be used alone or combined with any other MD of the same line, in order to create a personalized treatment based on the individual clinical picture.

► MD-MATRIX can also be used in patients who need anti-aging topical treatment.

MD-TISSUE

Also MD-TISSUE may be used alone or combined with any other MD of the same line, according to the individual clinical picture.

► MD-TISSUE can also be used in patients who need anti-aging topical treatment.

CONCLUSIONS

With increasing age (Mays et al., 1988), physical inactivity, intense physical activity or inadequate sports activity (Adam et al., 1984), postural alterations, nutrient imbalances, changes of the PNEI axis, the connective tissue and the collagen in particular (real tissue protein) gradually dete-
The non-invasiveness of the injections with Guna MD, the first ones in this field having reported therapeutic results in 7 controlled clinical trials (Registration report at the High Institute of Health - Italy), as well as their other characteristics such as efficacy, tolerability, absence of allergic and natural reactions, makes this a unique and valuable tool in the specialist and non-specialist praxis in improving the quality of life of patients who were intended - otherwise - to get worse or become chronic.

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Including the items shown in Figures and Tables

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Textbooks

Recommended readings

The author sincerely thanks Hippokrates Verlag and Guna Editore for the reproduction of the images in Figs. 1 (amended), 3, 5 (only 1, 2) from H. Heine - Manuale di Medicina Biologica. Regolazione di base e matrice extracellulare. 3rd edition, completely revised, 2009, and the Editors of the websites from which the images were taken:

- Figure 2 (only on the top): http://farm1.static.flickr.com/160/405756871_794fca5e86.jpg
- Fig. 6: http://www.helmholtz-muenchen.de/uploads/pics/fig4-2_textmedium.png
- Fig. 10:
  a: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig3.jpg
  b: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig4A.jpg
  c: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig2.jpg
  d: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig4B.jpg
- Fig. 11: http://rheumatology.oxfordjournals.org/cgi/content/full/43/1/27

Figs. 2, 4 (amended), 5, 7, 9 and Tabb. 1, 2, 3 belong to the author.

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