UP TO DATE

L. Milani

THE COLLAGEN MEDICAL DEVICES IN THE LOCAL TREATMENT OF THE ALGIC ARTHRO-RHEUMOPATHIES

– REVIEW OF THE CLINICAL STUDIES AND CLINICAL ASSESSMENTS 2010-2012

INTRODUCTION

Reliable epidemiologic data recorded in Italy (Mannaioni *et* Al., 2003) and in Europe [Jordan *et* Al., 2003-European League Against Rheumatism (EULAR)] show that **15-20%** of the general population suffers from pathologies involving the osteo-arthro-myo-fascial Apparatus (better defined as arthro-rheumopathies), representing **70% of the patients with chronic pain**.

– In the near future, these data will probably undergo an increase, especially due to increased life expectancy, overall average increase in body weight, greater propensity to inactivity amid people above 50, higher incidence of amateur sports activity and consequent traumas (mostly among people aged between 20 and 45), overuse of NSAIDs and unhealthy diet, basically high in proteins.

The arthro-rheumopathies (connective tissue inflammatory and/or degenerative diseases) are all characterized by **collagen disorders**.

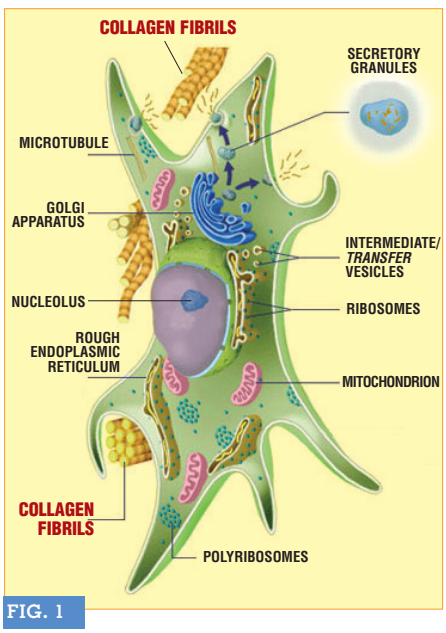


FIG. 1

Structural organization of the tenocyte.

Collagen's physiological tissue organization and quantitative and qualitative composition – which dramatically decrease from ≈ 60 years of age (Heine, 2009) – determines the organoleptic characteristics of connective tissues.

– Collagens are merged into a vast family of structural proteins of the extra-cellular matrix having unique and peculiar characteristics, also from the phylogenetic point of view (*in* Milani, 2010).

Up to the present more than 30 genetically distinct varieties (Types) of collagen have been identified.

- Genetic alterations of some Types of collagen determine complex and paradigmatic phenotypes (alterations in the collagen Type I: e.g. osteogenesis imperfecta; Type I, III, V: e.g. Ehlers-Danlos syndrome; Type IV: e.g. Alport syndrome; Type II, XI: e.g. cartilage genetic diseases).

The **fibrillar collagen Type I** (COL1A1 and COL1A2 coding genes) is the most abundant ubiquitous protein in adult humans, accounting for **90%** of the total collagen: it is involved in the

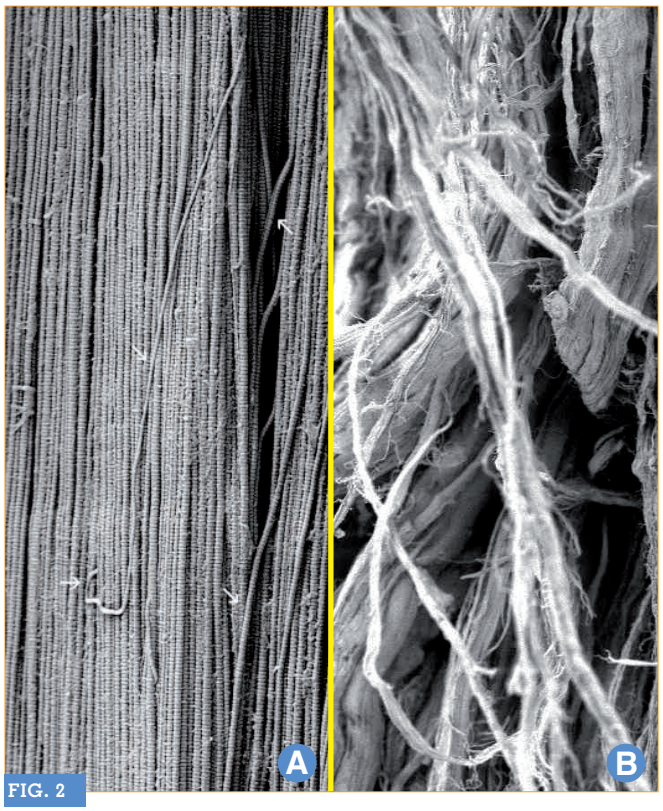


FIG. 2

A – Continuity of collagen fibers in the ligament of adult rats.
Electron Microscope images from Provenzano P.P. *and* Vanderby R. Jr. – Collagen fibril morphology and organization: Implication for force transmission in ligament and tendon. Matrix Biology 25(2006) 71-84.

B – Post-traumatic repair of the collagen texture.
Electron Microscope images from Provenzano P.P., Hurschler C., Vanderby R. Jr. – Connect. Tiss. Res. 42:123-133, 2001.

composition of the main connective tissues and represents the bulk of certain structures such as skin, dentine, cornea, **joint capsules**, **ligaments**, **tendons**, **aponeurotic layers** and **fibrous membranes**.

– In the **tendons**, for example, collagen Type I = **97%**; elastin = 2%; proteoglycans = 1-5%; inorganic components (Cu, Mn, Ca) = 0.2% (Jozsa *and* Kannaus, 1997; Lin *et* Al., 2004); in **ligaments**, collagen Type I = **85%** (Frank, 2004; Vereeke *et* Al., 2005).

The *in vivo* fibrillogenesis is a multi-step process involving both the intracellular compartment and the extracellular one, defined by **tenocyte** (a very specialized fibrocyte) (FIG. 1).
– The tenocyte, in addition to collagen Type I, also synthesizes the matrix proteoglycans (PGs) and the metalloproteinase (MMP) 1-interstitial which is involved, together with the MMP8-neutrophil, in the degradation of the fibrils, either because old or damaged by the inflammatory/traumatic process (Birk *et* Al., 1995; Canty, 2004).
The MMP1 is primarily involved in the processes of fibrillo-(collagen)-lysis: the study of Maeda *et* Al. (1995) highlights a very high concentration of MMP1 in the synovial fluid of patients with rheumatoid arthritis, which is related to the degree of inflammation (reliable marker of the disease status).

Provenzano *and* Vanderby Jr. (2006)), using the electron microscope, exhibit a wide range of very impressive photographs proving that healthy adults collagen fibrils (FIG. 2A) are very precise, parallel to each other, continuous and laid longitudinally along the main axes of the anatomical structures to which they belong and which characterize, transmitting the force directly and not through the PGs bridges.

– The collagen turnover is very slow.
The mechanical failure and the presence of free radicals can increase the degenerative process, causing a spontaneous, slow and imperfect neofibrillogenesis: the process of spontaneous repair leads to the neoformation of disordered, twisted, juxtaposed, discontinuous fibers, (FIG. 2B), morphologically much more similar to the fetal ones rather than the adult ones (Provenzano *et* Al., 2001). It also leads to increased vascularization and increased deposits and clusters of inflammatory cells.
These phenomena all contribute to the further weakening of collagen Type I (Shrive *et* Al., 1995; Frank *et* Al., 1999) and to the increased synthesis of collagen Type III (Liu *et* Al., 1995; Hsu *et* Al., 2010), which is functionally much less suitable.

During the fibrillogenesis process, the PGs play a crucial role in guiding and stabilizing neofibrils, assisted by the SLPR (Small Leucine Rich Proteoglycans) (Jepsen *et* Al., 2002), represented above all by decorin, lumican, and fibromodulin.
The rare overt genetic alterations of these 3 small PGs affect distinct phenotypes, clinically severe.
– Minor alterations with variable penetrance and expressivity are probably not diagnosed and are the primary cause of highly pathologically susceptible conditions: collagen fibrils altered in shape and diameter which affect the joints and posture long before the physiological decay.

– I conclude these brief topics on collagen, which supplement and detail what presented in a previous publication (Milani, 2010) to which I refer, indicating that collagen is also a template for bone mineralization, which promises new and revolutionary solutions in Orthopedics and Traumatology.

THE EXTRA-ARTICULAR ENVIRONMENT OF THE JOINTS

The anatomical structures composing the extra-articular environment of the joints – with containing and stabilizing functions – are represented by:

1) joint capsule, ligaments and fibrous membranes ("**direct hold**");
2) tendons and muscles ("**indirect hold**").

These elements – which unite and wrap the distal end of a bone and the proximal end of the adjacent bone (supero-inferior) (bone segments in connection) – are the actors of the **containment-stabilization** and of the **joint mobility**.
– Although anatomically distinct and functionally different, these structures are in close continuity (contiguous or overlapping anatomical planes; some collagen fibers of each structure merge with the neighboring ones) to form an elastic-stretch sleeve performing primarily two functions:
1) Articular establishment in static / dynamic physiological position;
2) Articular mobility with maximum range.

FIGURE 3 shows as exemplification the fibrous structures of the extra-articular environment of the elbow.
– In addition to the extra-articular structures, few joints also have intra-articular intrinsic ligaments that connect two skeletal segments inside the joint capsule (e.g. cruciate ligaments of the knee joint, coxofemoral round ligament).

– The extra-articular structures (primarily: joint capsule, ligaments and tendons) are constituted by collagen Type I: the quality and the quantity of this protein ensure a physiological joint movement, repeated over time and optimal movement.
Progressive depletion and / or damage to organoleptically suitable collagen Type I is produced by aging (discrepancy between neofibrillogenesis and fibrillo-lysis), misuse or disuse of the joints, traumas aggravated by the coexistence of internal diseases and – in some age groups – even by vitamin deficiencies (vitamin C, but also vitamin A and E), copper deficiency, noble proteins deficiency, and the use / abuse of drugs (particularly corticosteroids).
– In particular, Elder *et* Al. (2001), Warden (2005), and Warden *et* Al. (2006) show that NSAIDs COX-2 inhibitors inhibit the healing of injured ligaments, leading to the lack of mechanical strength (imbalance between joint stability and mobility) and causing extra- and intra-articular damages.
The trial of these drugs demonstrates unequivocally that the anti-inflammatory benefit in the short term is converted into serious harm in the medium and long term.
– Fournier *et* Al. (2008), and Ziltener *et* Al. (2010) maintain that the use of NSAIDs in the treatment of periarticular soft tissues (ligaments, capsule) should be very limited in time, or absent.

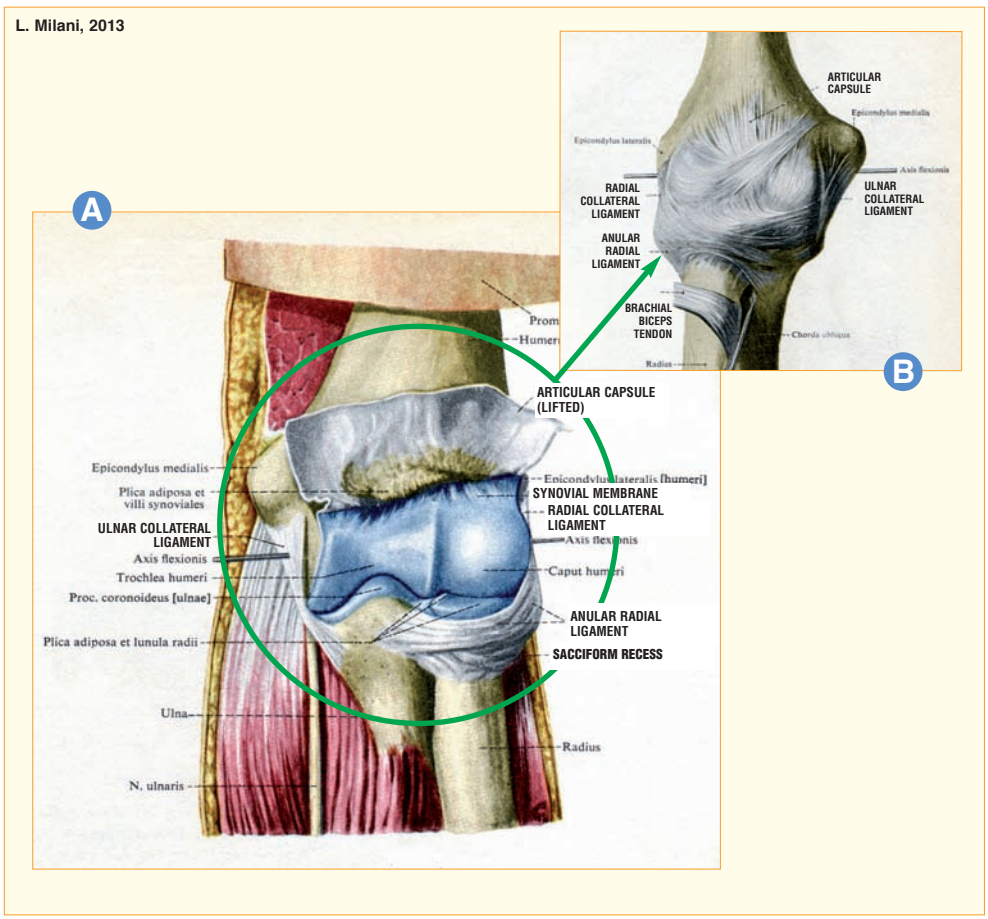


FIG. 3

A – Left elbow joint, front.
B – Right elbow joint, front.

The containing and stabilizing structures of the elbow joint are represented by extra-articular connective-collagen Type 1 structures.
They are represented by:
– ulnar collateral ligament (A, B);
– radial collateral ligament (A, B);
– anular radial ligament (A, B);
– sacciform recess (A);
– joint capsule (lifted in A; B);
– brachial biceps tendon (B).
All these structures allow the large variations in flexion, extension and torsion of the forearm on the arm.

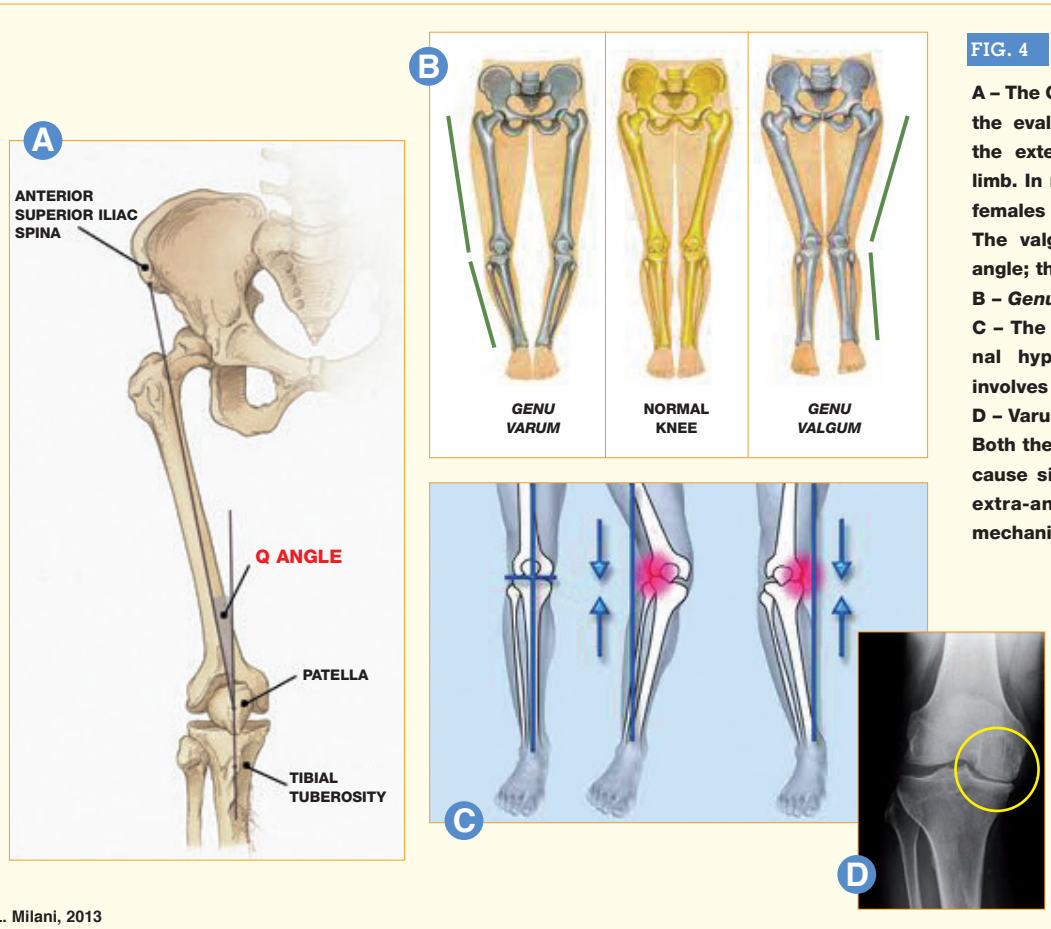
– Images translated and elaborated by the author from W. Spalteholz - R. Spanner, Atlante di Anatomia Umana. Società Editrice Libraria (Vallardi) - Milano, 5th Italian edition (1962) in the 16th German edition (1959-61); 1st Vol.; pp. 232-3.

Barton *and* Bird (1996) indicate the laxity or hyperlaxity of anatomical structures as the most important cause of pain of one or more joints.
The quoted authors' studies follow those by:
– Rotes-Querol (1957), which identified joint laxity as the main factor of altered posture;
- Teneff (1960), indicating the clinical significance of congenital joint laxity;
- Donayre *and* Huanaco (1966), which show that the orthopedic joint laxity is the cause of many diseases (defined by the authors as "arthrocalasis").
Recently:
- Philippon *and* Schenker (2005) show high incidence of coxofemoral traumas in athletes with femoral laxity;
- Paschkewitz *et* Al. (2006) describe the generalized ligament laxity associated with proximal dislocation of the tibio-peroneal joint;
- Hauser *and* Dolan (2011), indicate in joint instability and unhealed ligament injuries the primary cause of osteoarthritis.

These are just some historical data and the most recent ones among those that can be extrapolated from the available literature on the topic which indicate that the **joint hypermobility** due to deficiency of joint containment (ultimately: deficiency of collagen Type I in the extra-articular environment) is the **primary cause** of the arthropatic etiology.

It is necessary to distinguish between joint hypermobility due to impaired containment from the one due to paraphysiological laxity, such as:
– in childhood (Cheng *et* Al., 1993; Bird, 2005; Simpson, 2006);
– in females, especially during the menstrual cycle (Schultz, 2005);
– In individuals belonging to African (Beighton *et* Al., 1973) and eastern (Walker, 1975) anthropological varieties,
and the one due to joint instability of various pathological degree, which starts when the contiguous bone segments forming a joint do not respect the optimal axes and - consequently - the angles among them.

Paradigmatic examples – not the only ones, though – of such situations are:
– valgus/varus tibio-femoral joint (FIG. 4) and valgus/varus coxo-femoral joint,
– the extra/internal rotation of the head of the femur in the acetabulum,
– the lordosis/kyphosis of the rachis segments,
– cavus/flat foot.



L. Milani, 2013

FIG. 4

A – The Q angle measurement allows the evaluation of the alignment of the extensor system of the lower limb. In males the Q angle is 12°; in females it is 16°.
The valgus knee increases the Q angle; the varus knee decreases it;
B – *Genu varum* and *valgum*;
C – The valgus knee involves external hyperloads; the varus knee involves internal hyperloads;
D – Varus knee Rx.
Both the varus and the valgus knee cause significant alterations of the extra-and intra-articular fixation mechanisms.

The collateral ligaments and the joint capsule are *in toto* subject to pathological stretching, shortening, and twisting, thus compromising the optimal joint function → pain → movement impairment.

Situations that can worsen joint hypermobility are paraphysiological variations and real alterations of the diaphyseal shape, the alteration of the muscle tone and abnormal proprioception.

All the above conditions necessarily lead to **pathological osteo-cartilaginous hyperload** which cause the overuse processes. The bone reacts with the production of marginal osteophytes, subchondral bone cysts, subcortical hardenings or deformities and/or epiphyseal osteopenia.

These extra-physiological forces cause, especially in the load joints, slippage of the adjacent bone heads, which are anteroposterior, medium-lateral and rotational of greater or lesser severity.

– In such situations the loose structures of the extra-articular environment are exposed to mechanical stress: the pain due to extra-articular cause is added to the one due to intra-articular cause (which is frequently inflammatory), thus aggravating the status and prognosis of the disease.

The organism performs mechanisms of local and remote compensation by establishing the activation (hyperactivation) of ascendants and descendants muscle-proprioceptive chains which only rarely get the desirable effect: the control of the vascular tone is unintentional and self-organizing, at central and peripheral level.

– Currently, the treatment of arthro-reumopaties offers different options; it includes different, unique treatments or – more frequently – a combination of:
1) non-pharmacological treatments (e.g. ultrasound therapy, magnetic therapy, laser therapy, TENS, acupuncture, moxibustion, etc.);
2a) conventional pharmacological treatments [e.g. COXIB, NSAIDs, paracetamol, corticocosteroids (the latter also intra-articularly injected)];
2b) unconventional pharmacological treatments [e.g. specific medicines formulated by Homeopathy, Homotoxicology (the latter also via intra-articular injection, periarticular injection, mesotherapy, homosiniatry treatment), Physiological Regulating Medicine, Herbal Medicine];
3) physical-rehabilitation treatments (see review by Di Domenica *et* Al., 2004);
4) surgical treatment: mobile (prosthesis, especially hip, knee, shoulder) or fixed (arthrodesis).

Symptomatic slow-acting treatments include viscosupplementation with hyaluronic acid (see review by Bellamy *et* Al., 2008) or with hylan G-F 20 (derived from the hyaluronic acid) (see review by Conrozier *and* Chevalier, 2008), administered mainly via injection into the knee, hip and shoulder. They are viscous lubricants whose prevailing action is supplementary and cushioning.

– The viscosupplementation replaces the (usually degraded) hyaluronic acid of the synovial fluid of the joints of the patients affected by osteoarthritis.

The hyaluronic acid is mostly used to inject the knee in order to treat gonarthrosis.

– Nevertheless, the members of the EULAR (European League Against Rheumatism) Committee for clinical trials on osteoarthritis of the knee met in 1998 and came to the conclusions that the hyaluronic acid and symptomatic slow-acting antiarthritic drugs have modest efficacy in gonarthrosis. Moreover, they stated that the patients who may benefit from this therapy are hardly identifiable and that pharmacoeconomic data are uncertain. The opinion of 21 experts has placed the use of the hyaluronic acid for the treatment of gonarthrosis in 13th place out of 23 entries (Pendleton *et* Al., 2000).

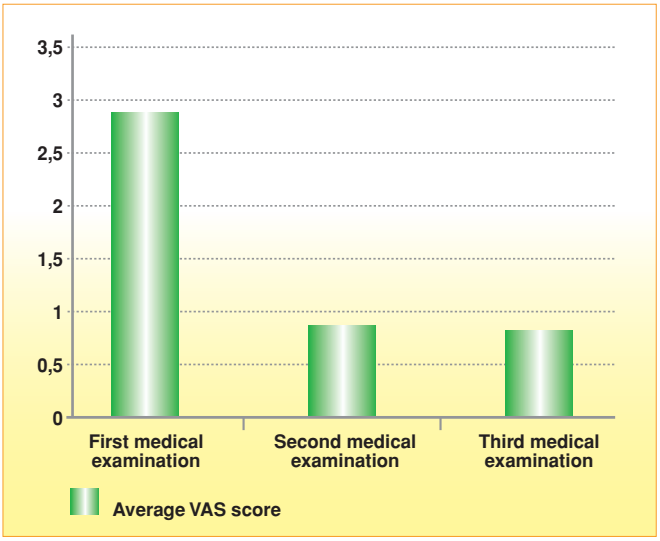
▶ Since 2010, also the treatment of algic/degenerative diseases of the musculoskeletal system takes advantage of the use of the injectable Collagen* Medical Devices (MDs) (Guna Laboratories, Milan - Italy).

The Collagen MDs can be used alone (e.g. MD-Lumbar: low back pain with high arthritic imprint), or – more frequently – variously mixed according to the patient's clinical and functional needs (e.g. MD-Lumbar + MD-Neural: low back pain with algic nerve imprint; MD-Lumbar + MD-Muscle: low back pain with prevailing myo-fascial imprint).

The Collagen MDs are applied locally through:
1) periarticular injections
2) intra-articular injections (obviously in the joints allowing a clear intra-articular approach: knee, hip, shoulder)
3) subcutaneous and/or intradermal injections (in trigger points, in spontaneously painful points, in points where average digitopressure causes pain, in local acupuncture points, etc.).
or systemically:
– intramuscular injections (into muscle trigger points), and in supportive treatment (mainly at home).

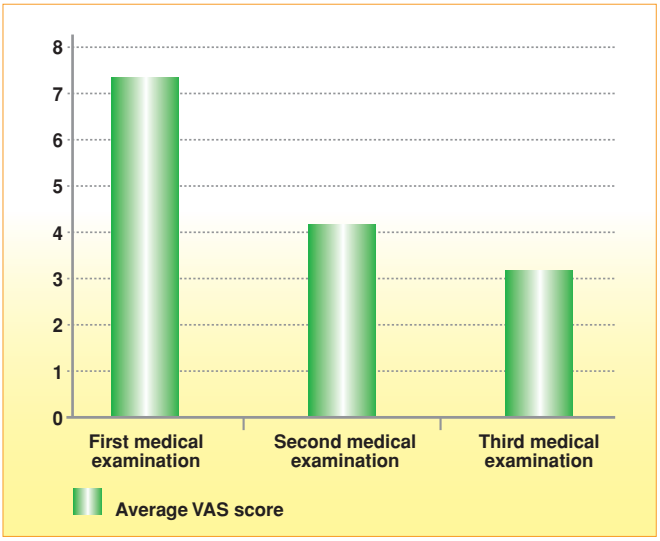
The **13 Collagen Medical Devices** are produced from dermal tissue of swine origin (trophism) + ancillary excipients of natural origin allowing an efficient and specific positioning on site (tropism).

* The term **Collagen Medical Devices** appears in Autori Vari. Terapie d'Avanguardia – *Compendium*. Nuova Ipsa Ed., 2012.
– Previously the term used to refer to the same products was: Guna Medical Device, as in Compendium Guna, 16th-17th ed. (2010), and 18th ed. (2011).



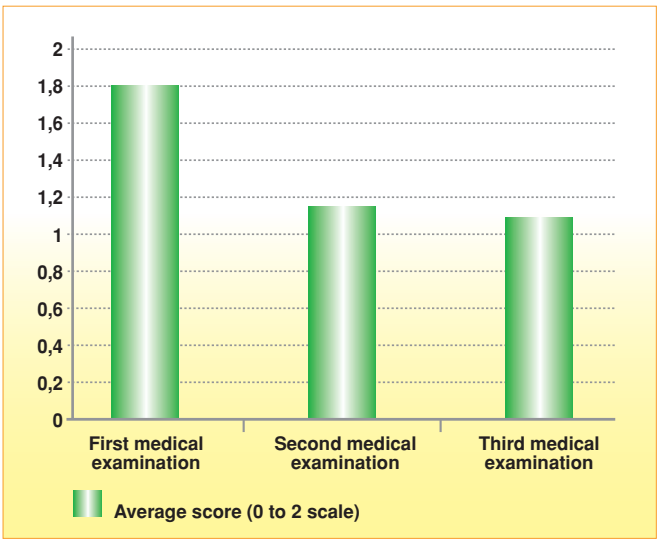
TAB. 1

VAS scale (0 to 10 points) – Patients' assessment of pain at rest.



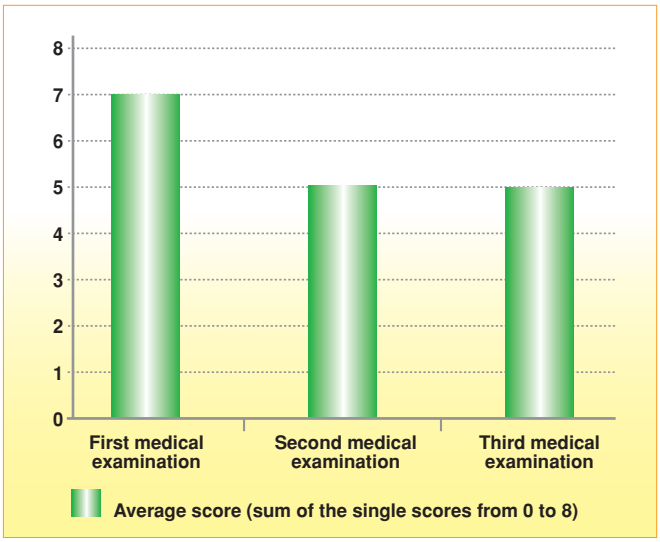
TAB. 2

VAS scale (0 to 10) – Patients' assessment of pain during movement.



TAB. 3

Lequesne Algofunctional Index – Evaluation of knee pain during movement (0 = absent; 1 = increasing after a due distance; 2 = increasing when starting).



TAB. 4

Lequesne Algofunctional Index – Evaluation of pain when performing other activities (climbing up and down the stairs, kneeling down and squatting down, walking on uneven ground; all 0 to 2 points).

The ancillaries were selected according to different criteria such as: traditional use, dedicated literature, clinical evidence, quality profiles, etc.

The swine's dermal tissue contains ≈ 50% of collagen Type I (Gly = 22.8%; Pro = 13.8%; OH-Pro = 13%).
– The purpose of the *in situ* injections of the Collagen MDs is essentially structural.

▶ From 2010 to 2012 **10 clinical trials on humans** were carried out, involving most of the treatable anatomical districts with Collagen MDs: **3** gonarthrosis, **1** patello-femoral arthropathy, **2** coxarthrosis, **2** shoulder pain, **1** PMID (Painful Minor Intervertebral Dysfunctions) of cervical rachis, **1** acute lumbar back pain.

– In the following pages it is presented the synopsis of the experiments; the Authors' conclusions of the 10 trials are faithfully reported.

THE INJECTABLE COLLAGEN MDs – REVIEW OF 10 TRIALS 2010-2012

FEMOROTIBIAL AND PATELLO-FEMORAL JOINTS

▶ EFFICACY AND SAFETY OF THE GUNA MDs INJECTIONS IN THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE

Authors: Rashkov R., Nestorova R., Reshkova V.
– Clinical Assessment presented at the Bulgarian National Congress of Rheumatology - Pravets (October 2011), at the European Congress on Osteoporosis and Osteoarthritis - Bordeaux (F) (March 2012), and at the 3rd Bulgarian National Congress on Osteoporosis and Osteoarthritis - Sandanski (November 2012).
Experimental sites: Rheumatology Clinic of the Medical University of Sofia, Rheumatology Center St. Irina (Sofia - Bulgaria).
Pathologies considered: symptomatic gonarthrosis (Kellgren-Lawrence* Rx grade II-III) without aftereffects of the periarticular soft tissues.
Outcomes
1) assessment of pain at rest and during movement before and after treatment;
2) assessment of the Lesquesne Algofunctional Index** before and after treatment;
3) effectiveness of the MDs used (evaluation by the patient and by the physician).
Inclusion/exclusion criteria: stated.
Patients enrolled: 28 (12 M, 16 F, aged 55-70).
Treatment: **MD-Knee**, 1 ampoule + **MD-Muscle**, 1 ampoule: 2 intra-articular injections/week for 2 consecutive weeks + 1 intra-articular injection/week for the next 6 weeks (total: 10 injections in 2 months).
Results
Statistically significant reduction of pain (VAS *** = 0-10) at rest (maintained even 30 days after the end of the therapy) and during movement (VAS = 0-10) (maintained even after the end of the therapy) (TABLES. 1, 2).
2) Statistically significant improvement of the indicators of the Lesquesne Algofunctional Index (TABLES 3, 4).

– Authors' conclusions:
1) Intra-articular administration of MD-Knee + MD-Muscle in gonarthrosis Kellgren-Lawrence Rx grade II-IIII reduces significantly pain at rest and during movement and improves the functional activity of patients, who assessed excellent + good in 65% of cases.
2) The effect persists even after treatment.
3) There were no adverse effects in any case. □

▶ EFFECTIVENESS OF THE GUNA COLLAGEN MDs INJECTIONS IN PATIENTS WITH GONARTHROSIS, ANALYSED CLINICALLY AND WITH ECOGRAPHY

Authors: Nestorova R., Rashkov R., Reshkova V., Kapandjieva N.
– Clinical Assessment presented at the 9th Central Congress of Rheumatology (CECR 2012) 3rd Annual Meeting of the Polish Rheumatologists - Krakow (Poland) (September 2012), and at the European Congress on Osteoporosis and Osteoarthritis - Bordeaux (F) (March 2012).
Article published in Rp./Orthopedic 2011/3, Medicine and Sport 2011/4 and PRM 2012; 37-39.
Experimental sites: Rheumatology Center St. Irina (Sofia); Rheumatology Clinic MBAL "St. Ivan
Experimental sites: Rheumatology Center St. Irina (Sofia); Rheumatology Clinic MBAL "St. Ivan Rilski" (Sofia); Rheumatology Center MBAL - Rousse (Bulgaria).
Pathologies considered: symptomatic gonarthrosis (Kellgren-Lawrence* Rx grade III-IV) with aftereffects of the periarticular soft tissues.
Outcomes
1) assessment of pain at rest and during movement (VAS = 0-10; Lesquesne Algofunctional Index**);
2) ecographic evaluation before treatment, after 30 days and at the end of the treatment;

Author's notes

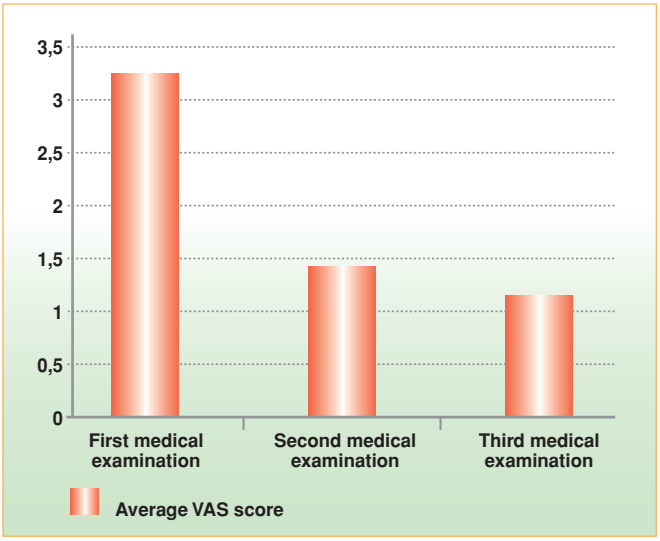
* The **Kellgren-Lawrence Scale** Kellgren J.H., Lawrence J.S. – Radiological Assessment of Osteo-Arthrosis. Ann Rheum Dis, 1957 Dec 16(4): 494-502.) describes **4 radiological degrees** of arthrosis:
– **Grade 1**: initial and doubtful narrowing of joint space and possible osteophytic presence.
– **Grade 2**: osteophytes, possible narrowing of joint space.
– **Grade 3**: moderate multiple osteophytes, definite narrowing of joints space, subchondral sclerosis and possible deformity of subchondral bone contour.
– **Grade 4**: severe arthrosis.

** The **Lequesne Algofunctional Index** (Lequesne M., Mery C. *et* Al. – Indexes of severity for osteoarthritis of the hip and knee. Scand J. Rheumatology. 1987; Suppl. 65:85-89) and the last version (Lequesne M. G. – The algofunctional indices for hip and knee osteoarthritis. J. Rheumatol. 1997; 24:779-781) assesses pain using 5 items; the longest walking distance is assessed by 7 or more items; difficulties in the daily routine are assessed by 4 or more items.

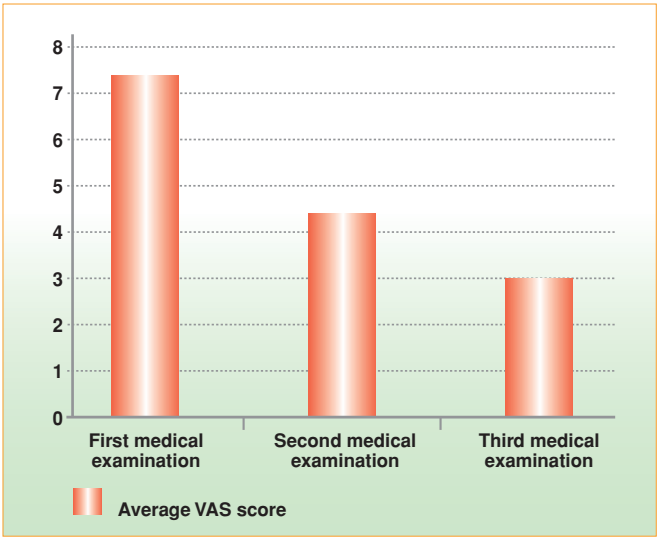
*** **VAS** = Visual Analogue Scale = **10 point** (from O = no pain to 10 = agonizing pain) or **100 point scale**).

3) evaluation of effectiveness of the MDs used.
Inclusion / exclusion criteria: stated.
Patients enrolled: 35 (aged 62-79).
Treatment: **MD-Knee**, 1 ampoule + **MD-Matrix**, 1 ampoule: peri-articular injections / week for 2 consecutive weeks + 1 peri-articular injection /week for 6 more weeks (total: 10 injections in 2 months).
Results
1) Statistically significant reduction of pain (VAS*** = 0-10) at rest (maintained even after the end of treatment) and during movement (maintained even 30 days after the end of treatment) (TABB. 5, 6).
2) Statistically significant improvement of all indicators of the Lequesne Algofunctional Index (examples in TABB. 7, 8).
3) 60% of patients do not have any edema; 30% achieved a reduction of edema

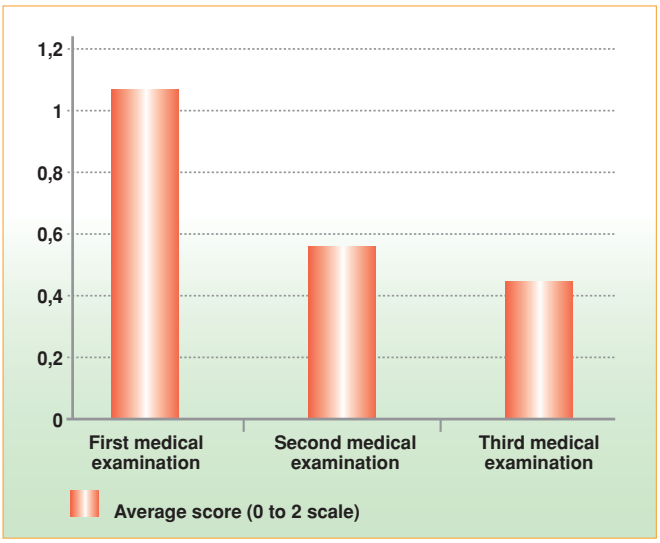
– Authors' conclusions:
1)) Intra-articular administration of MD-Knee + MD-Matrix in gonarthrosis Kellgren-Lawrence Rx grade II-IIII reduces significantly pain at rest and during movement and improves the functional activity of patients.
2) The effectiveness of treatment was evaluated as excellent + good in 68% of patients and 72% of physicians.
3) Periarticular edema improves in 90% of cases as proven by ecography.
4) The effect is maintained even after treatment.
5) The analysed MDs have a very high safety profile. □



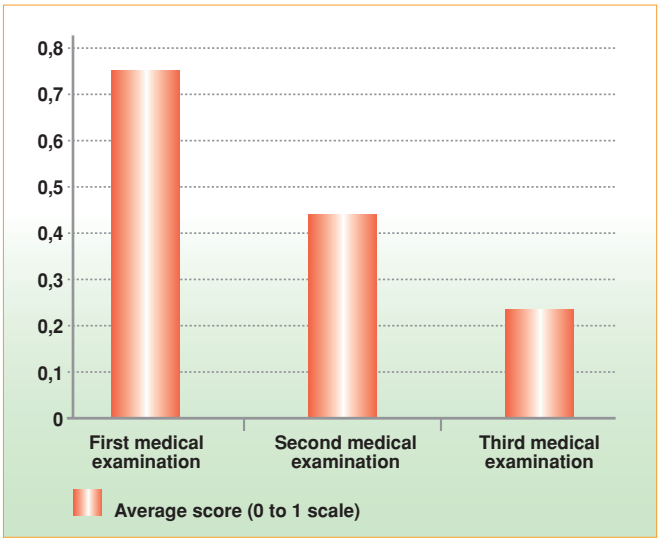
TAB. 5
VAS scale (0 to 10 points) – Patients' assessment of pain at rest.



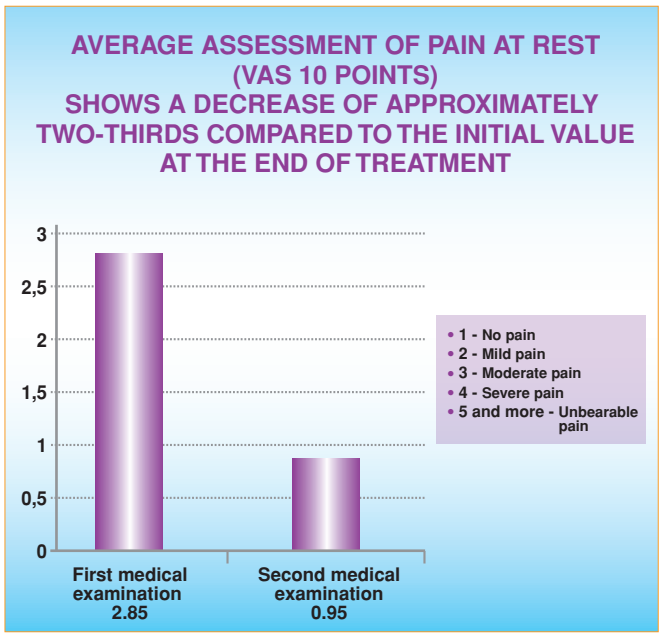
TAB. 6
VAS scale (0 to 10 points) – Patients' assessment of pain during movement.



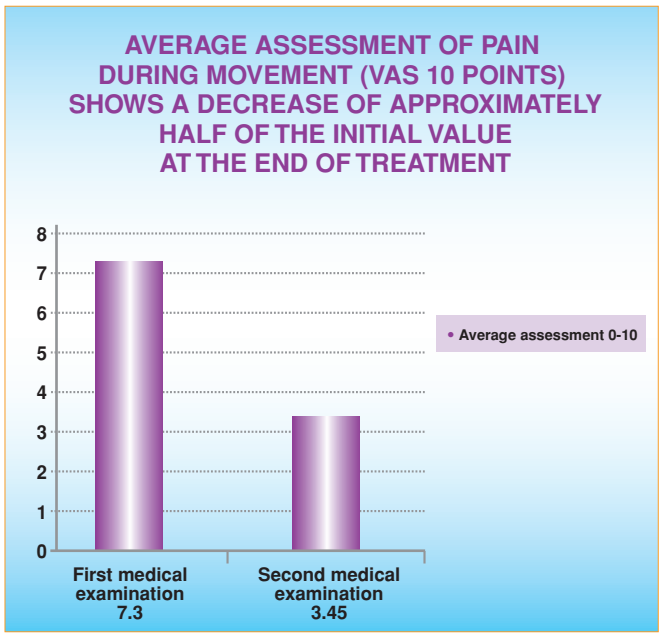
TAB. 7
Lequesne Algofunctional Index – Assessment of morning rigidity.



TAB. 8
Lequesne Algofunctional Index – Assessment of pain when standing.



TAB. 9

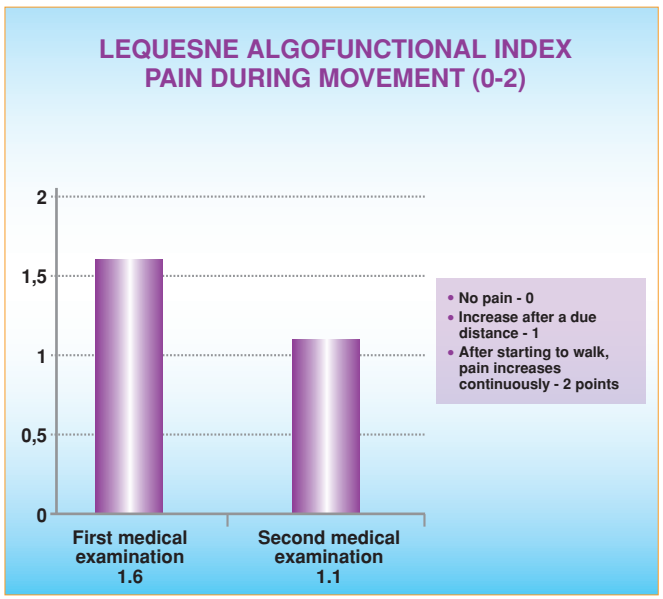


TAB. 10

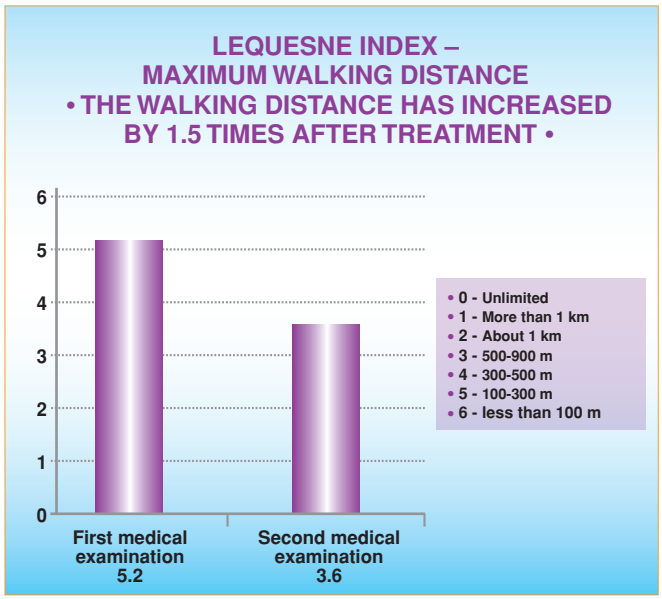
▶ APPLICATION AND ASSESSMENT OF EFFICACY OF COLLAGEN INJECTIONS GUNA MDs IN GONARTHROSIS

Author: Boshnakov D.
– Clinical Assessment presented at the XIX Days of Bulgarian Orthopedics and Traumatology, Tryavna, (September 2012).
Experimental sites: Saint Anne University Hospital, Varna (Bulgaria).
Pathologies considered: gonarthrosis.
Outcomes
1)assessment of pain at rest and during movement (VAS = 0-10);
2)assessment of Lequesne Algofunctional Index for:
a.pain when walking; b.maximum walking distance (in meters); c.daily activities;
3)assessment of efficacy of treatment from the patient's viewpoint.
Inclusion/exclusion criteria: unstated.
Patients enrolled: 14 (8 M; 6 F; aged 51-72).
Treatment: **MD-Knee**, 1 ampoule + **MD-Muscle**, 1 ampoule: 2 intra-articular and peri-articular injections/week for 2 consecutive weeks + 1 intra-articular and peri-articular injection/week for the following 6 weeks (total: 10 treatments in 2 months).

TAB. 11



TAB. 12



TAB. 13

A comparative analysis of the 4 clinical assessments on mild/moderate/severe gonarthrosis shows that Collagen MDs have been mainly administered through intra-articular and peri-articular injection and that: 1) they are are effective in 65-70% of cases on average; 2) the effects are long-lasting or improve over time; 3) they have a high safety profile.

Author/s	Year	Disease	Number of patients	Patient's age	Collagen MDs	Type of injection	Results
Posabella G.	2011	Patello-femoral chondropathy stage I-II-III according to Kellgren-Lawrence	20	31-66	**MD-Knee** + Zeel® T delivered through hyperbaric O2	Percutaneous	– Average WOMAC reduction from 50 to 39 points – Average reduction of Lequesne index from 17.05 to 10.4
Rashkov R. *et* Al.	2011	Gonarthrosis stage II-III according to Kellgren-Lawrence	28	55-70	**MD-Knee** + **MD-Muscle**	Intra-articular	Patients: excellent + good = 65%
Nestorova R. *et* Al.	2012	Gonarthrosis stage III-IV according to Kellgren-Lawrence	35	62-79	**MD-Knee** + **MD-Matrix**	Peri-articular	Patients: excellent + good = 68% Medical doctors: excellent + good = 72%
Boshnakov D.	2012	Gonarthrosis (without any other details)	14	51-72	**MD-Knee** + **MD-Muscle**	Intra-articular and Peri-articular	VAS – pain at rest: from 2.85 to 0.95 VAS – pain during movement: from 7.3 to 3.45 – Lequesne index from 1.6 to 1.1

L. Milani, 2013

Results

1) Pain at rest: VAS from 2.85 at treatment start (moderate pain) to 0.95 at the end of treatment (no pain) (TAB. 9).

2) Pain when moving: VAS from 7.3 at treatment start (unbearable pain) to 3.5 at the end of treatment (moderate/severe pain) (TAB. 10).

3) Lequesne Algofunctional Index: from 1.6 at treatment start to 1.1 at the end of treatment (TAB. 11); maximum walking distance from 100-300 meters before treatment (5.2 score) to 400-700 meters after treatment (3.6 score) (TAB. 12).

– Author's conclusions:

1)Intra-articular injections of Collagen MDs improve: a) localized pain; b) pain at movement; c) joint mobility.

2)Intra- and peri-articular injections improve the patients' functional activity and quality of life.

3)The injections of Collagen MDs are a new and effective method to treat gonarthrosis. □

▶ PATELLO-FEMORAL CHONDROPATHY TREATED WITH MD-KNEE + ZEEL® T TRANSMITTED WITH O2 *VERSUS* NIMESULIDE + CHONDROITIN SULPHATE

Author: Posabella G.

– Clinical trial presented at the Meeting Sport Medicine, the challenge for Global Health – Rome (September 2012). Article published in La Med. Biol., 2011/3; 3-11, and in PRM 2012/1; 3-10.

Pathologies considered: patella-femoral chondropathy stage I-II-III according to Kellgren-Lawrence.

Outcomes

assessment of clinical response (analytical WOMAC****; Lequesne Index) after administering **MD-Knee** + **Zeel®** T transmitted with hyperbaric O2 (Group A) versus nimesulide + chondroitin sulphate (Group B).

Inclusion/exclusion criteria: unstated; randomization.

Patients enrolled: Group A, 20 [15 M, 5 F; average age 46.4 years (31-66)]; Group B, 20 [15 M, 5 F; average age 46.9 years (28-65)].

Treatment: Group A – MD-Knee, 1 ampoule + Zeel® T, 1 ampoule, both applied onto the knee skin and transmitted with hyperbaric O2, 1 application/week.

Group B – nimesulide in 100 mg sachets + Condral (galacotosaminoglucuronoglycan sulphate sodium salt) 400 mg, 1/die per os.

Author's note

**** II **WOMAC** (Western Ontario and McMaster Universities Arthritis Index) measures 5 items for pain (score 1-20); 2 items for rigidity (score 0-8); 17 items for functional limitations (score 0-68).

Results
– After the first week of treatment the patients of both groups (A; B) showed a reduction of the total WOMAC score compared to baseline, even if not statistically significant.
WOMAC Group A = 50 points – Lequesne Index = 17.05
WOMAC Group B = 54 points – Lequesne Index = 17.9
-Second week
WOMAC Group A = 47 points
WOMAC Group B = 53 points
-Third week
WOMAC Group A = 44 points
WOMAC Group B = 51 points
-Sixth week (1st follow-up)
WOMAC Group A = 41 points
WOMAC Group B = 50 points
-Twelfth week (2nd follow-up)
WOMAC Group A = 39 points - Lequesne Index = 10.4
WOMAC Group B = 47 points - Lequesne Index = 15.3

– Author's conclusions:
1)Both Groups of patients (A; B) showed a considerable improvement of pain and functional limitation.
2)The data show a more rapid clinical and functional improvement in the patients of Group A compared to the patients of Group B.
3)No side effects in the patients of Group A. □

– For comparative analysis of the 4 clinical trials on the osteoarthritis of the knee *see* TAB. 13.

HIP JOINT

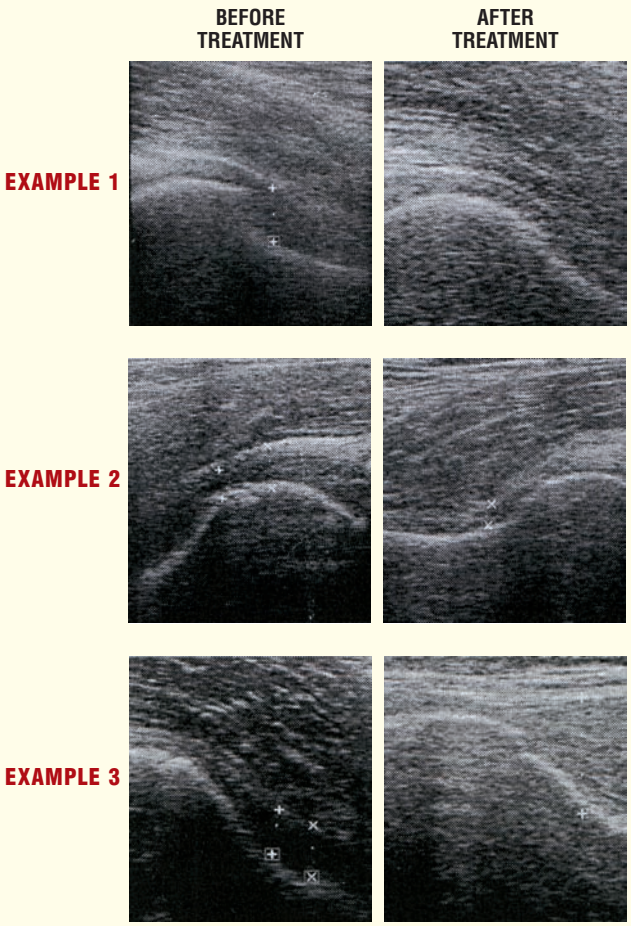
▶ INTRA-ARTICULAR ADMINISTRATION OF MD-HIP IN 7 PATIENTS AFFECTED BY HIP OSTEOARTHRITIS UNRESPONSIVE TO VISCOSUPPLEMENTATION. -SIX MONTH MULTICENTER TRIAL

Authors: Migliore A., Massafra U., Bizzi E., Vacca F., Tormenta S.
– Clinical trial presented at the International Symposium Intra Articular Treatment; Rome (October 2011).
Experimental sites: UOS (Simple Operating Unit) of Rheumatology – San Pietro Fatebenefratelli Hospital, Rome.
Pathologies considered: osteoarthritis X-Ray I-III stage according to Kellgren-Lawrence affecting the hip joint unresponsive to viscosupplementation with hyaluronic acid (6 patients) or hylan (1 patient) (2 ultrasound guided injections at least).
Outcomes
1)assessment of efficacy using VAS scale and Lequesne algofunctional Index;
2)NSAIDs consumption before treatment and during follow-up;
3)safety profile of MD-Hip.
Patients enrolled: 7
Treatment: **MD-Hip** (2 ampoules = 4 ml), 1 ultrasound guided intra-articular injection.
Results
1)VAS of osteoarthritis pain = from 6.15 (before treatment) to 4.23 (after 3 months), to 4.23 (after 6 months).
2)Lequesne Index = from 1.94 (before treatment) to 5.9 (after 3 months), to 5.83 (after 6 months).
3)NSAIDs consumption = from 7.57 (before treatment) to 4.25 (after 3 months), to 5.78 (after 6 months).

– Author's conclusions:
1)MD-Hip showed to be effective (all the average values of the results at 3 and at 6 months after the last treatment have been statistically significant) and safe in patients affected by hip osteoarthritis unresponsive to viscosupplementation.
2)The data suggest that the results can be evident from the very first injection and are stable for 6 months.
3)The preliminary data offer new research opportunities in the field of intra-articular therapy. □

▶ EFFICACY OF INJECTIONS MD-HIP AND MD-MATRIX IN TREATMENT OF COXARTHROSIS. – CLINICAL AND ULTRASONOGRAPHIC EVALUATION

Author: Tivchev P.
Article published in Bulgarian Journal of Orthopaedics and Traumatology. Vol 49/2012; 123-8
Experimental sites: Serdika Hospital (Sofia); Deva Maria Hospital (Bourgas – Bulgaria)
Pathologies considered: x-Ray stage I-II-III hip osteoarthritis according to Kellgren-Lawrence.
Outcomes
1)evaluation of pain at rest and when moving (VAS 0-10);
2)evaluation of Lequesne Algofunctional Index (hip) before and after treatment;
3)patient's evaluation after treatment;
4)evaluation of joint edema before and after treatment;
5)medical examination at day 60 and 90 after the beginning of treatment.
Inclusion/exclusion criteria: stated.
Patients enrolled: 16 (7 M; 9 F; aged 33-89; average age 65.5 years).
Treatment: **MD-Hip**, 1 ampoule + **MD-Matrix**, 1 ampoule: 2 intra-articular injections according to Scott-Pollock technique for 2 consecutive weeks + 1 intra-articular injection for the following 6 weeks (total 10 treatments during 2 months).
Results
1)Statistically significant reduction of pain at rest (VAS from 2.43 before treatment to 1.31 at day 60, to 1.62 at day 90).
2)Statistically significant reduction of pain when moving (VAS from 3.43 before treatment to 2.18 at day 60, to 2.37 at day 90).



TAB. 14

3)Statistically significant improvement of the single items and of the values expressed by Lequesne Algofunctional Index in general (hip); from 10.47 before treatment to 5.65 at day 60, to 5.78 at day 90.
4)Assessment of joint effusion: at day 90 after treatment start 12 patients out of 16 (75%) did not experience any effusion (examples in TAB. 14); 3 patients = effusion reduction; 1 patient = unchanged effusion.
5)Patient's assessment: efficacy in 87.5% of cases.

– Author's conclusions:
1)The Collagen Medical Devices MD-Hip + MD-Matrix showed to be clinically effective against pain due to X-Ray stage I-III hip osteoarthritis according to Kellgren-Lawrence.
2)The efficacy is long-lasting; it lasts over 3 months, i.e. for a longer period than that of the drugs that are usually used to cure the same disease.
3)The treatment leads to a general improvement of daily activities.
4)Stage III-IV hip osteoarthritis cannot be cured with Collagen Medical Devices, as the effect is poor and short-lasting.
5)The ultrasound examination showed a long-lasting effect on the resorption of the effusion, which continues 3 months after the last injection.
6)The patients have assessed the therapeutic results as very good + excellent in more than 80% of cases. This percentage is the same as for doctors.
7)The Collagen Medical Devices used in this clinical assessment did not show any negative side effect, and have an excellent safety profile. □

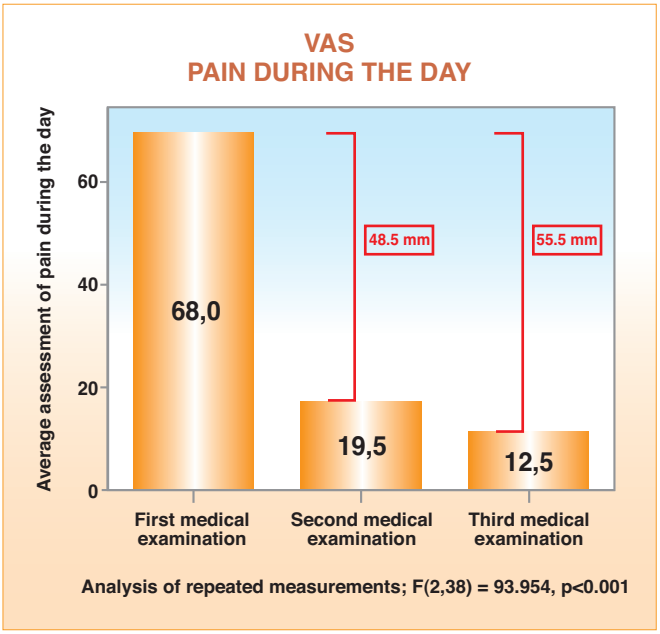
SHOULDER JOINT

▶ COLLAGEN INJECTIONS OF GUNA MDs IN PATIENTS WITH ACUTE SHOULDER PERIARTHRITIS – CLINICAL AND SONOGRAPHIC ASSESSMENT

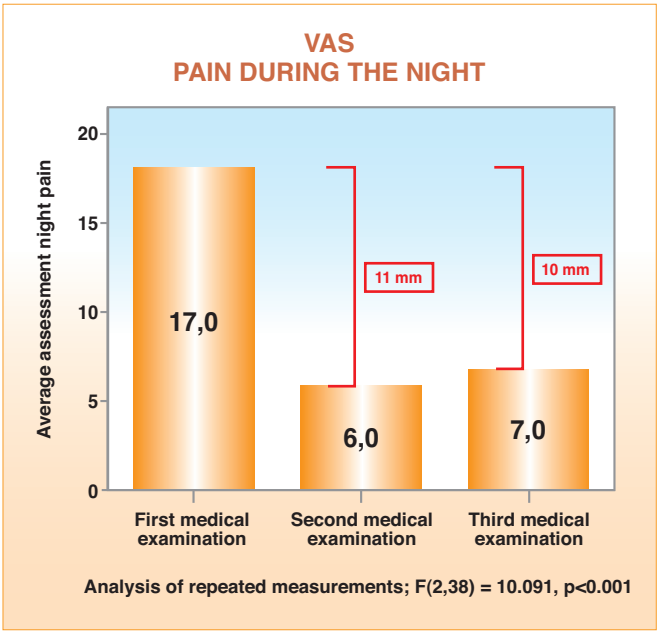
Authors: Nestorova R., Rashkov R.
– Clinical Assessment presented at 3rd Bulgarian National Congress on Osteoporosis and Osteoarthritis – Sandansky (November 2012).
Experimental sites: Rheumatological Division of the University of Medicine, Sofia (Bulgaria).
Pathologies considered: shoulder peri-arthritis lasting for more than 3 months accompanied by subacromial subdeltoid bursitis, VAS > 25 (1-100).
Outcomes
1) assessment of day and night pain (VAS 0-100);
2) assessment of shoulder mobility (Likert Scale***** 0-4);
3) assessment of shoulder function/SFA (author's note: *Schulter-Fix Abdukt*);
4) patient's and doctor's assessment of efficacy.
The 4 outcomes have been assessed before treatment, at day 60 and day 150.
Inclusion/exclusion criteria: stated.
Patients enrolled: 20.
Treatment: **MD-Shoulder**, 1 ampoule + **MD-Matrix**, 1 ampoule: 2 peri-articular injections/week for 2 consecutive weeks + 1 peri-articular injection/week for further 6 weeks (total 10 treatments during 2 months).
Results
1)VAS- day pain: from 68.0 to 19.5 (60 days), to 12.5 (150 days) (TAB. 15).
2) VAS- night pain: from 17.0 to 6.0 (60 days), to 7.0 (150 days) (TAB. 16).
3) Likert Scale: from 1.5 to 2.5 (60 days), to 2.6 (150 days) (TAB. 17).

Author's note

***** **Likert Scale** is a means to assess one's attitude. Likert Scale aims at being a simple method of assessment, submitting a series of statements to a patient concerning the object of attitude, asking to express a certain degree of agreement or disagreement with a certain statement.



TAB. 15

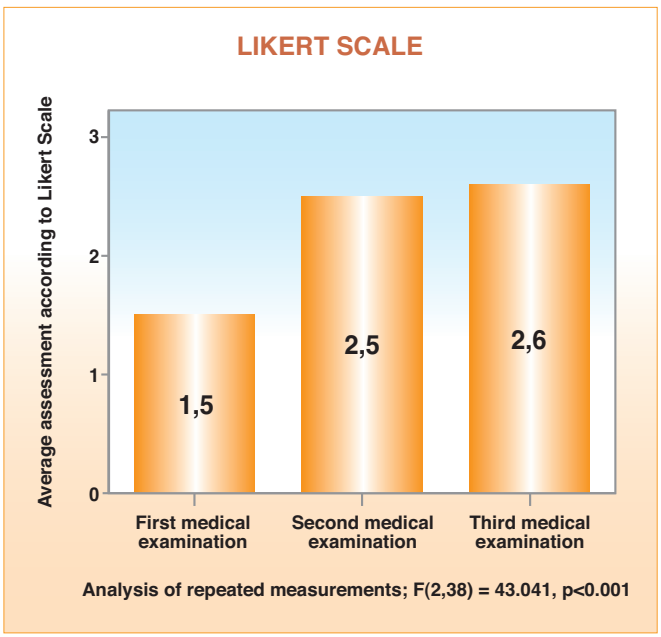


TAB. 16

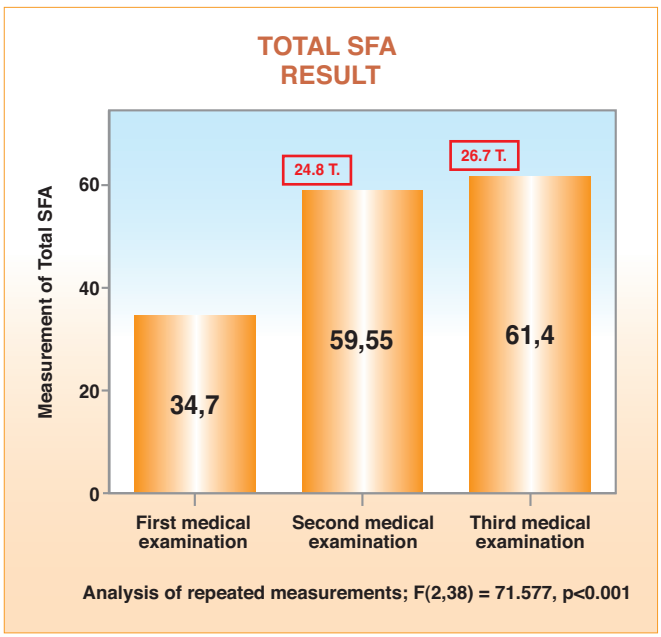
4) Total SFA: from 34.7 to 59.55 (60 days), to 61.4 (150 days) (TAB. 18).
5) Patients' assessment: excellent + good results = 80%
6) Doctors' assessment: excellent + good results = 85%
7) Ultrasound assessment of bursitis = from 1.0 to 0.2 (60 days), to 0.2 (150 days).

– Authors' conclusions:
Collagen MD-Shoulder and MD-Matrix:
1)Help strengthen and regenerate the collagen structures and improve significantly the shoulder pain and the functional status as well as the tension of the subdeltoid bursa.
2)The efficacy of the tested Collagen MDs continues to last after the end of treatment, and improves the patients' quality of life.
3)The Collagen MDs have shown to be completely safe (no side effects). □

TAB. 17



TAB. 18



▶ BENEFITS OF MD-SHOULDER + HYPERBARIC OXYGEN THERAPY IN THE POST-TRAUMATIC TREATMENT OF THE SHOULDER

Author: Posabella G.
– Clinical trial presented at the II Conference of Clinical and Forensic Traumatology – 9th Course of Orthopedics, Traumatology and Forensic Medicine, New approaches to the treatment of degenerative and traumatic diseases of the upper limbs. Salsomaggiore Terme (Parma, Italy) (November 2011).
Pathologies considered: Pain at rest and when moving in traumatized sportspeople.
Outcome
Verification of improvement after treatment through filling out the Shoulder Rating Questionnaire (SRQ) [min 12 (worst situation) – max 75 (best situation)].
Inclusion/exclusion criteria: unstated.
Patients enrolled: 18 (both genders; average age 34 years), amateur athletes of different sports.
Treatment: **MD-Shoulder**, 1 ampoule administered with hyperbaric oxygen 2 times/week for 5 consecutive weeks (total 10 treatments of 30 minutes each).
Results
The average score of the SQR goes from 42 ± 14.2 before treatment to 55 ± 11.0 after treatment.

– Author's conclusions:
1)A statistical analysis has shown a statistically significant difference between the data collected before and after treatment.
2)Pain at rest, pain when moving and functional limitations have improved. □

RACHIS JOINTS

▶ EFFICACY OF INTEGRATIVE MEDICINE IN BACK PAIN MANAGEMENT: OBSERVATIONAL STUDY

Authors: Zocco R., Crisciuolo S., Lorenzetti N., Senesi M.
– Clinical trial presented at the V European Congress for Integrative Medicine. The Future of Comprehensive Patient Care -ECIM 2012, Florence (September 2012).
Article published in PRM 2012/1 (abstract).
Experimental sites: Integrative Medical Practice for Pain Management of ASL (Healthcare Public Service) 7 of Siena, Italy; Hospital of Rehabilitation and Functional Rehabilitation.
Pathologies considered: spine disorders – Painful Minor Intervertebral Disorders (PMIDs): lumbar 92%; dorsal 68%; sacral 39% (lumbar + dorsal MIDs = 37%: dorsal + sacral MIDs = 13%):
– for 6 months at least
– unresponsive to physical and drug therapies.
Patients enrolled: 60 (19 M, 41 F; 19-70 years; average age 45.08 ± 13.52 years).
Treatment: acupuncture + specific MDs for the different segments of the spine: 1 application/week for 10 consecutive weeks; manipulative therapy according to Maigne; sessions of 3 consecutive weeks.

– Results and **Authors' conclusions:**
The benefits from manipulative therapy according to Maigne are more evident in the short run; the benefits from acupuncture + Collagen MDs are more evident in the long term. □

▶ MD-LUMBAR, MD-MUSCLE AND MD-NEURAL IN THE LOCAL TREATMENT OF LUMBAR PAIN

Authors: Pavelka K., Svodobová R., Jarõsová H.
– Clinical trial presented at the 26th Congress of Biological Medicine, Milan, Italy (May 2012).
Article published in La Medicina Biologica 2012/4 (Congress Proceedings); 13-17, and in PRM/2012; 3-6.
Experimental sites: Institute of Rheumatology of the First Faculty of Medicine – Charles University – Prague (Czech Republic).
Pathologies considered: acute back pain.
Outcomes
1) comparison of the different intensity between baseline pain and pain recorded in the 2 Groups at the final medical examination;
2) functional improvement measured according to Oswetry Low Back Pain Questionnaire;
3) comparison concerning the use of emergency drugs;
4) evaluation of tolerability.
Patients enrolled and **Treatment**:
Group A = 36 patients = **MD-Lumbar**, 1 ampoule + **MD-Muscle**, 1 ampoule + **MD-Neural**, 1 ampoule in 8 predefined subcutaneous points;
Group B = 12 patients = mesocain 1% (4 ml injected in the same 8 predefined subcutaneous points).
Results
1) Pain at rest:
– Group A: VAS from 59.6 ± 16.9 to 28.1 ± 24.1.
– Group B: VAS from 57.3 ± 16.4 to 25.1 ± 26.9.
2) Pain during movement:
– Group A: VAS from 70.1 ± 13 to 36.6 ± 23.5.
– Group B: VAS from 70.8 ± 11.5 to 31.9 ± 26.8.
3) Paracetamol consumption during the trial (total number of tablets): Group A = 14.4; Group B = 20.4.

– Authors' conclusions:
1) MD-Lumbar + MD-Muscle + MD-Neural are effective in acute back pain management;
2) MD-Lumbar + MD-Muscle + MD-Neural are well tolerated.

3) The Collagen MDs are an innovative, effective and safe option in acute back pain management. □

CONCLUSIONS

Ten clinical trials (or assessments) have been reported in this work in their most important and synoptic points. They represent the total number of trials (or assessments) carried out between 2010 and 2012 with Collagen Medical Devices (Guna Laboratories – Milan, Italy) for the local treatment of arthro-rheumatic pathologies. These trials (or assessments) have also been presented 2-3 times at national and international medical and scientific congresses (10 out of 10).
The analysis of these trials leads to drawing some general and specific considerations which help position the Collagen Medical Devices as a high quality innovative local treatment due to:

1) High individual clinical response (average assessment excellent + good in 75% of patients; the same percentage has also been indicated by medical doctors);

2) High objective clinical response according to Tests, Scales, Indexes widely used in medical and scientific international literature, such as VAS, WOMAC, Lequesne Algofunctional Index, Likert Scale, SRQ, SFA, Oswetry Low Back Pain Questionnaire, in addition to ultrasound examination in some trials (or assessments).

3) Maintenance of results beyond the last injection/application, as well as of the positive ultrasound variation, when indicated by the Author/s.

4) Total absence of adverse side effects in all the 10 clinical trials (or assessments) (very high safety).

5) No or very little use of analgesics/anti-inflammatory drugs during the clinical trial (or assessment) period.

6) The injectable Collagen Medical Devices used – when compared to conventional drugs of proven effectiveness (paracetamol, mesocain, NSAIDs) or physical therapy – have demonstrated therapeutic superiority or equality in both minor diseases such as X-Ray I, II Stage gonarthrosis according to Kellgren-Lawrence and PMIDs (Painful Minor Intervertebral Dysfunctions) and in major pathologies such as severe gonarthrosis (X-Ray stage IV according to Kellgren-Lawrence) and hip osteoarthritis unresponsive to viscosupplementation with hyaluronic acid and its derivatives.

7) Efficacy of Collagen Medical Devices also in acute cases.

8) Efficacy of Collagen Medical Devices also in the elderly (average age range for chronic diseases: ≈ 70-75 years).

9) Versatility and ease of use. The Collagen Medical Devices have been used alone or, more frequently, in combination with each other (mainly 2 - mixed in the same syringe) and have been injected: peri-articular (2 times out of 10), peri-articular + intra-articular (1 time out of 10), intra-articular (3 times out of 10), subcutaneous (2 times out of 10); percutaneous (2 times out of 10).

10) Possibility of combining the injectable local treatment with the Collagen Medical Devices with other physical therapies. ■

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See also:

1) Milani L. – La Med. Biol., 2010/3; 3-15.
2) Milani L. – La Med. Biol., 2011/1; 71-3 *(Lettere al Direttore).*

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Author's notes:

1) All the clinical trials and the clinical assessments collected into this Review were presented as Reports or in the Poster Session of national and/or international Congresses. Some of them have been published. Concerning all the others, some articles are being prepared in order to be submitted to the referees of some important international journals for publication.
   Those not yet published may be mentioned **only after their publication**.
   – As an alternative, they may be mentioned with specific reference to **this publication**.
2) Eight out of ten clinical trials or clinical assessments were conducted spontaneously and independently. The clinical trials of Migliore A. *et* Al., and Pavelka K. *et* Al. are part of the Guna's Clinical Research Project (see Milani L. *and* Ricottini L. - La Med. Biol. 2012/4, 29-39).
3) In order to be brief, not all the Tables attached to the original works of the Authors of all the clinical trials and Clinical Assessments have been reported.
4) The Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17 and 18 have been translated and assembled for graphic needs and editorial consistency and are faithful to the original graphics and text.
5) The following Figures:
   1 was translated and developed by the author (author's caption).
   3 and 4 have been assembled by the author (author's captions).
6) Table 13 has been developed by the author.

The author thanks the editors of the Web sites from which the pictures have been taken:

Fig. 1: http://www.bio-collagene.com/images/fibroblast.jpg
Fig. 2A e 2B: fonti bibliografiche nel testo *(vedi).*
A: http://www.sciencedirect.com/ e
B: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig4B.jpg
Fig. 3A e 3B: fonte bibliografica nel testo *(vedi).*
Fig. 4A: http://www.aafp.org/afp/2003/0901/afp20030901p907-f2.jpg
B: http://www.fitmed.ro/afectiuni/genu%20valgum.jpg
C: http://www.knee-replacement-explained.com/images/OSTEOTOMY.jpg
D: http://www.stevewhitekneeclinic.com/wp-content/uploads/2010/10/kneeclinic30-505x358.jpg

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