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CLINICAL

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THE TREATMENT OF RHIZOARTHROSIS WITH COLLAGEN MEDICAL DEVICE SMALL JOINTS

SUMMARY

Rhizoarthrosis is a very widespread disease; it affects 20% of the adult population and represents about 10% of all osteoarthritic locations; it is more frequent in females than in males (4:1 ratio). The initial symptom is TM pain followed by difficulty in performing daily activities such as turning a key or opening a bottle. The treatment is initially conservative with the application of immobilization braces and the simultaneous use of chondroprotectors. If this treatment is not effective, before undertaking the definitive surgical treatment, infiltrative therapy with Collagen may be considered. Collagen MDs improve the mechanical qualities of the joint capsule by restoring the anisotropic characteristics of the tissue with an evident positive effect on the "joint hypermobility stabilisation", movement, pain and quality of life.

– The purpose of this trial is to evaluate the efficacy of the endo- and peri-articular injection of MD-Small Joints in patients suffering from rhizoarthrosis before undergoing definitive surgical therapy.

In this clinical study, 22 patients (3 M; 19 F) were included and assessed for 10 weeks with the DASH, VAS scales and Grind Test.

The treatment was well tolerated, and no side effects were observed. The improvement obtained was approximately 60-80% of all rating scales. This trial shows that clinical improvement is directly proportional to the reduction in joint laxity and is therefore a function of the effectiveness of MD-Small Joints on joint collagen.

KEY WORDS **RHIZOARTHOSIS, COLLAGEN MEDICAL DEVICE, MD-SMALL JOINTS, HAND PAIN, DASH, VAS, GRIND TEST, COLLAGEN**

RHIZOARTHROSIS

Rhizoarthrosis (RA) is a type of arthritis that affects the **trapeziometacarpal (TM) joint**. The etymology of the term 'rhizoarthrosis' is Greek: *rizos* means "root"; this joint, in fact, is located at the root of the thumb.

– RA is a widespread condition; it affects **20%** of the adult population (Barra *et* Al., 2003) and represents approximately **10%** of all osteoarthritic localisations in the human body (Sollazzo *et* Al., 2006). RA is more frequent in females than males (4:1 ratio) and generally occurs between the fifth and sixth decades of life.

In women, it frequently begins at menopause, while in men it is more related to overuse phenomena (Bonola *et* Al., 1981).

The TM joint plays a key role in normal thumb function: all gripping actions overload the TM joint because the axis of the thumb exerts force and acts as a fulcrum on this joint.

This force transmits a radial stress at the base of the metacarpal, which, over time, causes a reduction in the tension of the capsuloligamentous system (Bernardini, 2018), resulting in joint hyperlaxity and subluxation of the first metacarpal.

• The preternatural movement of the bone heads alters the joint surface; there is a progressive thinning of the cartilage and subsequent onset of pain and arthritis. Symptomatology is bilateral in 50% of cases.

FUNCTIONAL ANATOMY

The TM joint can be considered the most complex joint of the human body as it allows the thumb to perform volo-volar pincer grips with the long fingers; in other words, it allows the hand to perform its most distinctive function: opposition, that is, prehension (Caroli, 1996).

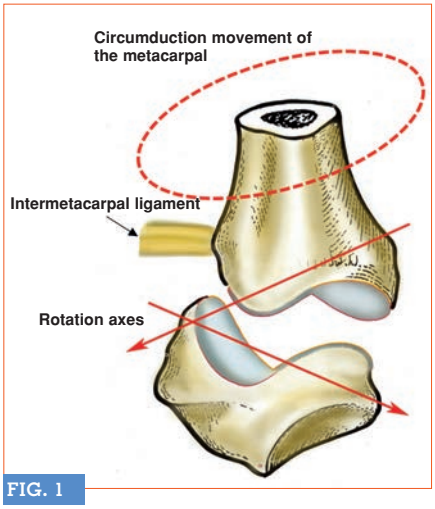


FIG. 1

Trapeziometacarpal joint.

Kapandji (1971) defined the TM joint as a reciprocal interlocking or saddle-shaped joint and compared it to a rider in the saddle with perfectly matching torus-shaped contact surfaces (Bonola *et* Al., 1981).

The movements take place on two perpendicular axes and their combination allows for a true circumduction, conditioned by the intermetacarpal ligament, which acts as a pivot (FIG. 1,2).

The structures that support and stabilize this joint are the capsule, the extracapsular ligaments and the intrinsic and extrinsic muscles.

The capsuloligamentous structures of the TM joint are extremely important, both in providing stability and in guiding the complex movements of the thumb.

The joint capsule is very lax and fits along the contour of the articular surfaces of the trapezium and the base of the metacarpal. This laxity is determined by the fact that the first metacarpal must allow for ample movement and rotation of the metacarpal along its own longitudinal axis (Caroli, 1996).

▶ Ligaments of the capsule

The ligamentous system is equally important because, in addition to ensuring the stability of the TM joint, its maximum tension allows stopping the various movements of the first metacarpal bone, assisted by the fascial and muscular structures in this function.

It should also be noted that the TM ligaments, through their insertion, help to guide the movements of the thumb and mainly those of axial rotation.

A number of thickenings depart from the joint capsule, giving rise to the following ligaments:

- the dorsoradial ligament (DRL) or Arnold's external trapeziometacarpal ligament stops abduction and favours rotation in pronation of the metacarpal joint;
- the dorsoulnar ligament (DUL) or Arnold's internal trapeziometacarpal ligament, which is very thick and wide, stops the retroposition movement and favours rotation in supination of the metacarpal;
- the anterior oblique ligament (AOL). Some authors describe two portions of this ligament: a superficial one and a deep one (beak ligament), which is particularly important in stabilising the TM joint in the degrees of maximum abduction and retroposition movement of the thumb;
- the fibrous, thick and short intermetacarpal ligament (IML): it stretches between the base of the first and second metacarpals; this ligament stops the abduction movement of the first metacarpal.

  The IML is crucial because its loosening causes external subluxation of the base of the first metacarpal, which, as explained below, is one of the most important causes of **joint instability** (Caroli, 1996) (FIG. 2).

- DRL = Dorsoradial Ligament
- DUL = Dorsoulnar Ligament
- AOL = Anterior Oblique Ligament *(beak ligament)*
- IML = Intermetacarpal Ligament

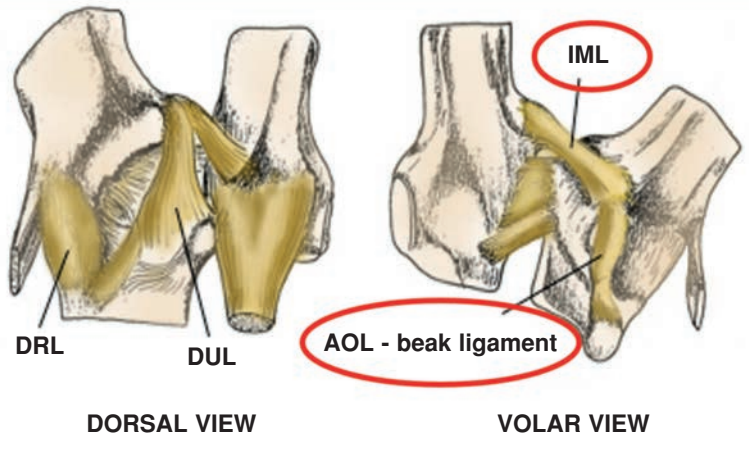


FIG. 2

Ligaments of the trapeziometacarpal joint.

▶ Motor muscles of the thumb

As indicated by Kapandji (1971), the TM joint works in compression as a joint. The intrinsic thenar muscles allow the first metacarpal to orient in all directions of space, as if it were a pile whose orientation can be changed by changing the tension of the cables. According to the author, the muscular components provide support to joint coaptation in all positions, resulting from the synergistic activation of agonist and antagonist muscles (Brunelli *and* Brunelli, 1996).

Mobility is the essential opposition function of the thumb; it is enabled by nine motor muscles:

- Four extrinsic or long muscles located in the forearm. Three are for grip opening movements: The *extensor pollicis longus*, *extensor pollicis brevis*, and *abductor pollicis longus*; and one for power grip: *flexor pollicis longus*. As a reminder, the extrinsic muscles are the motor muscles for power gripa;

- Intrinsic muscles located in the thenar eminence and first interosseous space; they provide for precision and coordination during different grips and opposition.
  – The external group is composed of three muscles (*opponens pollicis*, *abductor pollicis brevis*, and *flexor pollicis brevis*) that have a synergistic function of thumb opposition.
  – The internal group consists of the adductor and first palmar interosseous muscles.
  These are crucial for gripping/holding objects, because they also perform their action on the **MP (metacarpophalangeal)** and **IP (interphalangeal) joints** (flexion of the former and extension of the latter), making the opposition grip with the index finger more effective.

Opposition is not a fixed movement: indeed, there is a range of oppositions that execute a great variety of grips and actions according to the number of fingers involved and their mode of association (Kapandji, 1971).

- Bi-digital grips give the classic pincer grips between the thumb and index finger; there are 3 types: terminal, subterminal, and subterminolateral.

– The terminal opposition grip is the finest and most precise because it makes it possible to firmly grasp a small object or pick up a very thin object.
The thumb opposes the nail surface of the index finger with the fingertip.
In this grip, as the metacarpal wedges into the trapezius, it protects the joint capsule from any tensional forces and avoids degenerative effects on the joint (FIG. 3).
– The subterminal grip is the most recurrent and instinctive one: the thumb and the index finger oppose each other with the palmar face of the fingertip and this way can grip objects of different calibre, even thin ones, such as a sheet of paper or a pencil.
In this grip, a significant tensive force is created radially at the base of the metacarpal that stretches the joint capsule and the intermetacarpal ligament, making them increasingly lax over time.

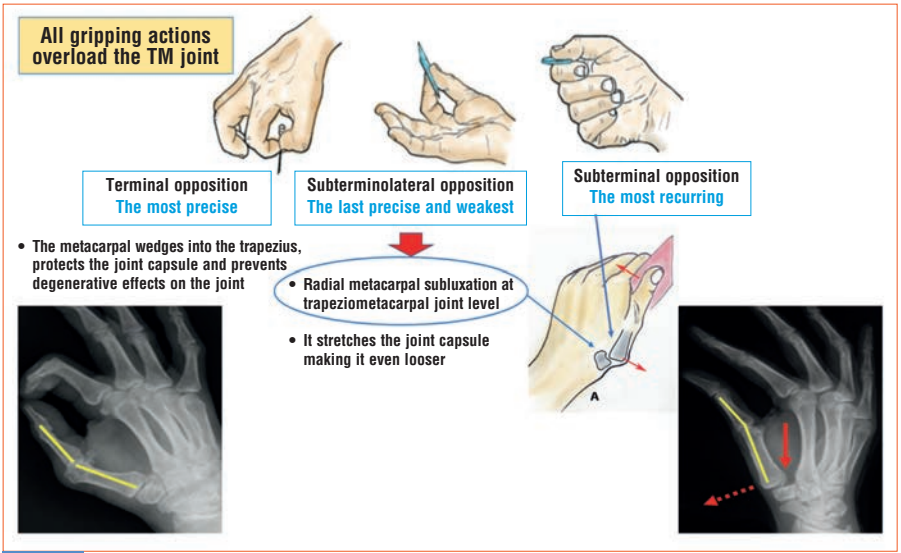


FIG. 3

Effects of grip on the trapeziometacarpal joint.

This laxity produces joint instability, the cause of radial subluxation of the metacarpal and joint degenerative processes.
– The subterminolateral grip is the least fine and weakest compared to the previous ones.
The palmar aspect of the pulp of the thumb rests on the external aspect of the first phalanx of the index finger, creating, in this case too, great radial tension at the base of the metacarpal resulting in the tendency of the TM joint to develop subluxation (Kapandji, 1971).

- The cause of RA always lies in TM joint **instability**.

It can be primary or secondary (TAB. 1).

In ligamentous hyperlaxity, instability is due to an excessive range of motion.
In this case, the palmar ligament (beak ligament) is of great importance, as it limits the hyperextension of the metacarpal and, above all, the intermetacarpal ligament between the base of the first and second metacarpals, which counters the subluxation of the first metacarpal radially, without limiting other movements (FIG. 2).
Laxity and/or degeneration of this ligament produce abnormal TM joint movements, with incongruity of the articular surfaces rapidly triggering degeneration.
– Another known cause that Brunelli (2007) considers to be the most frequent is instability due to the absence of ab-

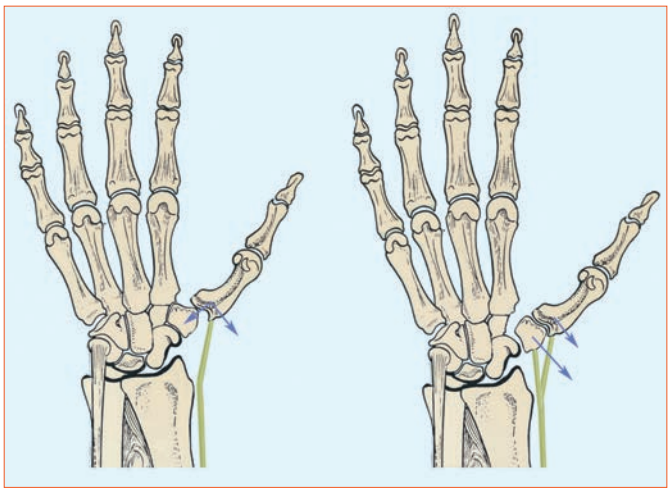
PRIMARY INSTABILITY	SECONDARY INSTABILITY
Hypoplasia of the trapezium, abnormal obliquity of its saddle	Traumatic capsular ligament lesion
Congenital capsular ligament laxity	Outcome of fracture of the trapezium or the base of the first metacarpal
Muscle imbalance due to the absence of insertion of one of the APL tendons on the trapezium	Operational stress due to repetitive work with strong thumb adduction
Muscle hypotonia of the non-dominant hand in elderly people	

TAB. 1

Causes of the trapeziometacarpal joint instability.

FIG. 4

Instability due to the absence of intersection of *abductor pollicis longus* in the trapezium. – Tensive forces.



ductor pollicis longus **(APL)** insertion on the trapezium. In cases where the APL has distal double insertion on the trapezium and on the base of the first metacarpal, with each contraction of the APL the entire thumb-metacarpal-trapezium column shifts in abduction, maintaining normal trapeziometacarpal joint relationships.
Conversely, if there is no insertion on the trapezium, all abductor force is exerted on the base of the first metacarpal, causing significant subluxation tension with a deleterious shear effect on, and cartilage damage, of the TM joint (FIG. 4).
– Repeated stress (overuse) is another frequent cause of TM joint arthritis; the TM joint is subjected to a considerable workload, as it is involved in approximately 50% of all actions of the hand.

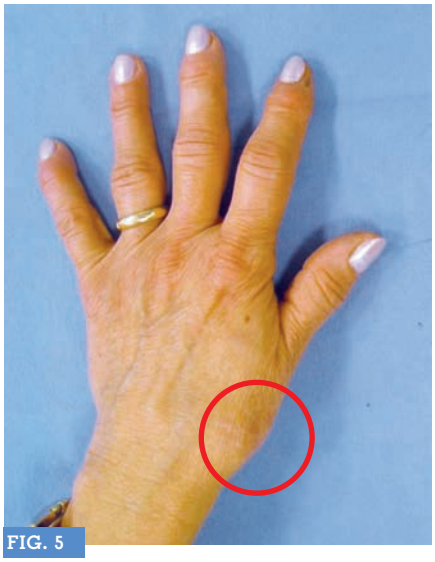


FIG. 5

Subluxation of the first metacarpus.

It is possible to distinguish some activities and habitual gestures that favour the deterioration of the articular surfaces: the repeated prehension of small objects exerts radial stress on the TM joint that does not allow the base of the metacarpal to stay in contact with the articular surface of the trapezium (FIG. 3).
The luxation force transmitted on the metacarpal can be multiplied up to 12-120 times (Cooney *and* Chao, 1977).

SYMPTOMATOLOGY

TM joint instability is often asymptomatic; over time, pain develops, leading the patient to consult a physician.
– The most frequent clinical picture is initially represented by an annoying pain localised at the base of the thumb that appears when active movements in radial abduction such as grips or pincer movements are performed, and/or passive movements in rotation-opposition such as turning a key, unscrewing a cap, turning a handle, writing with a thin pen or even just buttoning a shirt (Dias *et* Al., 2006).
The patient complains of decreased hand strength and mobility.
Later, the pain appears even at rest, at night, and may radiate to the wrist and forearm. In more advanced stages, pain is spontaneous and is associated with bone crepitus due to joint laxity.

– The patient does not "use" the thumb well to avoid pain: over time, this causes muscle weakness in the stabilisation structures of the TM joint; the metacarpal loses the ability to slide on the trapezium along the adduction-abduction axis, in addition to which there is a radial shift of the base of the metacarpal.

The loss of congruence between the bone heads affects the mechanical stability of the joint: it results in dislocation, consequently decreasing movement amplitude (Pomerance, 1995).
During abduction movements, the joint capsule is stretched.
Some capsular fibres are weakened, leading to the dorsal subluxation of the base of the metacarpal; therefore, when the *adductor pollicis* and *flexor pollicis brevis* muscles contract, they pull the distal part of the metacarpal toward the palm.
The result is a "tilt" of the articular surface at the base of the metacarpal on the saddle of the trapezium.

- This tilt, though imperceptible, is the cause of the pain.

That is why, in cases of RA, holding and turning a key, lifting a cup or writing are actions that cause pain: in fact, these actions, although with movements that require little articulation, stress the TM joint and its means of containment (Dias *et* Al., 2006).

– The prevalent clinical signs are:
- deformation and swelling at the base of the first metacarpal (FIG. 5), caused by a combination of dislocation, joint inflammation, and osteophyte formations;
- 1st ray in adduction, more common in advanced stages;
- pain on palpation;
- positive axial compression test or Grind test: the axial load on the trapezium, together with the rotation of the metacarpal, trigger pain at the base of the thumb;
- TM joint dislocation, with or without rotation, which causes stretching of the capsule, which, if inflamed, is painful.

As the disease progresses, TM joint subluxation produces a radial deviation of the MP of the thumb due to the contracture in adduction of the first metacarpal, which is followed by a flexion of the IP, generating a picture of "Z-thumb". This is an expression of one of the most compromised pictures of RA in which, in addition to the TM joint, the MP in hyperextension and IP in flexion are involved.

RADIOGRAPHIC PICTURE – THE EATON-LITTER CLASSIFICATION

RA can be diagnosed through a careful physical examination.
X-rays of the thumb in 3 planes and the particular stress view of the basal joint are necessary to confirm the diagnosis.
The view for the basal joint under stress, when performed correctly, provides an excellent image for assessing the degree of TM joint subluxation.
In this 30° oblique view, the patient is asked to press the tips of the thumbs against each other while the X-ray is being performed (FIG. 6).

X-rays should always be interpreted in relation to the patient's clinical situation. Often, patients with very compromised radiographic pictures report very little or no pain; others with negative or insignificant X-rays may present severe functional deficits with significant impact on daily and/or work activities. There is no indication for MRI and/or ultrasound; only CT may be useful as an additional preoperative investigation.

– Eaton and Glickel (Glickel, 2001) described a method for classifying pathological changes in RA based on the appearance in standard radiographic views and those under stress.
This method has also proven to be useful in medical planning and, if needed, surgery.
– At present, the most widely used classification is the Eaton-Littler classification modified by Brunelli (Barra *et* Al., 2003) which includes both the radiographic picture and clinical picture (TAB. 2).

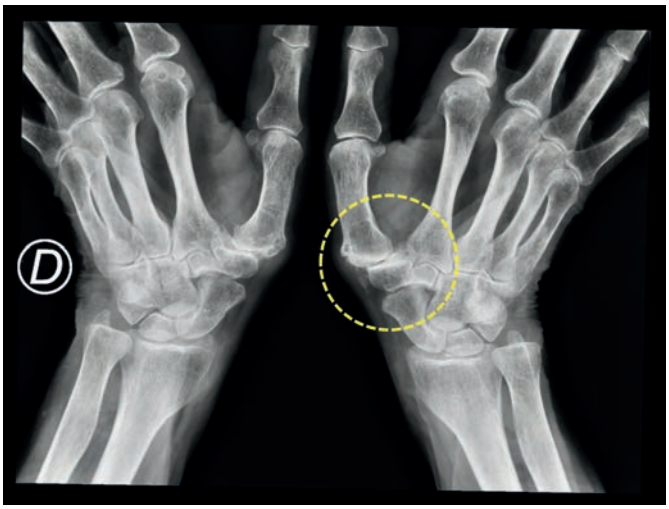


FIG. 6
Stress view.

RHIZOARTHROSIS – CONSERVATIVE TREATMENT

Treatment in all stages of the disease is initially conservative.
– The first step is the application of an immobiliser at night and possibly during the day for 2-3 weeks (Swigart *et* Al., 1999); the reduction in joint head movement and friction leads to decreased pain and stiffening of the capsuloligamentous structures with reduced subluxation (Pomerance, 1995). This can be associated to chondroprotectors that achieve their maximum therapeutic effectiveness if the joint is immobilised; in fact, since there is no wear effect, the cartilage can regenerate (Towheed *et* Al., 2005).
The synergy of these two measures can ensure a good outcome.
Conservative treatment requires early diagnosis of the degenerative process (Towheed *et* Al., 2005) because it is more effective, especially in the early stages (1st and 2nd).
The goals of conservative treatment are:

- to reduce pain at the base of the thumb, both at rest and while performing routine daily activities;
- avoid TM joint overload by teaching the patient correct prehension modes and favouring gripping with terminal opposition (FIG. 3);
- provide TM joint stability with the immobiliser while simultaneously reducing radial metacarpal subluxation.

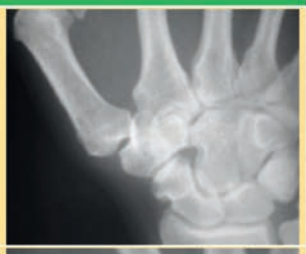
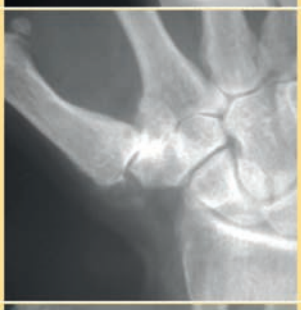
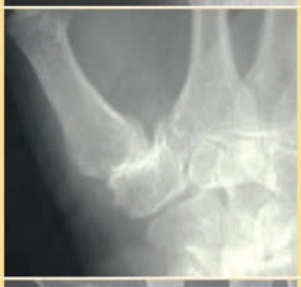
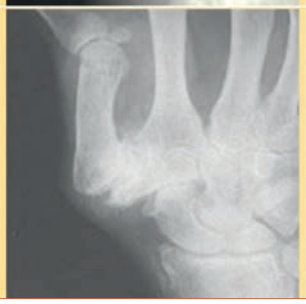
– Corticosteroid injections act on pain; they are sometimes used when the pain is unbearable (Pellegrini, 1992; Swigart *et* Al., 1999). These injections, if repeated, are less and less effective and irreparably damage the articular cartilage (Burton *and* Pellegrini, 1986; Swigart *et* Al., 1999).

RHIZOARTHROSIS – TREATMENT WITH MD-SMALL JOINTS

If initial conservative treatment does not produce positive effects, endo- and periarticular injection therapy may be considered before resorting to definitive surgical treatment.
The anatomical structures forming the containment/stabilisation system are: the joint capsule, ligaments and fibrous membranes that provide "direct seal", while the tendons and muscles provide "indirect seal".

- The extra-articular structures are made of Type I collagen (COL1): the quantity and quality of this triple helix macroprotein ensure optimal and repeated physiological articular movement over time.

– With ageing, all the COL1 forming the peri- and intra-articular structures undergoes important qualitative/quantitative changes (discrepancy between neofibrillogenesis and fibrillolysis) with progressive depletion and/or damage of adequate COL1, so that the articular bone heads are more mobile along the

STAGE	X-RAY	CLINICAL SIGNS	ACCESSORY ELEMENTS
1		TM joint subluxation is less than 1/3 Subchondral sclerosis begins to develop along with initial diastasis of the articular heads Instability, initial pain	Subluxation of the base of the first metacarpal under stress in abduction or in semeiologic manoeuvres (dynamic) Possible hypoplasia of the trapezium on X-ray examination
2		Subluxation is greater than 1/3 The capsule begins to be quite loose The first osteophytes of more than 2 mm in size appear Frequent pain on exertion Modest functional limitation	Instability Joint space narrowing, modest arthritic signs Osteophytes
3		The joint space is greatly reduced and sclerosis is increasingly evident Constant and stronger pain, stiffness Functional limitation Crepitus on palpation of the base of the thumb associated with more or less obvious deformities	Continuous pain Severe limitation
4		Severe anatomical and radiographic alterations resulting in functional impotence TM joint rigidity Severe functional limitation	Decreased pain related to stiffness, sometimes absent

TAB. 2

Eaton-Litter classification modified by Brunelli.

physiological excursion planes and are no longer firmly held in place. Hypermobility of the joints leads to abnormal support with consequent inflammation, first, and then degeneration of articular cartilage, the prime mover towards arthritic degeneration (Milani, 2019).

• In short: according to physiological biomechanics, the incorrect positioning of two contiguous joint heads forming a joint causes wear, pain and difficult movement. The tenocyte, a very specialised fibrocyte, is the cell that produces COL1; it also synthesizes matrix **Proteoglycans (PGs)** and Metalloproteinases (MMPs) (Bernardini, 2018) involved in the degradation of old or damaged fibres by the inflammatory/traumatic process.

– The primary event in the arthritic process is to be found in the reduction and alteration of PGs: mechanical, chemical or cytological factors lead to the depolymerization of the chains of Glycosaminoglycan (GAGs), which, by breaking, cause the decreased resistance of the articular cartilage matrix.

– As a consequence of these events, the collagen fibres that are not adequately protected by the matrix also break into fragments; the cartilage thus loses its elasticity and wears out (Scagliati, 1995).

All extra- and intra-articular structures are fundamentally made of collagen, hence the usefulness of deriving therapeutic means that allow the physician to counter osteo-arthro-myofascial pathologies (Stone *et* Al., 1997; Milani, 2010; 2013; 2019).

▶ MD-Small Joints

Guna Collagen Medical Devices are injectable products (p.a., i.a., s.c., i.d., i.m.) consisting of collagen of porcine origin (porcine collagen is the most similar and akin to human collagen) and one or more ancillary substances characterised by a particular tropism for the various and specific anatomical districts to which the collagen can be conveyed with greater effectiveness and specificity (Milani, 2013; 2019).

Guna Collagen Medical Devices provide collagen in the form of tropocollagen, which is assembled to collagen in the presence of the enzyme lysine hydroxylase, at the level of the extracellular matrix (ECM); it therefore acts as a bioscaffold (Milani, 2010).

– The deposition of neosynthesized collagen fibres in the damaged area secondary to loco-regional injection of the MDs produces a significant improvement in the mechanical qualities of the injured tissue; in particular, the anisotropic characteristics are restored.

Anisotropy is a mechanical property of collagen: it describes the ability of its fibres to propagate tensile forces in a single preferential direction.

Due to the orientation of the collagen fibres in a single direction, proper mechanical support is achieved for optimal function (Milani, 2019).

– Guna Collagen Medical Devices improve the histological make-up of anatomical structures in which collagen is present and provide a mechanical support (bioscaffold) with a clear positive effect on the stabilisation of joint hypermobility, movement, pain, and quality of life; they have a restructuring, repairing and remodelling action and contribute to the containment of the physiological deterioration of joints and tissues to counterbalance the effects due to various

causes including ageing, postural defects, chronic concomitant diseases, traumas and injuries (Various Authors, 2011).

– In addition to collagen, **MD-Small Joints** contains *Viola odorata*, an ancillary substance that is indicated – inter alia – in rheumatic pain of the wrist joints radiating to the forearm (Various Authors, 2011).

MATERIALS AND METHODS

Twenty-two patients (3 M; 19 F) suffering from RA were included in this clinical trial.
In 4 patients the pathology was bilateral; in this study, the most compromised side was considered.

– All patients were tested with the **DASH** questionnaire to assess loss of function (values 0 to 100; 100 = maximum disability), the VAS Scale (values 1 to 10), and the **Grind test** to assess capsuloligamentous laxity (G0 = no joint laxity; G1 = scarce laxity; G2 = lax; G3 = very lax).

– The mean age of the patients was 61.2 years (min. 44, max. 78): 12 patients in stage 2 and 10 patients in stage 3; 10 patients had maximum laxity G3, 5 had minor laxity G2, 7 had minimal laxity G1, and none G0.
All patients at the time of inclusion had decreased strength and functional limitation of the first ray. As regards laterality, 7 patients (33%) had RA in the nondominant hand.
This high percentage is explained by the fact that the nondominant hand, in many activities, must maintain a static grip for a long time thus resulting in severe overuse phenomena.
For example, suffice it to think of a patient who holds a sheet of metal or other material with strength in order to work it with the dominant hand.
In elderly patients, however, it is often due to muscular hypotonia of the nondominant hand: this explains how important the tendons and muscles, namely the structures involved in "indirect gripping", are.

	Age (years)	DASH	VAS	Grind test
Mean	**61.22**	**50.72**	**7.14**	**2.25**
Minimum	44	16.5	5	1
Maximum	78	75.25	9	3

TAB. 3
Patient assessment at inclusion.

The mean **DASH** was **50.72** at the first visit with a minimum of 16.5 and a maximum of 75.25; the mean **VAS** was **7.14** at the first visit with a minimum of 5 and a maximum of 9; the mean Grind test was **2.25** with a minimum of 1 and a maximum of 3 (TAB. 3).

– After one week of home therapy (low dose medicaments), patients began outpatient treatment with **MD-Small Joints** (1 vial = 2 mL), to which 0.5 mL of lidocaine 2% was added. Intra-articular injection was performed with 0.7-0.8 mL (i.e., the average capacity of the TM joint); the remaining amount (approx. 1.0 mL) in the periarticular site (FIG. 7).
In addition, approx. 0.5 mL were used for a second periarticular injection at the level of the 1st commissure in order to attack the deep part of the capsule between the first and second metacarpals, but above all to inject the intermetacarpal ligament in order to stabilise it and reduce the conflict due to its laxity (FIG. 2,8).
Injections were administered 3 or 4 times a week; the 4th or 5th were administered after 2 weeks.
In 8 patients, further treatment was required after another 2 weeks.

– Some patients experienced an exacerbation of symptoms after the 1st or 2nd administration; in 6 cases, therapy had to be temporarily suspended, but at the follow-up of the following week the worsening had completely regressed; in some cases, there was a clinical and

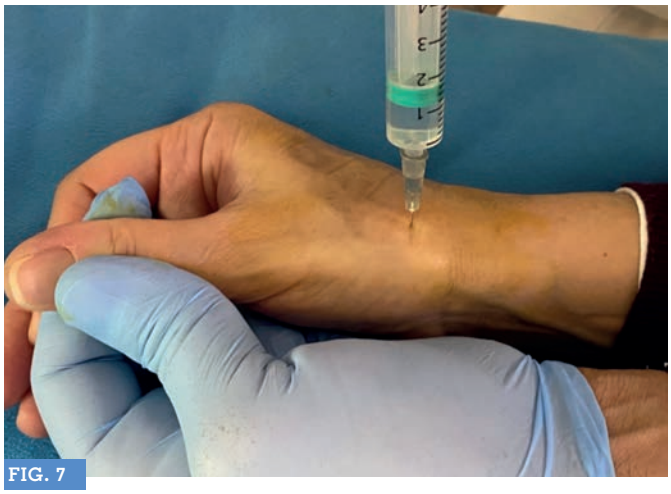


FIG. 7
Intra- and periarticular infiltration.

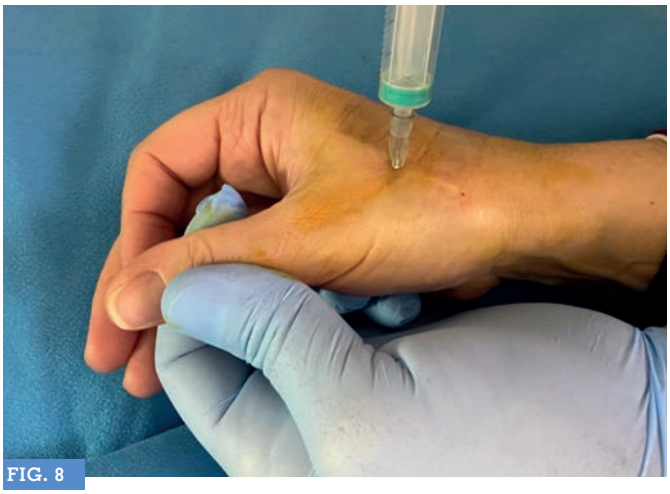


FIG. 8
Infiltration of the 1st commissure.

Weeks	0	1	Δ Week 1	2	3	4	5	6	7	8	9	10	Δ	%
DASH	50.72	39.87	21.39%	29.71	24.54	18.00	18.25	20.18	16.50	18.75	14.75	8.13	42.59	83.97
VAS	7.14	6.60	7.56%	5.06	4.44	3.85	3.60	4.20	4.29	2.80	3.33	3	4.14	57.98
Grind test	2.25	2	11.11%	1.367	1.233	0.923	1.111	0.714	0.8	0.667	0.5	0.5	1.75	77.7

TAB. 4

DASH, VAS, and Grind test values before and after treatment (10 follow-ups).

psychological improvement, so that treatment was resumed in all patients (no drop-out).

No patients required NSAIDs.
Only one patient, who was very anxious, was given anaesthesia in the superficial branch of the radial nerve, prior to the procedure described, to eliminate the pain of the i.a. and p.a. injections.
The addition of a minimal amount of lidocaine 2% resulted in significant patient compliance.
Case series confirmed the higher incidence of RA in the female gender.

RESULTS

This study enrolled: **1)** patients who had pain at stages that were too early to consider surgical treatment; **2)** non-responders to previous therapies, such as steroid therapy; **3)** patients who, despite having a surgical indication, refused surger.
In any case, it is believed that the earlier this treatment is initiated, the better the chance of an effective clinical response.

– Analysis of the DASH, VAS, and Grind test values showed that after the first week of treatment with low dose medicaments, there was a **21.39%** improvement in the DASH value, **7.56%** improvement in the VAS value, and **11.11%** improvement in the Grind test value. These data demonstrate the effectiveness of this preliminary therapeutic time (TAB. 4).

• Evaluating then the difference from the beginning to the end of the therapy, it can be seen that the DASH value decreased by **42.59 points** (**83.97%** increase in function); pain, according to the VAS Scale, decreased from **7.14** to **3** with a delta of **4.14** and consequently a **57.98%** decrease, while laxity went from a Grind test of **2.25** to a Grind test of **0.5** (**1.75**- point improvement), i.e., an increase in capsuloligamentous tension of **77.7%** (TAB. 4).

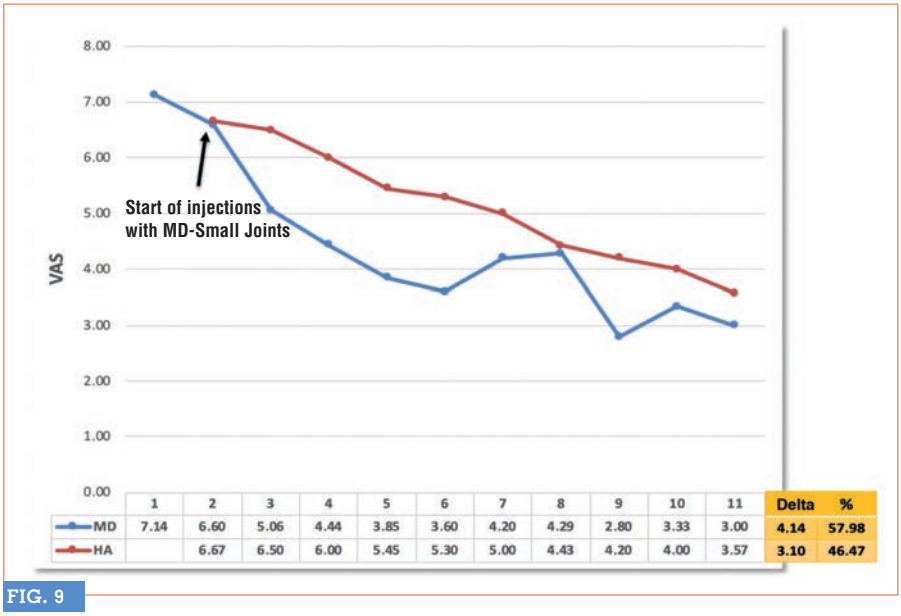


FIG. 9

VAS comparison: MD-Small Joints *vs* Hyaluronic Acid.

MD-SMALL-JOINTS VS HYALURONIC ACID

Intra-articular injection treatment with hyaluronic acid **(HA)** has been and still is another cornerstone of RA therapy, used by physiatrists and hand surgeons (Strass *et* Al., 2009; Volpi *et* Al., 2009; Iannitti *et* Al., 2011).
– Comparing the values obtained with MD-Small Joints with those obtained in a similar study carried out by the author (Brunato, 2012) on 51 patients treated with 3 intra-articular injections of HA administered 3 weeks apart, the following differences were recorded: at 10 weeks the VAS dropped from 6.67 to 3.57.
The difference was **3.10** points versus **4.14** points for MD-Small Joints, demonstrating a greater efficacy in pain control of **1.4 points** for MD-Small Joints (**+ 11,51%**) vs HA.
What is most striking is the early and marked decrease in pain from the first weeks of treatment with MD-Small Joints compared to HA (FIG. 9).
– Comparing the DASH values, the reduction was 42.59 points with MD-Small Joints compared to 27.51 points with HA, an improvement in hand function of **+ 25.7%**.
With MD-Small Joints, daily work activity, as verified with the DASH question-

naire, was maintained with significantly less pain (FIG. 10).

Converting all the values measured by DASH, VAS, and Grind test **to a scale of 10** shows that the improvement in DASH and VAS values is directly proportional to the decrease in Grind test, i.e., the reduction in joint laxity.
The recovery of joint tension is the result of the direct effect of injections with MD-Small Joints on the capsuloligamentous structures and in particular on the intermetacarpal ligament.

This is the clinical observational demonstration that local injection of MD-Small Joints restores the anisotropy of collagen and produces a significant and immediate improvement in the mechanical qualities of the damaged tissue, whence the clinical improvement of RA (FIG. 11).

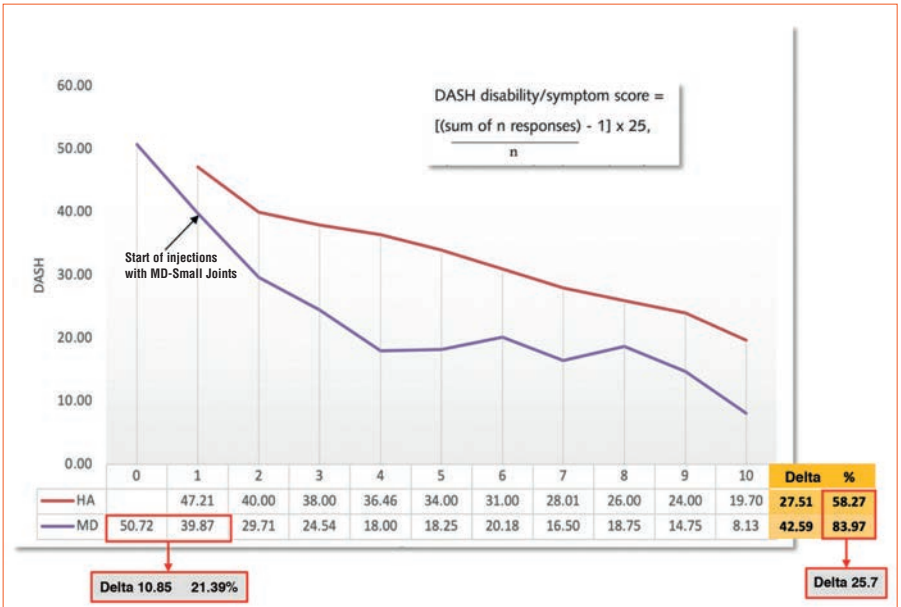


FIG. 10

DASH comparison: MD-Small Joints *vs* Hyaluronic Acid.

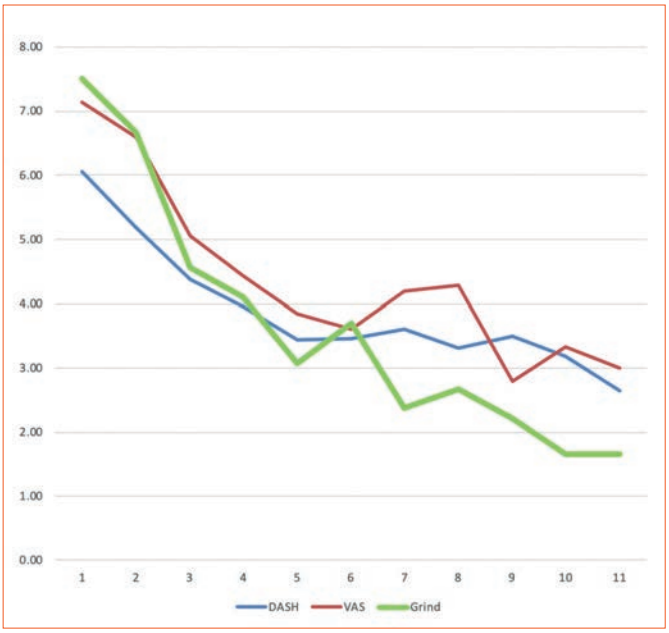


FIG. 11

Comparison of DASH and VAS values as a function of Grind test values.

DISCUSSION

Injection treatment of RA with Collagen Medical Device Small Joints significantly improved patients' symptoms in very few weeks; most importantly, pain clearly decreased, from the outset, as a result of the rapid reduction in joint laxity, proving to be more effective than HA therapy.

Most authors (Dias *et* Al., 2006) consider treating RA with immobilisation and taking NSAIDs for 2-3 months; if symptoms do not regress, surgery should be considered.
Corticosteroid injections act on pain and may be indicated when conservative therapy has not been effective (Pellegrini, 1992; Swigart *et* Al., 1999), but repeated injections have been found to have decreasing efficacy, in addition to irreparably damaging the capsule and articular cartilage (Burton *and* Pellegrini, 1986; Swigart *et* Al., 1999).
HA treatment has been shown to be less effective.

▶ MD-Small Joints has proven to be effective in delaying surgery, providing patients with rapid clinical improvement and an expectation of slowing down the pathology; all this in the absence of side effects and with excellent tolerability. ■

References

- AA.VV. – Guna Collagen Medical Device (Dossier). Guna Ed., Milano; **2011**.
- Barra V. *et* Al. – Artroplastica in sospensione secondo Ceruso nelle rizoartrosi di grado avanzato. Riv. Chir. Mano. **2003**, 40(3); 221-227.
- Bernardini G. – Rizoartrosi e omeosiniatria. Efficacia di Zeel®T e di MD-SMALL JOINTS a confronto. La Med. Biol., **2018**/2; 15-23.
- Bonola A., Caroli A., Celli L. – La Mano. Piccin Ed., Padova; **1981**.
- Brunato F. – Il trattamento della rizoartrosi trapezio-metacarpale con Acido ialuronico. Atti 50° Congresso Nazionale SICM, Padova; **2012**.
- Brunelli G.A. – La Mano. Manuale di chirurgia. Pagg. 340-349. Ed Hermes. Milano: **2007**.

- Brunelli G.R. *and* Brunelli G.A. – Considerazioni anatomo-patogenetiche. *In* La Rizoartrosi. Volume 1, pagg. 29-36. Monografie della Società Italiana di Chirurgia della Mano. Mattioli Ed., Parma; **1996**.
- Burton R.I. *and* Pellegrini V.D. – Surgical management of basal joint arthritis of the thumb. Part II: ligament reconstruction with tendon interposition arthroplasty. J Hand Surg Am. **1986** May; 11(3):309-24.
- Caroli A. – Anatomia descrittiva e funzionale della trapezio-metacarpica. *In* La Rizoartrosi. Volume 1, pagg. 7-28. Monografie della Società Italiana di Chirurgia della Mano. Mattioli Ed., Parma; **1996**.
- Cooney W.P. *and* Chao E.Y.S. – Biomechanical analysis of static forces in the thumb during hand function. J. Bone Joint Surg. 59A, 27; **1977**.
- Dias R., Chandrasenan J., Rajaratnam V., Burke F.D. – Basal thumb arthritis. Postgrad Med J. **2006** Jan; 83(975): 40-43.
- Glickel S.Z. – Clinical assessment of the thumb trapeziometacarpal joint. Hand Clin. 2001 May;17(2):185-95.
- Iannitti T. *et* Al. – Intra-articular injections for the treatment of osteoarthritis: focus on the clinical use of hyaluronic acid. Drugs R D. **2011**;11(1):13-27.
- Kapandji A. – La rotation du pouce sur son axe longitudinal lors de l'opposition. Rev Chir. Orthop. 57, 1, 3-12; **1971**.
- Milani L. – A new and refined injectable treatment for muskoloskeletal disorders. Bioscaffold properties of collagen and its clinical use. Physiological Regulating Medicine, **2010**/1: 3-15.
- Milani L. – I Collagen Medical Devices nel trattamento locale delle artro-reumopatie algiche. Rassegna degli Studi Clinici e *Clinical Assessment* 2010-2012. La Med. Biol., **2013**/2; 3-18.
- Milani L. – I Guna Collagen Medical Devices 10 anni dopo. - Analisi ragionata di 2 recenti importanti ricerche e *update* della letteratura. La Med. Biol., **2019**/2; 3-18.
- Pellegrini V.D. Jr – Osteoarthritis at the base of the thumb. Orthop Clin North Am **1992** Jan; 23(1):83-102.
- Pomerance J.F. – Painful basal joint arthritis of the thumb. Part II: treatment. Am J Orthop. **1995** Jun; 24(6):466-72.
- Scagliati A. – Quindici casi di artrosi polidistrettuale: un esempio di trattamento biologico. La Med. Biol., **1995**/Suppl. al n° 3; 48-50.
- Sollazzo V. *et* Al. – La stabilizzazione tendinea dinamica dell'articolazione trapezio-metacarpale con tendine dell'abduttore lungo del pollice nel trattamento chirurgico della rizoartrosi: la nostra esperienza. Giornale Italiano di Ortopedia e Traumatologia. **2006**, 32; 241-5.
- Stone K.M. *et* Al. – Regeneration of meniscal cartilage with the use of a collagen scaffold. Analysis of preliminary data. J. Bone Joint Surg. Am., **1997** Dec, 79(12); 1770-7.
- Strass E.J. *et* Al. – Hyaluronic Acid Viscosupplementation and Osteoarthritis. Current Uses and Future Directions. The American Journal of Sports Medicine, Vol. 37, N° 8; **2009**.
- Swigart C.R. *et* Al. – Splinting in the treatment of arthritis of the first carpometacarpal joint. J Hand Surg. **1999**; 24, 86-91.
- Towheed T.E. *et* Al. – Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev. **2005** Apr 18;(2): CD002946.
- Volpi N. *et* Al. – Role, metabolism, chemical modifications and applications of hyaluronan. Curr Med Chem. **2009**; 16 (14): 1718-45.

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EVALUATION OF PAIN RELATED TO INTERNAL MECHANICAL IMBALANCE OF THE TEMPORO-MANDIBULAR JOINT AFTER INTRA-ARTICULAR INJECTION OF MD-SMALL JOINTS

SUMMARY

– Introduction – Internal mechanical imbalance is one of the most frequent Temporomandibular Disorders (TMDs), and various drugs injected intra-articularly into the Temporo-mandibular Joint (TMJ) have been used to treat it.
Collagen, an essential molecule for maintaining joint integrity, has never been injected intraarticularly for the treatment of any TMD.
– Objective of the study – To evaluate the effects of intra-articular injection of collagen in pain related to internal TMJ imbalance.
– Materials and Methods – 20 patients (20 joints) undergoing treatment for internal TMJ imbalance were injected with 2 ml of MD-SMALL JOINTS (1 ml per week).
The patients were evaluated at 1 week, 1 month, and 3 months after the second injection according to the pain parameter of the modified Helkimo's Index for TMDs.
– Results – A statistically significant improvement of pain was found in all follow-up intervals.
– Conclusions – The results confirm the fundamental role of collagen in preserving the integrity of all joints. Furthermore, these results open the doors to further research on collagen as a treatment for TMDs.

KEY WORDS

TMJ, INTERNAL MECHANICAL IMBALANCE, COLLAGEN, INTRA-ARTICULAR INJECTION, MEDICAL DEVICE, MD-SMALL JOINTS

https://www.towsonmddentist.com/dental-services/restorative-dentistry/tmj-treatment/

INTRODUCTION

Temporo-mandibular Disorders **(TMDs)** are nosologically classified into extra- and intra-articular types.

– The internal imbalance of the Temporo-mandibular Joint **(TMJ)** implies an altered condyle-disc-fossa connection so to interfere with the joint smooth function.
It accounts for **25%** of all TMJ disorders (Hall *et* Al., 1984; Daif, 2012).

– To treat the internal imbalance of the TMJ, different solutions have been proposed, both nonsurgical, including Physiotherapy, pharmacological therapy, functional devices, arthrocentesis, intra-articular injections – and surgical options, such as disc repair and repositioning, discectomy, condylotomy, etc. (Slater & de Leeuw, 2019).
Some substances have been proposed as an intra-articular injection material for the treatment of anterior disc displacement with reduction; these include corticosteroids, hyaluronic acid **(HA)**, non-steroidal anti-inflammatory drugs **(NSAIDs)**, dextrose, blood concentrates like Platelet Rich Fibrin **(PRF)** and Platelet Rich Plasma **(PRP)**, ozone

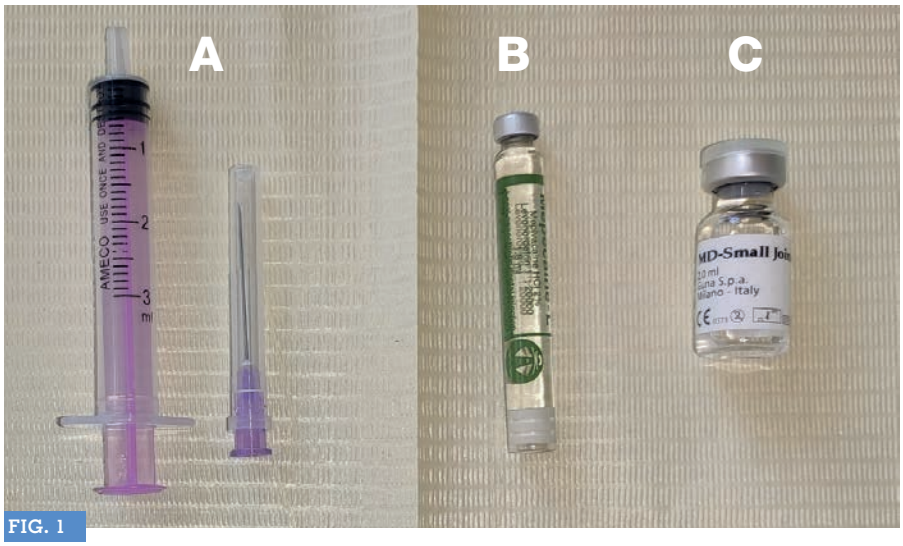


FIG. 1

Materials used in the study.
A - Plastic disposable syringe (3 cc) with 25-gauge needle.
B - Mepivicaine HCl 2% with Levonordefrin 1:20,000.
C - MD-SMALL JOINTS.

gas, and botulinum toxin type A (Botox) (Daif, 2012; Gencer *et* Al., 2014; Fernández-Ferro *et* Al., 2017; Bahgat *et* Al., 2018; Slater & de Leeuw, 2019).

– Collagen represents a quarter of total protein mass in Mammalians.
This protein plays a crucial role in dealing with the loads on the joint structures (discs, capsules, ligaments, muscles, tendons) thanks to anisotropy, which is considered one of its most prominent properties.
Lately in various studies (e.g., Reshkova *et* Al., 2016), collagen has been injected intra-articularly in knees and in some small joints for the treatment of clinical signs and symptoms of osteoarthritis and myofascial pain (Alfieri, 2016).

As far as we know, up to now no clinical studies evaluating the effects of collagen intra-articular injections in temporo-mandibular disorders have been published (Milani, 2013; 2019; Alfieri; 2016).

MATERIALS AND METHODS

Twenty patients (20 joints; 19 F and 1 M) suffering from symptoms of internal mechanical imbalance of the TMJ have been selected from the Outpatient Clinic of

Scoring		
Pain on movement of the mandible		
Criteria:	No pain on movement	0
	Slight pain on maximal mouth opening	1
	Pain on two or more movements	2
	Spontaneous or severe pain	5
Temporo-mandibular Joint pain		
Criteria:	No tenderness to palpation	0
	Discomfort to palpation	1
	Tenderness to palpation	2
	Severe tenderness to palpation	5
Maximal mouth opening		
Criteria:	≥ 40 mm	0
	≥ 35 mm	1
	≥ 30 mm	2
	< 30 mm	5
Signs of Temporo-mandibular Joint noise and disc displacement		
Criteria:	No joint noise	0
	Occasionally joint noise	1
	Palpaple clicking	2
	Audible clicking	3
	Absence of previous clicking (closed block)	4
	Crepitation	5
Muscle pain in masticatory muscles		
Criteria:	No tenderness to palpation	0
	Discomfort to palpation	1
	Tenderness to palpation	2
	Severe tenderness to palpation	5

TAB. 1

Clinical signs evaluation.
– Clinical dysfunction of Helkimo's Index, modified.

Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Mansoura University (Egypt) to undergo treatments.

The diagnosis was Anterior disc displacement with reduction (ADDWR), confirmed through clinical signs and symptoms. The patients' age ranged from 18 to 50 years, mean age 31 years.

– All patients were injected collagen (**MD-SMALL JOINTS** – Guna Spa, Milan) through 2 injections over 2 consecutive weeks (1 ml/week) (FIG. 1).

Clinical manifestations were evaluated according to Helkimo's Index modified for TMDs (Kurita *et* Al., 1997), regarding **1) pain on movement (P)** and **2) pain/muscle soreness on palpation (M)** (TAB. 1).

Each sign and symptom was scored from 0 to 5 according to clinical severity.
Before the injection of MD-SMALL JOINTS every patient was informed about the aim of the study, procedures, and possible complications.
Each patient was asked to sign the informed consent form.

– After appropriate disinfection of the skin overlying the TMJ with 10% Povidone-iodine solution and after plugging the external auditory meatus with a cotton pledge, auriculotemporal nerve was anesthetized (FIG. 1).

The superior joint space was localized 10 mm anterior to the tragus and 2 mm below the canthal tragus line; in this point was injected 1 ml of MD-SMALL JOINTS, drawn from a ready-made vial (2 ml) with a plastic disposable 3 cc 25G syringe (FIGS. 2-4).

Patients were required to eat a light diet and practice home physical therapy (application of moist heat and mandibular exercises 4 times daily for 1 month) as well as to take antibiotic: Amoxicillin + Clavulanic acid (Augmentin®) 625 mg tablets, 3 times/day for 5 consecutive days for prophylaxis of any joint space infection.

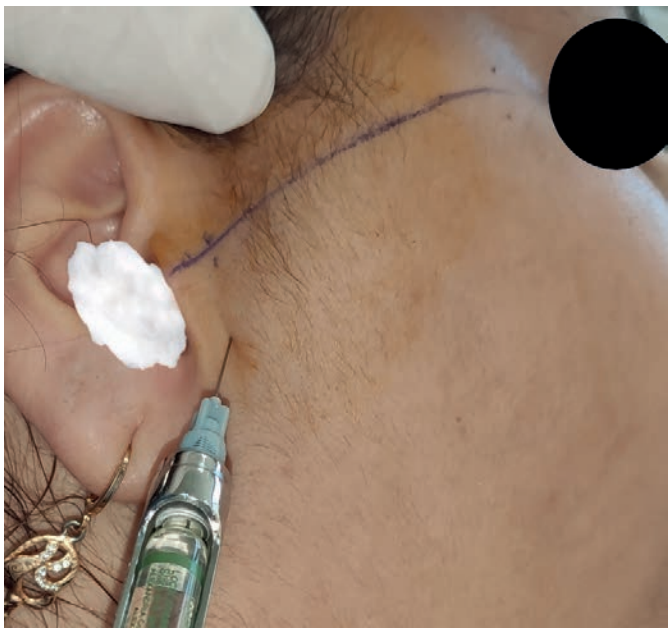


FIG. 2

Needle insertion for auriculotemporal nerve block.

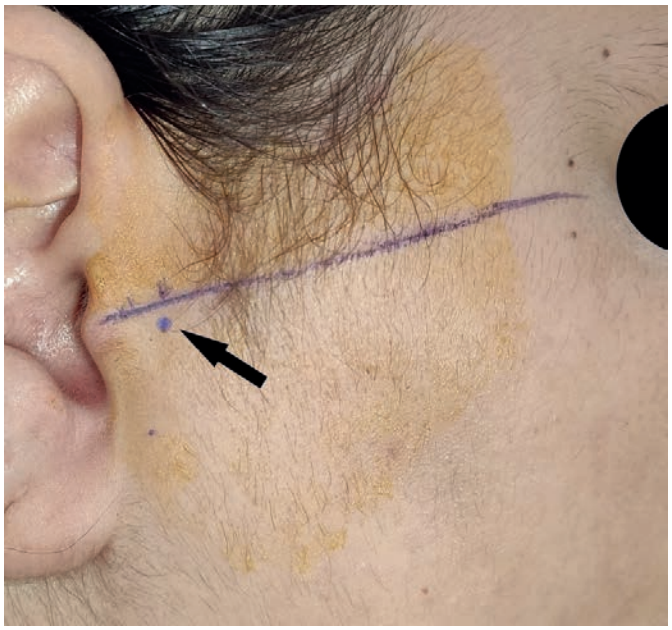


FIG. 3

Marking of the anatomical landmarks used for the injection in the superior auricular space of the TMJ and penetration point (black arrow).

Ibuprofen (Brufen®) 600 mg tablets x 3/day, as an anti-inflammatory, was also prescribed in case of need.

Patients were evaluated at **1 week**, **1 month** and **3 months** after the second injection, for improvement of signs and symptoms according to Helkimo's Index, modified for the evaluation of TMJ dysfunctions (Kurita *et* Al., 1997) regarding pain (**P**) and muscle pain and tenderness to palpation (**M**).
Finally, the collected data were analyzed to evaluate post-operative results.

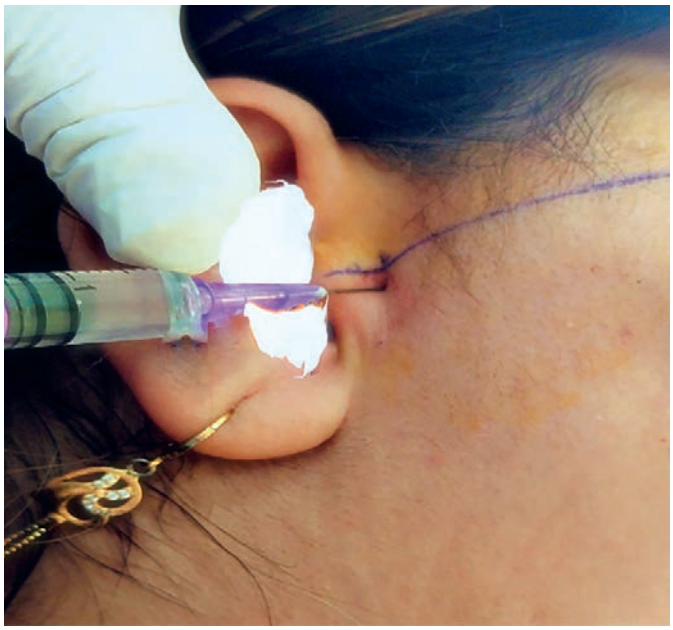
RESULTS

Regarding **pain on movement (P)**, there was a significant difference between all intervals ($p = 0.00$). A significant improvement in pain (p value < 0.05) was found when pre-operative pain was compared to that of 1 week ($p = 0.001$), 1 month ($p = 0.005$), and 3 months after the second injection.

– No significant improvement was found in the degree of pain when comparing in 1 week versus 1 month

FIG. 4

Needle insertion during the injection of MD-SMALL JOINTS.



(p = 0.34), 1 week vs 3 months (p = 0.11) or 1 month versus 3 months (p = 0.18) (TABLES 2-3).

As far as **muscle pain and tenderness to palpation (M)** are concerned, statistically, there was a significant difference among the pre-operative and all follow-up intervals (p = 0.00).
A significant improvement in signs of muscular tenderness to palpation (M) (p < 0.05) was noticed when pre-operative Muscular pain (M) was compared to that after 1 week (p = 0.00), 1 month (p = 0.00), and 3 months (p = 0.00) from the second injection.

– No significant difference (p value > 0.05) in the degree of pain when comparing 1 week versus 1 month (p = 0.00), 1 week versus 3 months (p = 0.74) or 1 month versus 3 months (p = 0.32) (TABLES 4-5).

N	14
Chi-Square	20.532
df	3
Asymptotic significance (P value)	0.00

TAB. 2

Test of Friedman for (P).

DISCUSSION

Up to now, several preparations such as HA, corticosteroids, NSAIDs, PRF, PRP, and dextrose have been injected intra-articularly for the treatment of many TMDs.

• This study evaluated the effect of intra-articular injection of MD-SMALL JOINTS for the treatment of pain of anterior disc displacement associated to reduction.
– This is the first study to include intra-articular injection of collagen in the TMJ.
In previous studies Collagen Medical Devices had been used in other joints such as knee, ankle, shoulder, etc.

This study evaluated the effect of collagen injection according to Helkimo's Index, modified for TMDs (Kurita *et* Al., 1997).
– This Index provides an evaluation of most of signs and symptoms of TMDs with scores that cover the different degree of severity of each factor.
Moreover, this Index does not depend on the patients' feedback like the VAS scale, which covers only the pain variable and depends completely on the patient's evaluation of the degree of pain and, therefore, is less accurate.

Due to the lack of previous studies covering the injection of collagen in the TMJ, dosage was compared to that used in other joints, knee for instance.

– Reshkova *et* Al. (2016) used 2 ml of collagen in every knee injection. Since the width of the knee joint space is nearly double that of the TMJ [knee JSW medial and lateral is 4.7 mm and 5.6 mm respectively (Anas *et* Al., 2013); TMJ joint space range from 2 mm to 3.2 mm (Mahmood *et* Al., 2015)], the dose of collagen used in this study was half of that used in the knee (1 ml/treatment).
The number of injections administered was equal to 2.

Besides, the fact that 95.0% of patients are females and 51.7 % of patients were aged from 18 to 30 years, is compliant with what reported by Bagis *et* Al. (2012) and Bueno *et* Al. (2018).
These Authors have – in fact – referred an increase of TMDs in females more than in males, especially in patients ranging between 30 and 40 years of age.

Regarding pain (P), patients showed a significant improvement, coherent with the results reported by Hynes (2002), Friedrichs *et* Al. (2007), and Del Nogal *et* Al., (2012); they all described the collagen fibers anisotropy and its crucial role in force distribution and transmission to the fibroblasts which forms collagen itself and helps in Tissue repair.
– The results of this study confirm the efficacy and tolerability of the intra-articular injections of Collagen Medical Devices (Milani, 2019).

Concerning muscle tenderness (M), it's worth mentioning that the results which showed significant improvement confirm what reported by Ayesh *et* Al. (2008); i.e., painful TMJ increase skin and muscle sensitivity of the TMJ area, as well as finger-applied pressure stimuli.
These results are also confirmed by Tanaka *et* Al. (2008) who proposed that chronic TMJ pain leads to reflex masticatory muscle spasm.

Intervals	Mean Rank		Z value	P value
	Positive	Negative		
Pre-operative (P) **vs** 1 week (P)	0.00	6.50	-3.18	0.001
Pre-operative (P) **vs** 1 month (P)	0.00	5.00	-2.81	0.005
Pre-operative (P) **vs** 3 months (P)	0.00	4.50	-2.64	0.008
1 week (P) **vs** 1 month (P)	5.00	2.00	-0.097	0.34
1 week (P) **vs** 3 months (P)	4.50	1.50	-1.62	0.11
1 month (P) **vs** 3 months (P)	1.50	0.00	-1.34	0.18

TAB. 3

Ranks test (Wilcoxon) and relevant statistical significance for pain improvement in different intervals according to Helkimo's Index, modified.

Wang *et* Al. (2004) mentioned that patients with anterior disc displacement without reduction showed improvement in muscle tenderness after injection of Lidocaine in TMJ.
Therefore, reduction of muscle tenderness and sensitivity can be attributed to the reduction of TMJ pain.

– We think that the limitations of this study are **1)** a relatively small sample (20 patients), **2)** lack of knowledge of the appropriate dose and number of collagen injections, due to the absence of previous use of collagen in the treatment of TMJ disorders.

CONCLUSIONS

The positive results of our study open the doors to further investigations on intra-articular injection of collagen in TMJ and the possible use of MD-SMALL JOINTS in other types of internal mechanical imbalance or other TMDs. ■

References

– Alfieri N. – MD-Muscle in the management of myofascial pain syndrome. Physiological Regulating Medicine. **2016**;17:23-4.
– Anas I. *et* Al. – Digital radiographic measurement of normal knee joint space in adults at Kano, Nigeria. The Egyptian Journal of Radiology and Nuclear Medicine. **2013**; 44(2):253-8.

N	14
Chi-Square	21.217
df	3
Asymptotic significance (P value)	0.00

TAB. 4

Test of Friedman for (M).

TAB. 5

Ranks test (Wilcoxon) and relevant statistical significance for pain/muscle soreness on palpation (M) in different intervals according to Helkimo's Index, modified.

Intervals	Mean Rank		Z value	P value
	Positive	Negative		
Pre-operative (M) **vs** 1 week (M)	0.00	6.00	-3.21	0.00
Pre-operative (M) **vs** 1 month (M)	0.00	5.00	-2.72	0.00
Pre-operative (M) **vs** 3 months (M)	0.00	4.50	-2.60	0.00
1 week (M) **vs** 1 month (M)	3.00	3.00	-0.45	0.66
1 week (M) **vs** 3 months (M)	4.00	3.00	-0.33	0.74
1 month (M) **vs** 3 months (M)	1.00	0.00	-1.00	0.32

– Ayesh E.E. *et* Al. – Effects of intra-articular ketamine on pain and somatosensory function in temporomandibular joint arthralgia patients. Pain. **2008**;137(2):286-94.
– Bagis B. *et* Al. – Gender difference in prevalence of signs and symptoms of temporomandibular joint disorders: a retrospective study on 243 consecutive patients. Int J Med Sci. **2012**; 9(7):539-44.
– Bahgat M.M. *et* Al. – Botulinum toxin type-A. An evolving treatment modality in the management of temporomandibular joint disc displacement. Alex Dent J. **2018**;43(2):57-61.
– Bueno C.H. *et* Al. – Gender differences in temporomandibular disorders in adult populational studies: A systematic review and meta-analysis. J Oral Rehabil. **2018**;45(9):720-9.
– Daif E.T. – Role of intra-articular ozone gas injection in the management of internal derangement of the temporomandibular joint. Or Surg Or Med Or Pa. **2012**;113(6):e10-e4.
– Del Nogal M. *et* Al. – Balance between apoptosis or survival induced by changes in extracellular-matrix composition in human mesangial cells: a key role for ILK-NFκB pathway. Apoptosis. **2012**;17(12):1261-74.
– Fernández-Ferro M. *et* Al. – Comparison of intra-articular injection of plasma rich in growth factors versus hyaluronic acid following arthroscopy in the treatment of temporomandibular dysfunction: A randomised prospective study. J Cranio Maxill Surg. **2017**;45(4):449-54.
– Friedrichs J. *et* Al. – Cellular Remodelling of Individual Collagen Fibrils Visualized by Time-lapse Afm. J Mol Biol. **2007**;372(3):594-607.
– Gencer Z.K. *et* Al. – A comparative study on the impact of intra-articular injections of hyaluronic acid, tenoxicam and betametazon on the relief of temporomandibular joint disorder complaints. J Cranio Maxill Surg. **2014**; 42(7):1117-21.
– Hall M.B. *et* Al. – Oral medicine, oral pathology. Histologic appearance of the bilaminar zone in internal derangement of the temporomandibular joint. Or Surg Or Med Or Pa. **1984**; 58(4):375-81.
– Hynes R.O. – Integrins: bidirectional, allosteric signaling machines. Cell. **2002**;110(6):673-87.
– Kurita H. *et* Al. – Clinical effect of full coverage occlusal splint therapy for specific temporomandibular disorder conditions and symptoms. J Prosthet Dent. **1997**; 78(5):506-10.
– Mahmood H.A. *et* Al. – Assessment of tempromandibular joint space and condylar position in patients with myofacial pain dysfunction syndromes by using cone beam computed tomography. Zanco Journal of Medical Sciences. **2015**;19(1):929 34-34.
– Milani L. – A new and refined injectable treatment for musculoskeletal disorders. Physiological Regulating Medicine **2010**;1:3-15.
– Milani L. – The collagen medical devices in the local treatment of the algic arthro-rheumopathies – Review of the clinical studies and clinical assessments 2010-2012. Physiological Regulating Medicine. **2013**; 21-36.
– Milani L. – I Guna Collagen Medical Devices 10 anni dopo. Analisi ragionata di 2 recenti importanti ricerche e *update* della letteratura. La Med. Biol., **2019**; 3-18.
– Reshkova V. *et* Al. – Efficacy and safety evaluation of Guna collagen MDs injections in knee osteoarthritis. A case series of 30 patients. Physiological Regulating Medicine. **2016**; 27-29.
– Slater J.J.H., de Leeuw R. – Internal Derangements of the Temporomandibular Joint. Contemporary Oral Medicine: A Comprehensive Approach to Clinical Practice. **2019**:1881-918.
– Tanaka E. *et* Al. – Degenerative Disorders of the Temporomandibular Joint: Etiology, Diagnosis, and Treatment. J Dent Res. **2008**;87(4):296-307.
– Wang K. *et* Al. – Reduction of clinical temporomandibular joint pain is associated with a reduction of the jaw-stretch reflex. J Orofac Pain **2004**;18(1).

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CLINICAL

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COPD COMPLICATED BY BRONCHIECTASIS – OBSERVATIONAL STUDY

SUMMARY

COPD complicated by Bronchiectasis is one of the chronic degenerative pathologies that has always involved the General Practitioner in dealing with its frequent exacerbations during the cold season, despite the administration of influenza vaccination, pneumococcal vaccination, bronchodilators (steroids, inhalers and not, long acting beta-2-agonists, and antimuscarinics) as prescribed according to the GOLD guidelines.
– This observational study has been conducted for 5 consecutive years on 12 patients aged between 54 and 99 years. All patients have been treated according to the GOLD guidelines; a Group of 6 was also given, from October to May of each year, BrSM and PRM medicines for the prophylaxis of the seasonal colds.
The aim of this study was to detect whether there is a significant difference between the 2 Groups in relation to the recovery from the disease, assessing indicators such as:
1) home/medical clinic on-demand visits, 2) sick days, 3) use of antibiotics, 4) use of steroids and/or other drugs.
To demonstrate if the preventive overlapping therapy (conventional + BrSM and PRM therapies) is a feasible strategy for General Medicine, it is important: 1) to reduce the prescriptions of antibiotics (resistances), 2) to comply with the programmed spending limits (prescription appropriateness), 3) to comply with the state law (spending review), and, last but not least, 4) to improve the patient's well-being.

KEY WORDS

COPD, BRONCHIECTASIS, SPIROMETRY, CITOMIX, GUNA-FLU, GUNA-ANTI IL 1, GUNA-INTERLEUKIN 10, ECHINACEA COMPOSITUM S, UBICHINON COMPOSITUM, COENZYME COMPOSITUM®

https://elite24er.com/chronic-obstructive-pulmonary-disease-copd/

INTRODUCTION

COPD (Chronic Obstructive Pulmonary Disease) is a major public health problem and one of the leading causes of mortality (Lozano *et* Al., 2012) and chronic morbidity the world over.

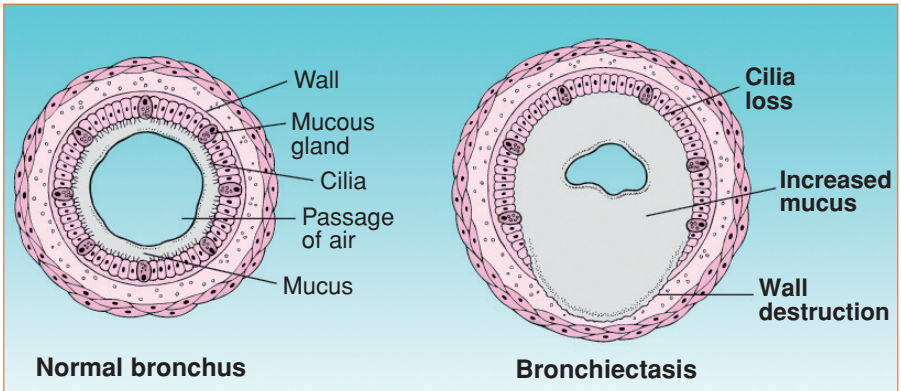
– Over the next few decades, it is anticipated that COPD will be the third cause of death worldwide, after cardiovascular disease and cancer, and that its social cost will increase as a result of continuous exposure to risk factors and the ageing of the population (Mathers *and* Loncar, 2006).

THE DISEASE

COPD is a disease characterised by persistent breathing difficulties and limitation of the airflow in the small airways (obliterative bronchiolitis) and subsequent parenchymal involvement, with rupture of the interalveolar septa resulting in the formation of air bubbles (emphysema) that reduce the capacity for gas exchange between the pulmonary capillary blood and inhaled air, with consequent initial and progressive hypoxaemic and/or hypercapnic respiratory failure.

– Bronchiectases are chronic dilations of the bronchii with a calibre greater than 2 mm due to the destruction of their walls (FIG. 1).
Bronchiectasis can be congenital or acquired, due to illness, such as chronic bronchitis, inflammation, or other factors.
The most common initial symptoms include **dyspnoea**, **cough** and/or **production** of **sputum**.
These symptoms are often underestimated by patients.

Although the main risk factor for COPD is inhaled cigarette smoke, environmental exposure, such as biofuel vapours and atmospheric pollution, can also be a causal factor (Paulin *et* Al., 2015).



Bronchiectases are chronic dilations of the bronchii, with a calibre greater than 2 mm, due to the destruction of their walls.

FIG. 1

– In addition to environmental exposure, there are also a number of host-related factors that make an individual more susceptible to the development of COPD, including: **1)** genetic abnormalities; **2)** abnormal lung development (Stoller *and* Aboussouan, 2005), and **3)** premature ageing.

COPD can be characterised by acute periods in which there is a considerable deterioration in the respiratory symptoms.
In most patients, COPD is associated with significant chronic diseases that increase its morbidity and mortality.

DIAGNOSIS

A clinical diagnosis of COPD should be considered in all patients experiencing dyspnoea, chronic cough, sputum production and/or a history of exposure to the risk factors for the disease.

Collection of a detailed medical history is fundamental in the case of confirmed or suspected COPD (TAB. 1).

Spirometry is essential for clinical diagnosis in this setting (Buist *et* Al., 2007); the presence of a post-bronchodilator FEV1/FVC ratio **<0.70** confirms the presence of a persistent bronchial obstruction and – consequently – COPD in patients with appropriate symptoms and considerable exposure to harmful stimuli.

– Spirometry is the most reproducible and objective measurement of airflow limitation and a readily available and non-invasive technique.

Despite its good sensitivity, the measurement of peak exhalatory flow alone cannot be reliably used as the sole diagnostic test, due to its poor specificity (Jackson *and* Hubbard, 2003).

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis is with asthma.

– In certain patients with chronic asthma, it is not possible to make a clear distinction from COPD using the imaging techniques and functional tests currently available.
In patients with COPD, treatment is similar to that for asthma.
Other potential diagnoses are usually easier to distinguish from COPD (TAB. 2).

Alpha-1 antitrypsin deficiency (AATD) screening.

TAB. 1
Key indicators for the diagnosis of COPD.

A diagnosis of COPD should be considered and spirometry performed if any of the following indicators are present in an individual over 40 years of age. – These indicators are not diagnostic per se; the presence of multiple indicators increases the likelihood of a diagnosis of COPD. Spirometry is required to confirm the diagnosis of COPD.	
Dyspnoea	Worsens over time Usually gets worse with physical exertion Persistent
Chronic cough	May be intermittent and/or non-productive Recurrent wheezing
Chronic sputum production	Any type of chronic sputum production can indicate the presence of COPD
Recurrent lower respiratory tract infections	
History of exposure to risk factors	Host factors Tobacco smoke Smoke from biofuels used for home cooking and heating fuels Occupational dusts, vapours, fumes, gases and other chemicals
Family history of COPD and/or childhood factors	Low birth weight, childhood respiratory infections

COPD	Onset in mid-life Symptoms slowly progressive History of tobacco smoking or exposure to other types of smoke
Asthma	Onset early in life (often childhood) Symptoms vary widely from day to day Symptoms worse at night/early morning Allergy, rhinitis and/or eczema also present Family history of asthma Obesity coexistence
Congestive heart failure	Chest x-ray shows dilated heart, pulmonary oedema. Pulmonary function tests indicate volume restriction, not airflow
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Chest x-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages Chest x-ray shows lung infiltrate Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset at younger age, non-smokers May have history of rheumatoid arthritis or acute fume exposure Seen after lung or bone marrow transplantation
Diffuse panbronchiolitis	Primarily seen in patients of Asian descent Most patients are male and non-smokers Almost all have chronic sinusitis Chest x-ray and HRCT show diffuse, small, centrilobular nodular opacities and hyperinflation

These factors tend to be characteristic of the respective diseases, but are not mandatory. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than smoking); asthma may develop in adult and even in elderly patients.

TAB. 2

COPD – Differential diagnosis.

The World Health Organisation recommends that all patients with a diagnosis of COPD should be screened for this condition at least once, especially in areas with a high prevalence of Alpha-1-antitrypsin deficiency (WHO Meeting Participants, 1997).

– A low concentration (<20%) is highly suggestive of homozygous deficiency.

Family members should also be screened.

CLASSIFICATION OF OBSTRUCTION SEVERITY

The classification of airflow limitation severity used in COPD is shown in TAB. 3. Specific spirometric cut-points are used for purposes of simplicity.

Spirometry should be performed after the administration of an adequate dose of at least one short-acting inhaled bronchodilator in order to minimise variability.

– It should be noted that there is only a weak correlation between FEV1, symptoms and impairment of a patient's health status.

For this reason, formal symptomatic assessment is also required.

STUDY DESIGN

This clinical study is based on the observation of COPD patients subject to frequent exacerbations, often with 3-4 or more episodes in the same winter, especially when living in large families or with children, who are particularly susceptible to seasonal viral illnesses.

– In these conditions, it is not possible to adopt the strategies indicated in the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Guidelines – LAMAs and/or LABA + seasonal influenza vaccination + one-off pneumococcal vaccination – for disease maintenance and prevention of exacerbations.

– When a COPD patient has an exacerbation, the pharmacological therapy is somewhat consistent: antibiotics, corti-

In patients with FEV1/FVC <0.70:

GOLD 1:	**Mild**	**FEV1 ≥80% of predicted**
GOLD 2:	**Moderate**	**50% ≤ FEV1 <80% of predicted**
GOLD 3:	**Severe**	**30% ≤ FEV1 <50% of predicted**
GOLD 4:	**Very severe**	**FEV1 <30% of predicted**

TAB. 3

COPD
– Classification of airflow limitation severity.
– Specific spirometric cut-points can be used.

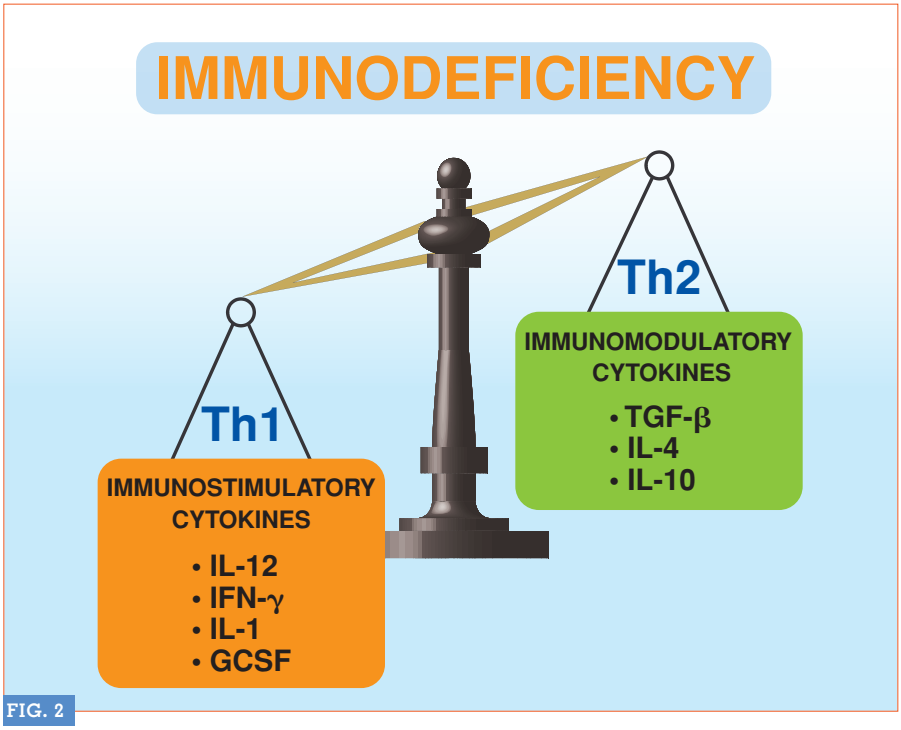


FIG. 2

sones by mouth and/or nebuliser + LAMAs and/or LABA, fluidifiers and expectorants, often combined with O_2 gas (especially when SAT values drop to between 82% and 90%).

– In this situation, the patient presents asthma-like symptoms, with dyspnoea and shortness of breath, as well as a persistent hacking cough, signs of bronchiolitis (involving the lesser airways) and bronchospasm of the same with severe airflow limitation.

This condition is extremely familiar to general practitioners **(GPs)**, who know that therapeutic intervention must be swift and aimed at evaluating whether the patient can be treated at home or whether hospitalisation is required, especially when patients present comorbidities that may complicate the clinical situation.

The more frequent the exacerbations, the more medicinal products (especially antibiotics and steroids) required and the more exposed the patient is to recurrences, due to the down-regulation of the Th1 side of the immune balance (FIG. 2) with inappropriate innate immune response induced by the pro-inflammatory cytokines TNF-α, IFN-γ and IL-1, which constitute this side of the balance.

It also goes without say that during the exacerbation phase, due precisely to the complexity and instability of the clinical setting, there is no place for either Bioregulatory Systems Medicine - **BrSM**, or for Physiological Regulating Medicine - **PRM**.

TAB. 4

Can **BrSM/PRM**
• prevent exacerbations?
• reduce use of medicinal products [antibiotics (resistance), cortisones]?
• help maintain prescriptive appropriateness in compliance with the national and regional budgets established for general medicine?

– I asked myself whether this might be useful in reducing the number of exacerbations; this would obviously have made it possible to use less antibiotics and cortisones, with a doubtless advantage for the patient, who would experience fewer side effects and less bacterial resistance, which is increasingly frequently reported due to excessive, and often inappropriate, use of these drugs. Furthermore, it would make it possible to ascertain whether using BrSM and PRM in this way might help GPs in the management of prescriptive appropriateness in order to meet national and regional targets *(spending review)* (TAB. 4).

MATERIALS AND METHODS

The study was conducted on a population of patients with COPD, some of whom with concomitant bronchiectasis (confirmed diagnosis in accordance with the GOLD guidelines).

– The study enrolled **12 patients** (6 M; 6 F, aged 54 - 99 years, mean age 75.5 years); 4 patients were GOLD stage 2 and 8 patients were GOLD stage 3; of whom 5 with concomitant bronchiectasis.
The patients were split into 2 groups (FIG. 3):

- **Group A**: **6 patients**, mean age 74.1 years, who received LAMAs and/or LABA + influenza vaccination + pneumococcal vaccination.
  2 GOLD stage 2 patients, **4** GOLD stage 3 patients; **2** patients with concomitant Bronchiectasis.
- **Group B**: **6 patients**, mean age 77.0 years, who received LAMAs and/or LABA + influenza vaccination + pneumococcal vaccination + **preventive overlapping therapy with BrSM** and **PRM**.
  2 GOLD stage 2 patients, 4 GOLD stage 3 patients; **3** patients with concomitant bronchiectasis.

The observation started in September 2015 (T0) and ended in March 2019 (T6). As indicators, the following were

taken into account: **1)** the demand for home/ambulatory visits; **2)** prescriptions for antibiotics and corticosteroids; **3)** treatment days.

The BrSM and PRM therapy prescribed to Group B (FIG. 4) consists in medicinal products for the treatment and prevention of colds:
Guna-Flu, 1 dose/week, taken in October, November, January, February, April, and May;
Citomix, 5 granules/day, taken from October to May;
Guna-Anti IL 1 and **Guna-IL 10**, 20 drops of each medicinal morning and evening from October to May; these medicinal products were prescribed with the aim of restoring the immune balance (stimulation of the Th2 side);
Echinacea compositum s, Ubichinon compositum, Coenzyme compositum®, 1 vial of each multicomponent-multitarget medicinal product by *mouth* via the sublingual route, on waking in the morning, once a week from October to May.

RESULTS

The following data were recorded regarding the **demand for home/outpatient clinic appointments** during the years of observation (FIG. 5):

Gruppo A (LAMAs and/or LABA):
▶ **80** outpatient/home appointments over 5 years
▶ average **16** appointments/year
▶ **2.66** appointments per patient/year.

Group B (LAMAs and/or LABA + BrSM and PRM medicinal products):
▶ **36** outpatient/home appointments over 5 years
▶ average **6** appointments/year
▶ **1** appointment/patient/year.

During appointments, patients were prescribed medicines, especially antibiotics and cortisones, in order to rapidly reduce the septic state-inflammatory agent causing the bronchiolitis and changes in airflow in the lesser airways responsible for the acute symptoms with considerable distress for the patient, dyspnoea, cough, and malaise.

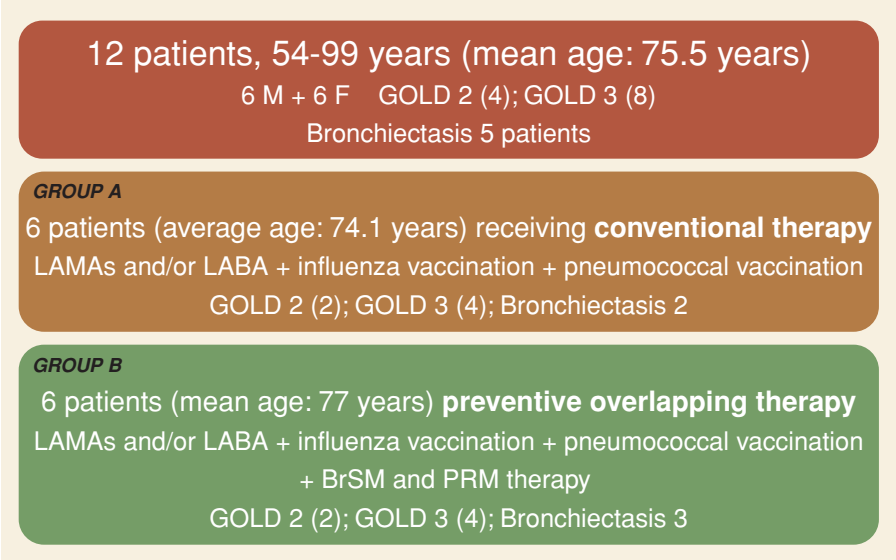


FIG. 3

• Data regarding the **prescription of antibiotics** (FIG. 6):

Group A (LAMAs and/or LABA):
▶ **71** packs prescribed over 5 years
▶ **308** days of therapy over 5 years
▶ **10.3** days of therapy/year/patient.

Group B (LAMAs and/or LABA + BrSM and PRM medicinal products):
▶ **17** packs prescribed over 5 years
▶ **90** days of therapy over 5 years
▶ **3.0** days of therapy/year/patient.

• Data regarding the **prescription of cortisones** (FIG. 7):

Group A (LAMAs and/or LABA):
▶ **35** packs prescribed over 5 years
▶ **200** days of therapy over 5 years
▶ **6.6** days of therapy/year/patient.

Group B (LAMAs and/or LABA + BrSM and PRM medicinal products):
▶ **7** packs prescribed over 5 years
▶ **45** days of therapy over 5 years
▶ **1.5** days of therapy/year/patient.

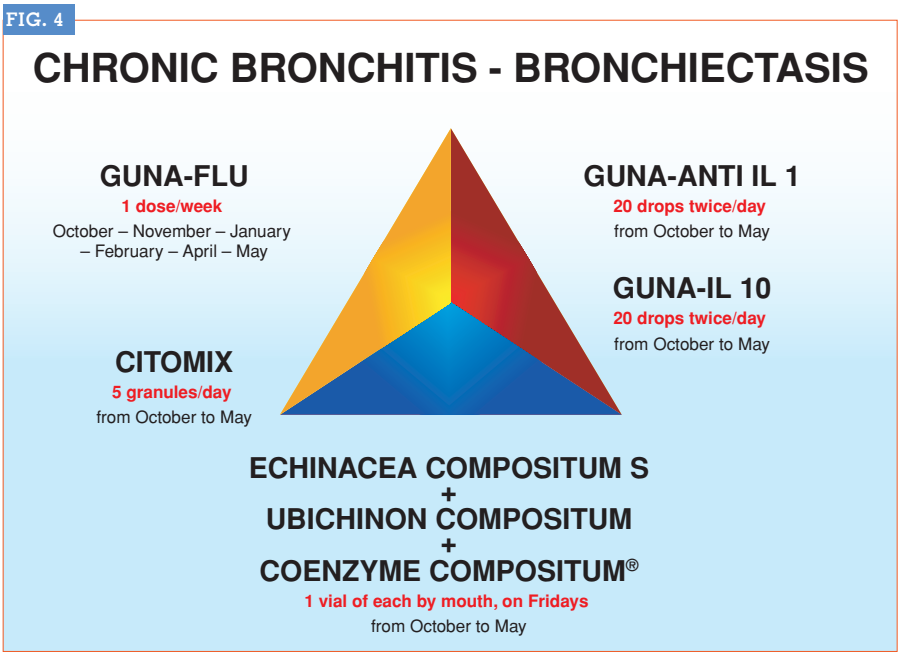


FIG. 4

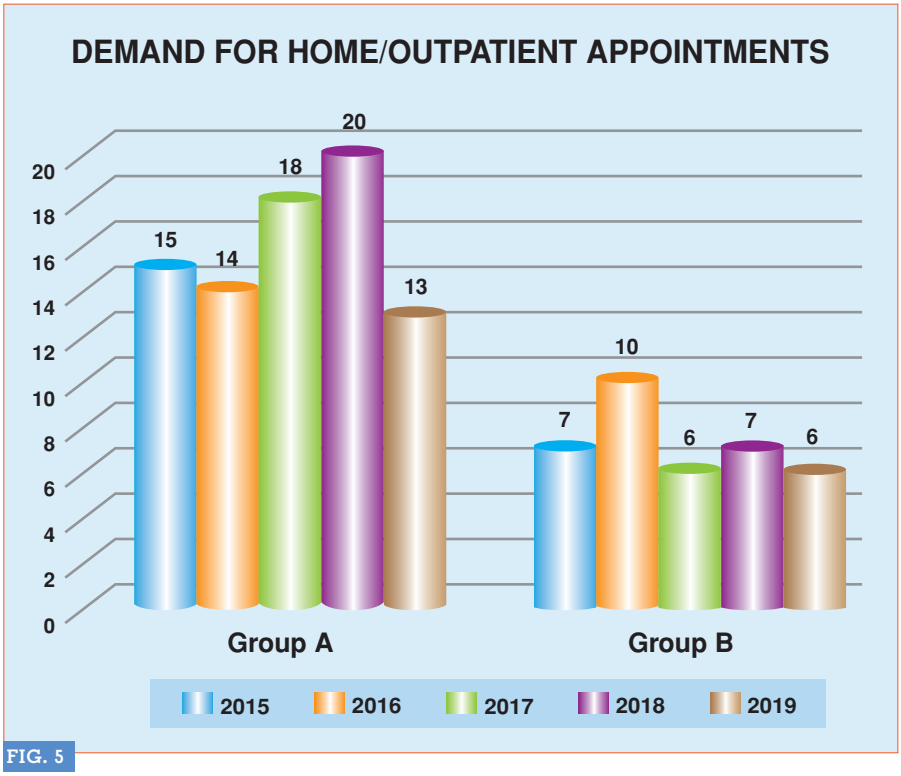


FIG. 5

The other indicators considered were **1)** prescriptive appropriateness **2)** compliance with national, regional and hospital pharmaceutical budgets, general practice governance targets, with which all general practitioners are familiar and for which they are monitored by the competent authorities.

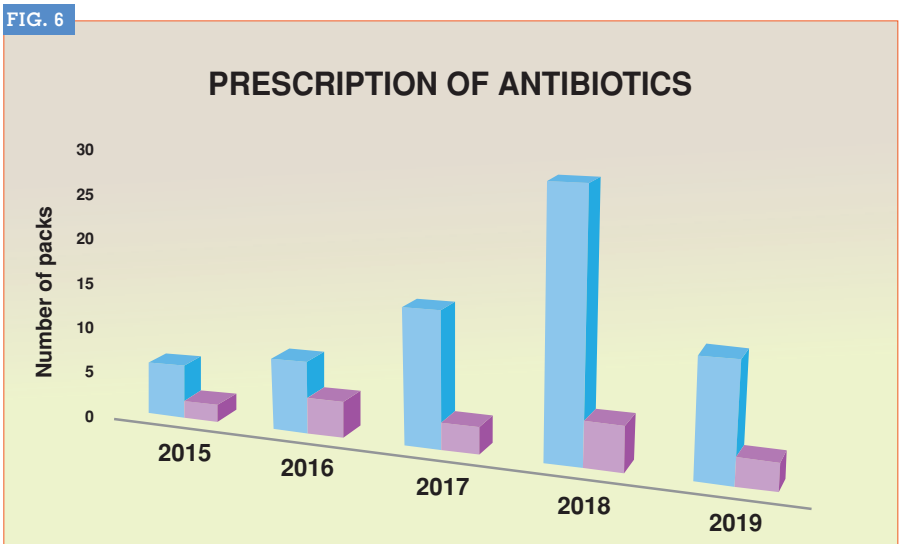
Keeping the healthcare budget under control means keeping the overall Regional budget under control, as **80%** of the entire Regional budget is allocated to healthcare (TAB. 5).

Incidentally, in the region of Umbria where I practice, pharmaceutical prescriptions can only be issued by general practitioners; specialists are merely able to suggest therapeutic indications, but they cannot personally prescribe them using regional or NHS prescriptions.

The *pro capite* pharmaceutical spending target set by Umbria Regional Authority for 2018 was EUR 180.00; the spending target established by Umbria 2 Local Health Authority for the same year was EUR 154.00.

The Umbria 2 Local Health Authority website indicates some of the classes of medicinal products prescribed; the "general antimicrobial agents", class consists primarily of "antibiotics"; personal prescriptions are considerably lower than the average for Umbria 2 LHA **(about 1/3 lower)**, most likely as a result of a different prescriptive behaviour influenced by personal training in BrSM and PRM.

FIG. 6



	2015	2016	2017	2018	2019
Group A	6	8	15	29	13
Group B	2	4	3	5	3

CONCLUSIONS

As mentioned previously, in the COPD exacerbation phase, as in the acute phase of other degenerative diseases, there is no place for BrSM and PRM; however, this does not preclude their use in the **prevention** of the **exacerbations** of these conditions.

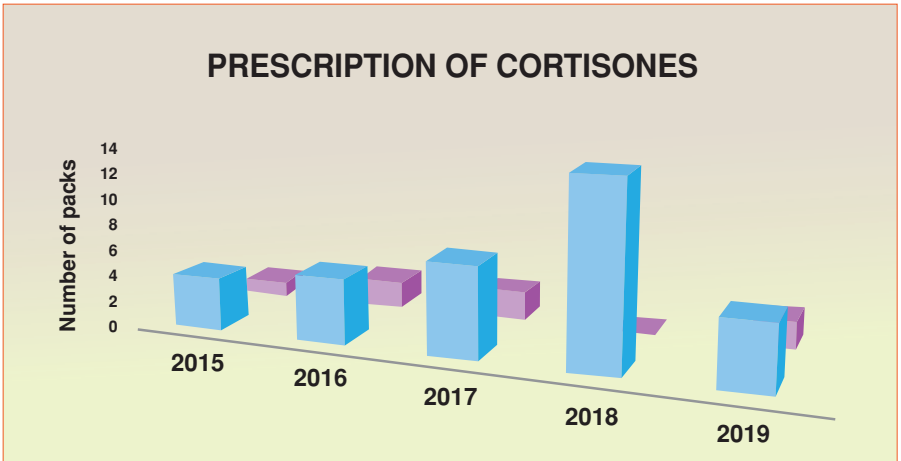
Multicomponent-multitarget and PRM medicines make it possible to act on homeostatic regulation systems by restoring the immune balance and actually reducing inflammation, with a positive effect on the number of COPD exacerbations.

– By doing so, it is possible to limit the medicinal products required during the acute phase of the disease:
less antibiotics and less cortisones, with fewer side effects and a reduced risk of antibiotic-resistance.

It goes without say that this does not mean not using antibiotics when they are necessary, rather avoiding an excessive and often inappropriate use of these medicinal products.

Using fewer medicinal products (antibiotics/cortisones) also means making the patient prone to fewer recurrences, as these medicinal products can contribute to reducing the innate immune response mediated by TNF-α, INF-γ and IL-1, which constitute the Th1 side of the balance, that in these situations can cause cytokine down-regulation.

– GPs who use BrSM and PRM in their clinical practice obtain better results in terms of patients' quality of life (for the reasons outlined above) and are facilitated in complying with the parameters of prescriptive appropriateness established for the national and regional spending budgets.



	2015	2016	2017	2018	2019
Group A	4	5	7	14	5
Group B	1	2	2	0	2

FIG. 7

TAB. 5

RESULTS

- Prescriptive appropriateness and compliance with national, regional and LHA pharmaceutical spending budgets are expenditure governance objectives: regional and national law.
- (< EUR 180.00 pro capite region of Umbria; < EUR 154.00 pro capite Umbria 2 LHA - 2018).
- 80% of the regional budget is dedicated to spending on healthcare.
- In the region of Umbria, pharmaceutical prescriptions can only be issued by GPs; specialists can merely suggest therapeutic indications, but cannot personally prescribe them using regional or NHS prescriptions.

References

– Buist A.S., McBurnie M.A., Vollmer W.M. *et* Al. – International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet **2007**; 370(9589): 741-50.
– Jackson H., Hubbard R. – Detecting chronic obstructive pulmonary disease using peak flow rate: cross sectional survey. BMJ **2003**; 327(7416): 653-4.
– Lozano R., Naghavi M., Foreman K. *et* Al. – Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet **2012**; 380(9859): 2095-128.
– Mathers C.D., Loncar D. – Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med **2006**; 3(11): e442.
– Paulin L.M., Diette G.B., Blanc P.D. *et* Al. – Occupational exposures are associated with worse morbidity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med **2015**; 191(5): 557-65.
– Stoller J.K., Aboussouan L.S. – Alpha1-antitrypsin deficiency. Lancet **2005**; 365(9478): 2225-36.
– WHO Meeting Participants – Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. Bull World Health Organ **1997**; 75(5): 397-415.

Fig. 1
https://www.msdmanuals.com/it/casa/disturbi-polmonari-e-delle-vie-respiratorie/bronchiectasie-e-atelettasie/bronchiectasie

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MD-SHOULDER IN THE INTEGRATED REHABILITATION TREATMENT OF SHOULDER PAIN IN POST-STROKE HEMIPLEGIC PATIENTS

SUMMARY

Shoulder pain (SP) is the most frequent complication in patients with post-stroke hemiplegia.
– SP can occur either in the first few weeks after the stroke (most frequently in the first 3 months), or 6-8 months after the acute cerebrovascular event (chronic shoulder pain).
– We recruited 40 patients undergoing ordinary hospitalisation in a Level II rehabilitation hospital for ischaemic stroke (transferred from acute hospital Stroke Units). All patients complained of shoulder pain on the hemiplegic side that presented in the first 3 months after the ischaemic event. The diagnosis of adhesive capsulitis was based on clinical findings and symptoms, as well as standard X-ray and musculoskeletal ultrasound.
– Patients were randomised to 2 treatment groups (Group A and Group B), stratified by age, gender and pain intensity. Outcomes were assessed at 1, 6 and 10 months. Group A was treated with intra-articular injection of Triamcinolone 40 mg 1 vial and Ropivacaine 2% 3 mL (total volume 4 mL) weekly for the first 2 weeks; the third treatment was administered 15 days after the second.
Group B was treated with injection of Guna MD-Shoulder 3 vials (for a total volume of 6 mL) intra-articularly (4 mL) and in the pericapsular area (the remaining 2 mL).
Use of Guna MD-Shoulder made it possible to obtain a biological effect of organic reconditioning of the compromised anatomical structures, and thus obtaining a positive result on the stabilisation of the glenohumeral joint, its range of motion and, therefore, on the pain symptom, not only in the early stage, but especially in the weeks following the treatment, with a continuous improvement of the outcomes recorded at the follow-up time-points.

KEY WORDS

SHOULDER PAIN, POST-STROKE HEMIPLEGIA, MD-SHOULDER

https://www.homeceuconnection.com/blog/proper-positioning-for-stroke-patients/

INTRODUCTION

Shoulder pain (SP) is the most commonly observed complication in patients with post-stroke hemiplegia.
Its incidence varies greatly according to the different clinical studies published in literature, with estimated rates ranging from **16%** to **72%** of cases.

– SP may present either in the first few weeks after the stroke (usually within the first 3 months), or later, 6-8 months after the acute cerebrovascular event (chronic shoulder pain).
For precisely this reason, SP is a complication that can condition the patient's neuromotor rehabilitation treatment and can have even significant repercussions on the functional recovery required for the activities of daily living.
According to the studies consulted, SP is most common **1)** in subjects with right brain injury, **2)** in subjects with spasticity scoring > 1 on the Ashworth scale, **3)** in ischaemic stroke, **4)** among females and **5)** in elderly patients.

– The aetiopathogenesis of shoulder pain in hemiplegic patients is still unclear.
In the late 1950s, Basmajian & Bazant attributed hemiplegic shoulder pain to the **dislocation** of the **glenohumeral joint (GHJD)**.
– This hypothesis, better known as the "Basmajian Theorem", resulted in many

FIG. 1

PROM (Passive Range of motion)

– Absolute values.

PROM – *PASSIVE RANGE OF MOTION*

		GROUP A	GROUP B
T0	ABD	120	122
	ER	94	93
	FLEX	35	34
T1	ABD	130	125
	ER	110	98
	FLEX	50	40
T2	ABD	131	135
	ER	100	100
	FLEX	54	55
T3	ABD	125	140
	ER	100	120
	FLEX	45	60

ABD = Abduction
ER = External rotation
FLEX = Anterior flexion

rehabilitation practitioners using orthoses to prevent dislocation. However, in the 1990s, some authors expressed certain doubts regarding the "responsibility" of GHJD in hemiplegic shoulder pain, claiming that the albeit common association does not necessarily mean there is a cause-effect relationship.

– Nowadays, the Literature is concordant in identifying three possible causes:

1) Conditions affecting the periarticular soft tissues of the GHJ: rotator cuff injury, rotator cuff tendinopathy (most commonly affecting the tendons of the *supraspinatus*, *subscapularis* and *biceps brachii* muscles), glenohumeral dislocation and, most commonly, **adhesive capsulitis**.

– The causes are undoubtedly the consequences of a functional imbalance of the agonist and antagonist muscles of the scapulohumeral girdle and consequently of the overload the shoulder joint is subject to in the course of post-stroke clinical evolution, as muscle flaccidity transitions to hypertonus;

2) CRPS (Complex Regional Pain Syndrome);

3) Central Hypersensitivity: in this case, the brain damage often has a precise location that can be seen on the MRI (thalamus, basal ganglia, cerebellopontine angle, bulb).

Pinpointing the cause of the SP is often rather challenging as, depending on the brain damage, the patient may have an even very complex neurological situation, with cognitive, motor and verbal impairment with aphasia. Furthermore, the clinical signs and symptoms are often rather generic and difficult to correlate with a single aetiology.

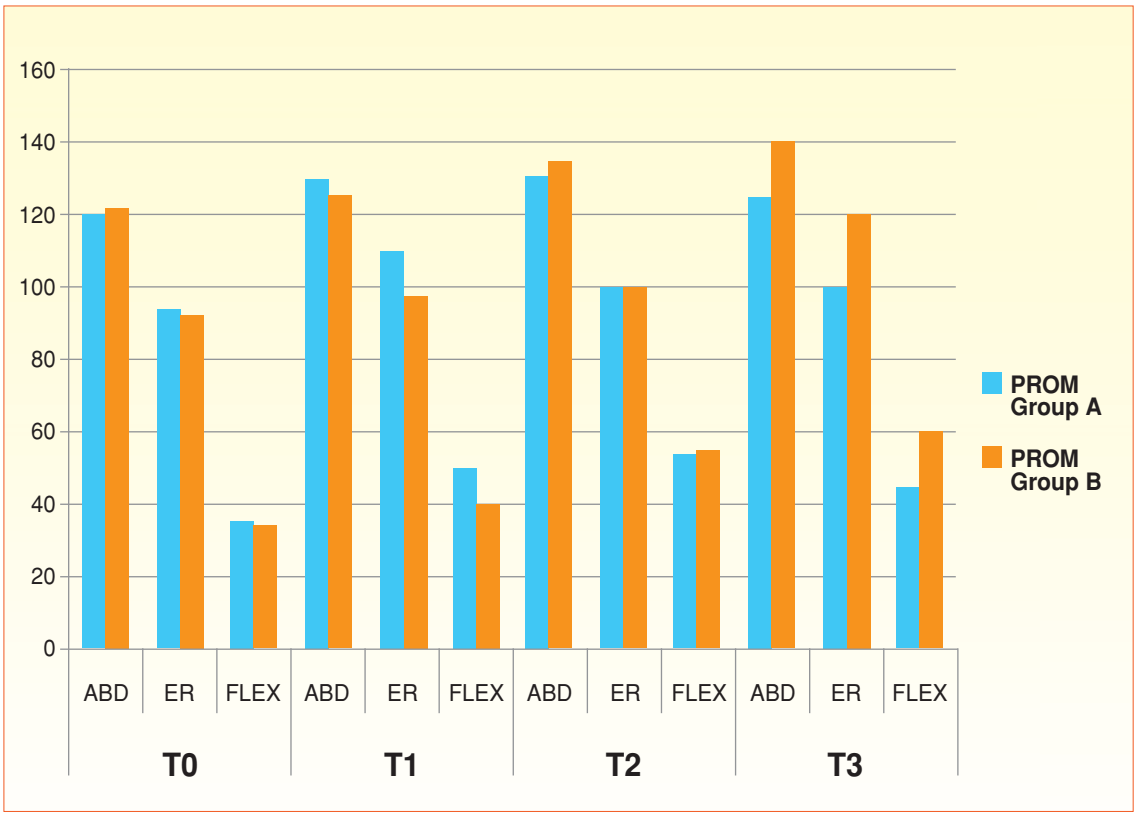
It is also necessary to remember that the clinical complexity of cases of SP may be due to the existence of multiple concurrent causes.

– In literature, the factors that may have an impact on the onset and evolution of SP are indicated as being the presence

FIG. 2

PROM (Passive Range of motion)

– Histograms representing the values presented in Fig. 1.



of severe motor damage (according to the Daniels Scale), significant changes in muscle tone in both the flaccidity and the hypertonic stages, and speech disorders (consistent with cognitive impairment).

Conventional treatment, which is not always satisfactory in clinical practice and is often conditioned by the fact that these patients are extremely frail, involves the prescription and use of **1)** upper limb orthoses, **2)** pharmacological therapy with analgesics, anti-inflammatories and a central muscle relaxant, **3)** peri/intra-articular injections with cortisone derivatives, and **4)** an adequate neuromotor rehabilitation protocol, with or without **5)** a combination of analgesic physiotherapy and functional electrical stimulation (FES).

Research conducted to optimise conservative rehabilitation treatment in post-stroke SP with an essentially musculoskeletal aetiopathogenesis (adhesive capsulitis) taking into consideration all the anatomical structures involved, has made it possible to formulate a number of considerations.

The use of medical devices for injection containing porcine collagen (Medical Device) allows a more effective and specific *in situ* positioning of the collagen, which serves a carrier and stabilisation function.

– This makes it possible to replace, strengthen, structure and protect (barrier against adhesion) cartilage, tendons, ligaments and joint capsules, consequently improving the status of the collagen fibres and all the other anatomical structures it contains and therefore to provide mechanical support to the affected anatomical segment.

MATERIALS AND METHODS

Therefore, the hypothesis on which our study was based was that injection treatment with **Guna MD-Shoulder** would recondition the compromised anatomical structure and improve the stability of the shoulder; a "combined" treatment can improve the functional outcomes of rehabilitation and/or produce better pain control in the subacute phase, as well as having a positive impact on the progression of the disease (less frequent exacerbations).

– We recruited **40 patients** undergoing ordinary hospitalisation in a Level II rehabilitation hospital for ischaemic stroke (transferred from acute hospital Stroke Units).
All patients complained of shoulder pain on the hemiplegic side that appeared in the first 3 months after the ischaemic event (SP appearing after 3 months is more often due to central hypersensitivity or CRPS).
The diagnosis of adhesive capsulitis was based on clinical findings and symp-

WBS – DAYTIME AND NIGHT-TIME PAIN

		GROUP A	GROUP B
T0	N	4,2	3,5
	D	7,1	6
T1	N	3,5	3
	D	4,2	5,2
T2	N	2,1	2,1
	D	4	4
T3	N	2,3	2,1
	D	6	3,2

FIG. 3

WBS (Wong-Baker Scale)
– Absolute values.

N – Night-time
D – Daytime

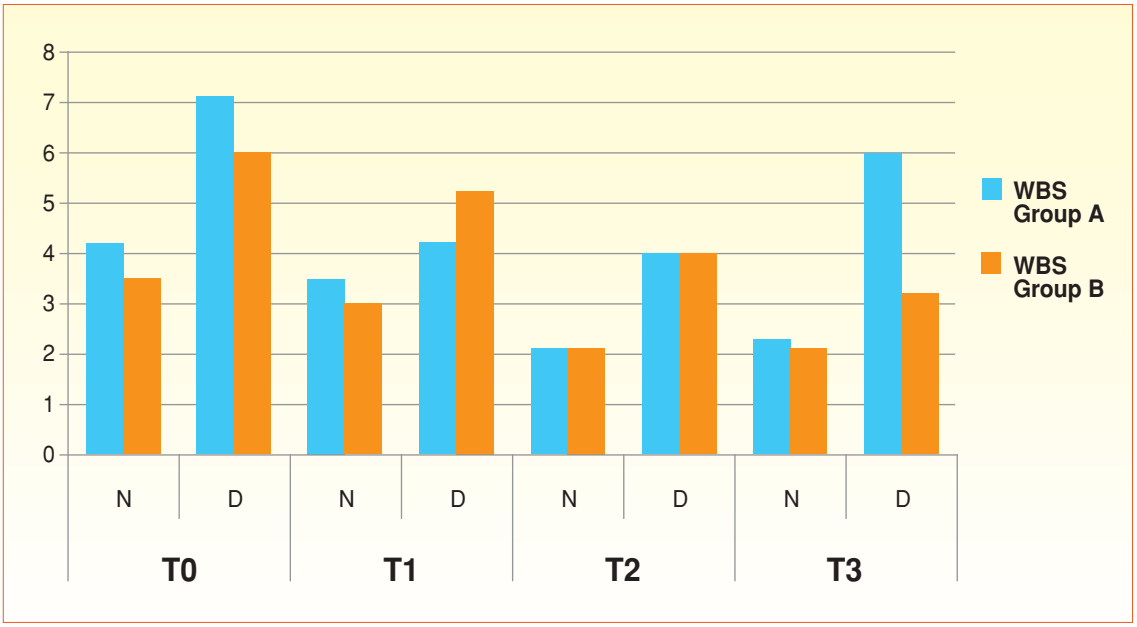


FIG. 4

WBS (Wong-Baker Scale)

– Histograms representing the values presented in Fig. 3.

N – Night-time
D – Daytime

toms, as well as standard X-ray and musculoskeletal ultrasound.

– Patients were randomised to **2** treatment groups (**Group A** and **Group B**), stratified by age, gender and pain intensity (Wong-Baker Scale). The outcomes were assessed at 1, 6, and 10 months.

– Inclusion criteria: F and M patients aged between 55 and 75 years who recently had a stroke; clinical and instrumental diagnosis of SP on the hemiplegic side due to adhesive capsulitis, from less than 3 months after the cerebral ischaemic event; WBS (Wong-Baker Scale) > 5, not using NSAIDs, cortisones or opiates.

– Exclusion criteria: past history of SP secondary to musculoskeletal conditions; prior shoulder and elbow fracture; rheumatoid arthritis; current diagnosis of rotator cuff tear and calcified tendinopathy; episodes of shoulder dislocation during the muscle flaccidity stage; serious comorbidity (CIRS 4); Parkinson's disease; dementia (evaluated using the Mini-Mental State Examination); severe neurological damage (emineglect*, speech disorders, Ashworth > 3 muscle hypertonus, severe residual motor damage according to the *Daniels Scale*); use of anticoagulants (warfarin or new oral anticoagulants); use of opiates or cortisone derivatives during the previous month; intra/peri-articular injections to the shoulder in the previous 3 months.

Both groups (A and B) received treatment with the same multidisciplinary rehabilitation protocol (inter-hospital therapeutic and diagnostic pathway) focussing on neuromotor treatment (mobilisation of the paralysed limb, facilitation of active neuromuscular unit recruitment, inhibition of muscle hypertonus and coordination of the inhibitory and excitatory activities of the agonist and antagonist muscles during the performance of the different motor tasks), neuropsychiatric treatment to stimulate the cognitive-motor afferences, ergonomic education and occupational therapy to recover activities of daily living and occupational activities.

The multidisciplinary rehabilitation treatment during the 60 days of ordinary hospitalisation was administered for 3 hours every day.
The patient then switched rehabilitation setting to a daily outpatient treatment with approximately one-hour sessions, for a total of 10 sessions.

• Both treatment groups (A and B) also received ultrasound-guided (Clarius Ultrasound portable linear probe) injection therapy.

Group A was treated with intra-articular injection of **Triamcinolone** 40 mg 1 vial and **Ropivacaine 2%** 3 mL (for a total volume of 4 mL) weekly for the first 2 weeks; the third treatment was administered 15 days after the second.

Group B was treated with injection of **Guna MD-Shoulder** 3 vials (for a total volume of 6 mL) intra-articularly (4 mL) and in the peri-capsular area (the remaining 2 mL).

The following were then analysed as clinical and functional outcomes **1)** daytime and night-time pain **(WBS)**; **2)** passive ROM **(PROM)** of the hemiplegic shoulder in anterior flexion **(FLEX)**, abduction **(ABD)** and external rotation **(ER)** (using a protractor), in addition to records of NSAID use during the follow-up period (FIGS. 1-4).

▶ The results obtained make it possible to conclude that in the multidisciplinary neuromotor rehabilitation protocol for ischaemic stroke patients, ultrasound-guided injection treatment with MD-Shoulder plays a decisive role when the complication known as SD, with a prevalent musculoskeletal aetiology (adhesive capsulitis), presents at an early stage.

Evidently the greater the residual neurological damage and the later the complication presents, the less effective the ultrasound-guided treatment will be, because other non-musculoskeletal causes (CRPS and central hypersensitivity) will sustain the pain symptoms.

CONSIDERATIONS

In the early stage, the injection treatment with cortisone derivative was undeniably effective on both the pain and the passive range of motion of the shoulder, before losing its beneficial effect over time.

On the other hand, in literature, the cortisone derivative is extensively reported as having a "toxic" effect on biological tissues with a prevalent collagen component.
Furthermore, the use of these medicinal products is potentially hazardous when they are used on a frail population such as that considered in this study.
In approximately half of all cases, patients experienced adverse effects such as blood pressure increases, onset of headache and facial rash. It goes without say that this treatment was not offered to diabetic subjects or those with poor glycaemia control.

– The injection treatment with Guna MD-Shoulder, on the other hand, did not give rise to any adverse reaction, confirming that it is absolutely safe.

The use of Guna MD-Shoulder made it possible to obtain a biological effect of organic reconditioning of the impaired anatomical structures, together with a hydraulic distension associated with the volume of product injected, making it possible to achieve a positive result on the stabilisation of the glenohumeral joint, its range of motion and, consequently, on the daytime and night-time pain symptoms, not only in the early stage, but especially in the weeks after the treatment, with a continuous improvement in the outcomes recorded at the follow-up time-points.

* **Ed. Emineglect**: Clinical deficits such as poor left visual exploration, inaccurate identification of the midpoint on a line, left limb hypokinesia and anosognosia. This kind of deficit is usually caused by right brain injury.

These results obviously allowed the patient to obtain greater benefit from the neuromotor rehabilitation treatment provided.

The injection treatment with MD-Shoulder would also appear to better control the progression of the shoulder condition, by reducing the frequency of exacerbations over time (control of the pro-inflammatory cytokine network).

– In coming months, it will be necessary to confirm the results achieved by expanding the study case load and, in particular, attempting to identify the correct timing for subsequent injection treatments as part of a personalised rehabilitation project (maintenance treatment). ■

References

- Basmajian J., Bazant F. – Factors preventing downward dislocation of the adducted shoulder joint. An electromyographic and morphological study. J. Bone Joint Surg Am., **1959** Oct.
- Feninno D., Bonacina A. – Associazione di Collagen MDs e CHELT terapia nel dolore osteo-articolare di spalla e di ginocchio. La Med. Biol. **2017**/2; 37-42.
- Guna Collagen Medical Devices. Il trattamento iniettivo delle affezioni osteo-artro-mio-fasciali. Dipartimento Scientifico & Medico Guna S.p.a. Settembre **2018**.
- Hun Jang M. *et* Al. – Effect of Intra-articular Hyaluronic Acid Injection on Hemiplegic Shoulder Pain After Stroke. Ann. Rehabil. Med. 40 (5): 835-844; **2016**.
- Lingren I., Brogardh C. – Post stroke shoulder pain and its association with upper extremity sensorimotor function, daily hand activities, perceived participation, and live satisfaction. PM & R. **2014**; 6; 781-789.
- Martinez-Calderon J. *et* Al. – The role of psychological factors in the perpetuation of pain intensity and disability in people with chronic shoulder pain: a systematic review. BMJ Open. **2018** Apr 13;8(4): e020703.
- Milani L. – Un nuovo e raffinato trattamento iniettivo delle patologie algiche dell'Apparato locomotore. Le proprietà *bio-scaffold* del collagene e suo utilizzo clinico. La Med. Biol., **2010**/3; 3-15.
- Milani L. – I Guna Collagen Medical Devices 10 anni dopo. Analisi ragionata di 2 recenti importanti ricerche e *update* della Letteratura. La Med. Biol. **2019**/2; 3-18.
- Nestorova R. *et* Al. – Bulgarian experience with injectable Collagen Guna Medical Devices in Shoulder periarthritis. Physiological Regulating Medicine **2020**; 9-16.
- Randelli F. *et* Al. – The Collagen-Based Medical Device MD-Tissue Acts as a Mechanical Scaffold Influencing Morpho-Functional Properties of Cultured Human Tenocytes. Cells, **2020**, 9, 2641: doi 10.3390/cells9122641.
- Soo Hoo J. *et* Al. – Central Hypersensitivity in chronic hemiplegic shoulder pain. Am J Phys Med Rehabil. **2013**; 92(1); 1-13.
- Torres-Parada M. *et* Al. – Post stroke shoulder pain subtypes classifying criteria: towards a more specific assessment and improved physical therapeutic care. Braz. J. Physical Therapy **2020**; 24 (2); 124-134.
- Wu T. *et* Al. – The application of sonography in shoulder pain evaluation and injection treatment after stroke: a systematic review. J. Phys Ther. Sci. 27: 3007-3010; **2016**.
- Zhu Y. *et* Al. – Pain management of hemiplegic shoulder pain post stroke in patients from Nanjing, China. Neural Regen Res. **2013**, Sep 5; 8 (25): 2389-2398.

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CLINICAL

TREATMENT OF HIP OSTEOARTHRITIS WITH MD-HIP – CLINICAL AND FUNCTIONAL EVALUATION USING A GAIT ANALYSIS SYSTEM

SUMMARY

In Italy, 8% of all forms of osteoarthritis (OA) are localised at the acetabulofemoral joint, with considerable impairment of quality of life due to pain and lameness, and consequent reduction of movement. Conventional medical treatment of OA is based on the use of analgesics, NSAIDs, corticosteroids and physiotherapy.
– In this observational study, 15 patients (mean age = 62 years) with grade II-III hip OA according to the Kellgren-Lawrence Scale were enrolled and treated solely with the MD-HIP medical device (2 vials = 4 mL/treatment) injected subcutaneously into the periarticular and peritrochanteric regions once a week for 4 consecutive weeks.
Evaluations were performed at the beginning of therapy (T0) and at one week after the 4th and last treatment session (TF).
Results obtained:
– NRS (Numeric Rating Scale): from 7.26 at T0 to 0.8 at TF;
– ROM (Range of Motion): from 78° at T0 to 88° at TF;
– WOMAC (Western Ontario and McMaster Universities Arthritis Index) scale: from 52.05 at T0 to 15.88 at TF;
– Support phase: from 62.77 at T0 to 59.74 at TF;
– Flight phase: from 37.38 at T0 to 40.28 at TF;
– Propulsion: from 6.05 at T0 to 6.81 at TF;
– Gait quality: from 91.95 at T0 to 97.08 at TF.
The values of the last 4 parameters considered were obtained using the BTS G-Walk analyser.
The statistical significance of all the results obtained ($p < 0.01$) and the absence of side effects show that MD- HIP is an effective and highly reliable tool for the treatment of hip OA.

KEY WORDS

HIP OSTEOARTHRITIS, MEDICAL DEVICE, MD-HIP, GAIT ANALYSER

https://stiwell.medel.com/orthopaedics/hip-arthrosis

INTRODUCTION

Osteoarthritis (OA) is a chronic, debilitating disease with a multi-factorial aetiology; the major causes of this complex condition include age, obesity, metabolic disorders, inflammatory diseases, and genetic factors.

– In Italy, approximately 5 million patients suffer symptomatic forms of OA, characterised predominantly by pain and reduced joint mobility.
Conventional conservative treatment aims to reduce pain and increase the joint's range of motion using analgesics, NSAIDs, steroidal anti-inflammatories, and physiotherapy (1).

8% of all forms of OA are localised at the acetabulofemoral joint that, as in all other forms of OA, is characterised by pain and a reduced range of motion (lameness), resulting in an impaired quality of life.

The osteoarthritic process is characterised by a vicious circle that results in the degradation of the articular cartilage matrix **(ACM)** and chondrocyte death, causing changes in the neosynthesis of collagen-rich ACM, whose function is to absorb the mechanical stress placed on the joints.

– The 2003 EULAR (European League Against Rheumatism) Guidelines (2) in-

GENDER	AGE	SIDE
F	77	R
F	65	R
M	50	R
M	50	L
F	67	L
F	69	L
F	57	R
F	43	L
M	73	L
M	72	R
F	63	R
F	72	R
F	71	L
M	54	R
F	47	R

TAB. 1

dicate, among the treatment options for OA, the use of SySADOA (Symptomatic Slow-Acting Drugs for OsteoArthritis) able to modify the evolution of OA.
Of these options, in recent years the use of hyaluronic acid **(HA)** has become popular due to its synovial fluid viscosupplementation properties, which make it possible to restore the biological and organoleptic properties of the normal HA present inside the joint capsule, which, in the case of OA, is deficient (3).

HA is used in certain forms of OA, such as osteoarthritis of the knee and shoulder.

When HA is used in hip OA, ultrasound guidance is used to obtain optimal control of the position of the needle, as the hip is a deep joint and, therefore, it is more difficult to reach (4).

– Of the various treatment options for OA, in order to reduce the cartilage degradation process, it is necessary to consider products containing collagen, which can be administered both in hydrolysed form via the oral route, and – far more effectively – by injection (5).

Lastly, although many studies have investigated the effects of these treatments before and after local injection, very few have evaluated them in terms of gait quality (6).

PURPOSE OF THE STUDY

The purpose of this observational study was to evaluate the outcomes of use of **MD-HIP** medical device for injection containing collagen in the treatment of **hip osteoarthritis**.
– The primary outcome was the evaluation of the pain and functional parameters;
– The secondary outcome was the correlation of these data with gait quality.

MATERIALS AND METHODS

Between January and October 2020, we enrolled **15 consecutive patients** with hip OA referred to our Physical Medicine & Rehabilitation Unit. Patient characteristics are provided in TAB. 1:

- 10 F
- 5 M
- mean age: 62 years
- right hip OA: 9 pat.
- left hip OA: 6 pat.

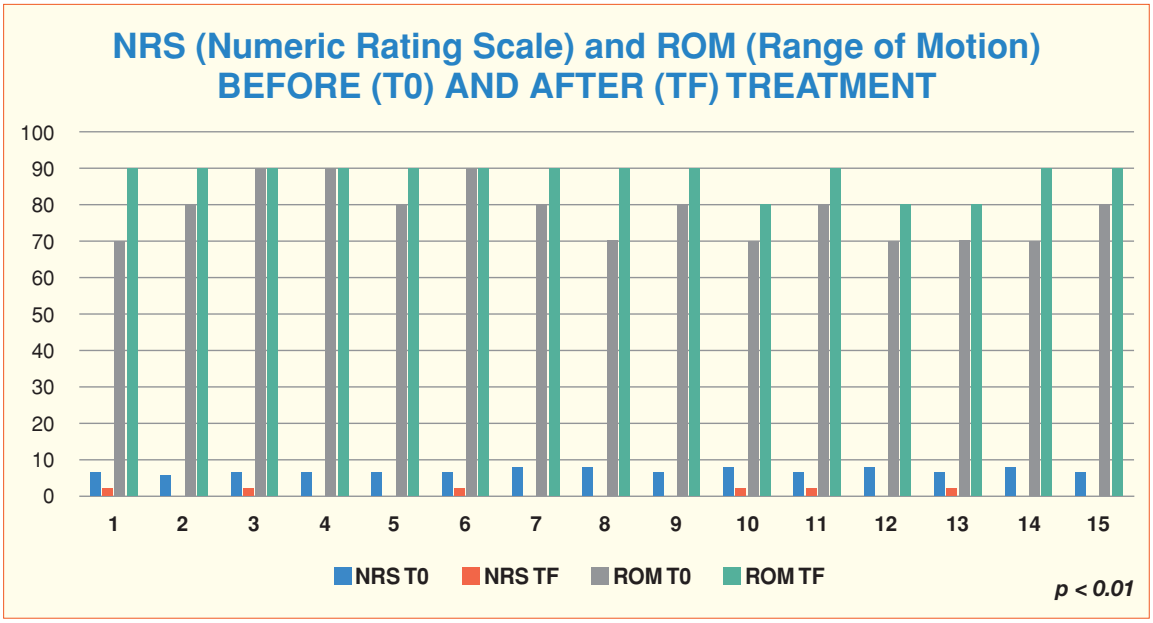
Each patient was assessed before the injection **(T0)** and 5 weeks later **(TF)**, one week after the last treatment session.

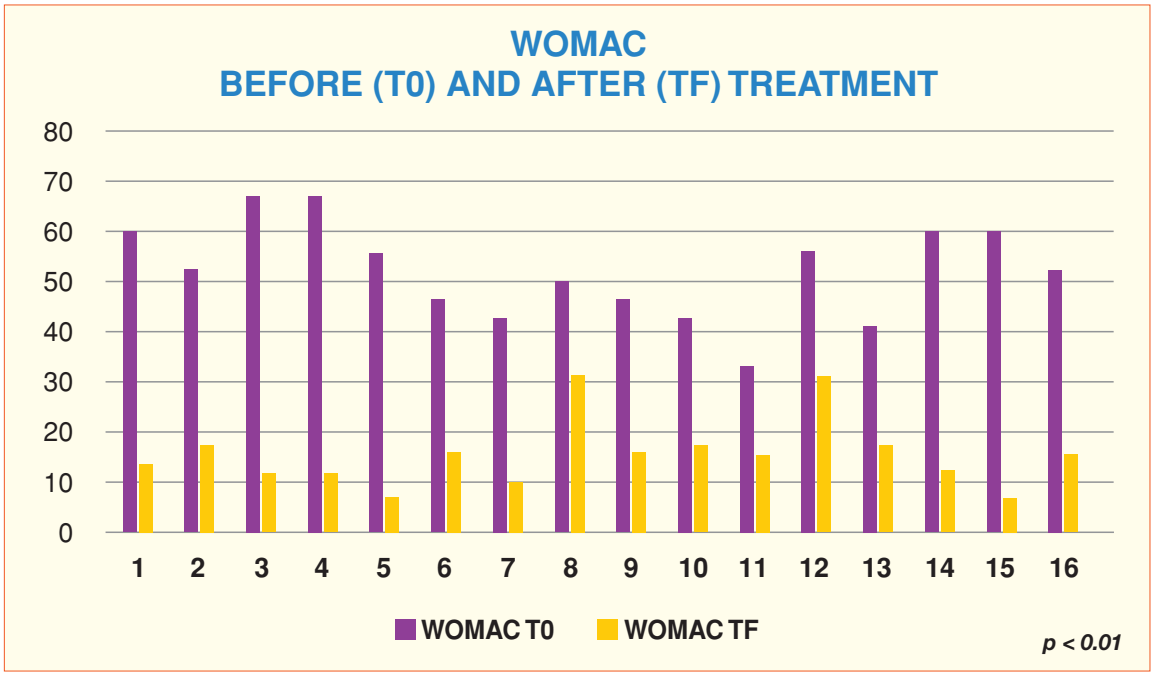
The study inclusion and exclusion criteria are indicated below.

– Inclusion criteria:

- age between 40 and 80 years;
- grade II-III hip OA defined by radiographic grading using the Kellgren-Lawrence Scale (7);
- absence of pharmacological treatments for active OA;
- good treatment compliance in all steps of the study.

TAB. 2





TAB. 3

– Exclusion criteria:
- poor treatment compliance;
- presence of other conditions involving the acetabulofemoral joint such as tumours, necrosis of the head of the femur, dysplasia; patients eligible for hip replacement surgery;
- patients who received steroids in the previous 6 months;
- anti-coagulant therapy;
- active skin infections or disease at the treatment site.

– Treatment was carried out solely with **MD-HIP** (Guna Spa, Milan - Italy), a medical device for injection containing collagen, developed specifically for the hip joint.
The chosen injection route was **subcutaneous**; the injection sites were **1)** the periarticular region of the hip, and **2)** the peritrochanteric regions.
– During each treatment session, patients were injected **2 vials** of MD-HIP (4 mL).
The sessions were once-weekly for **4 consecutive weeks** (total of 8 vials injected).
The final assessment was performed one week **after** the last treatment session (week 5).
The assessments were carried out using:
- the **NRS** (Numeric Rating Scale) for the **pain evaluation**;
- the **WOMAC** (Western Ontario and McMaster Universities Arthritis Index) scale for the **functional assessment**;
- **Gait analysis** using the **BTS G-Walk** analyser [BTS Bioengineering, Garbagnate Milanese, Milan - Italy].

The WOMAC (8) scale is used to assess the conditions of patients with hip or knee OA.

The test rates the main aspects of the condition, such as pain, joint stiffness and function of the considered joint.
The score is the sum of the 3 groups of questions with 5 possible answers to choose from to rate pain, stiffness and functional limitation of activities of daily living such as going up stairs, lying down on and getting up from a bed, walking, etc.
• The BTS G-Walk gait analyser consists of a wireless system connected to a computer.

This instrument consists of 1) a triaxial accelerometer, 2) a magnetic sensor and 3) a triaxial gyroscope positioned at L5. BTS G-Walk analyses a number of gait parameters, such as speed, cadence and symmetry index and therefore provides valuable information on pelvic movements on three axes.

In this study, the parameters considered were:
- propulsion, to assess functional recovery;
- the support phase (normal value: 58.98 +/- 1.97) and the flight phase (normal value: 40.03 +/- 3.56), to evaluate gait quality in relation to pain;
- the gait quality index.

INJECTION TECHNIQUE

Each treatment was administered with a 16 mm 25 G needle, via the subcutaneous route.

– The injection sites were the periarticular region, with injections perpendicular to the skin plane, and the peritrochanteric region with the needle slanted to an angle of about 30° to the skin plane.

The subcutaneous route was used considering the specific tropism and trophism of MD-HIP for the acetabulofemoral joint.

The injection treatment was also expanded to the peritrochanteric region as we believe that these patients also have a concomitant functional stress-induced

tendinopathy of the greater trochanter insertion site that contributes to the symptoms experienced.

STATISTICAL ANALYSIS

For data analysis, we calculated the mean with its pre- and post-treatment variations and, using an appropriate programme, the achievement of statistical significance, using a comparison of means test.

RESULTS

The analysis of the results showed a considerable decrease/ increase in both the clinical and functional values.
– The NRS (Numeric Rating Scale), values, used to rate pain, and ROM (Range of Motion), showed a significant decrease in the former, with a mean value of **7.26** at **T0** and of **0.8** at **TF**, and an increase in the range of motion for femur flexion in relation to the pelvis, with a mean value of **78°** at **T0** and of **88°** at **TF** (TAB. 2).
– The functional indices, evaluated using the WOMAC scale, showed a significant improvement with a mean value of **52.05** at **T0** and of **15.88** at **TF** (TAB. 3).
– For the gait quality analysis, the indices considered were **1)** the flight phase; **2)** the support phase, to be correlated with pain; **3)** propulsion, to be correlated with speed and therefore the extension of the acetabulofemoral joint; **4)** the gait quality index as a general assessment index considering various parameters.

– The analysis of these data showed a decrease in the mean support phase value from **62.77** at **T0** to **59.74** (normal value: 58.98 +/- 1.97) at **TF** and – consequently – an increase in the flight phase from a mean value of **37.38** at **T0** to **40.28** at **TF**.
In both cases this variation achieves statistical significance ($p < 0,01$).

These changes show an improvement in gait quality, to be correlated with an improvement in propulsion (from **6.05** at **T0** to **6.81** at **TF**) and a reduction in pain at weightbearing and walking [detected by means of the reduction in the mean NRS values at TF (see before)], which, in turn, indicates the better flexion-extension of the hip associated with the increase in ROM [mean of the TF values equal to 88° (see before)] and of the gait quality with a mean value of **91.95** at **T0** and of **97.08** at **TF** ($p < 0.01$) (TAB. 4).

DISCUSSION

The purpose of this study was to evaluate treatment with MD-HIP in patients with grade II or III hip osteoarthritis according to the Kellgren-Lawrence Scale.

OA is currently common in Italy, where it is estimated to affect approximately 5 million people.
In approximately 8% of cases, the disease involves the hip joint.

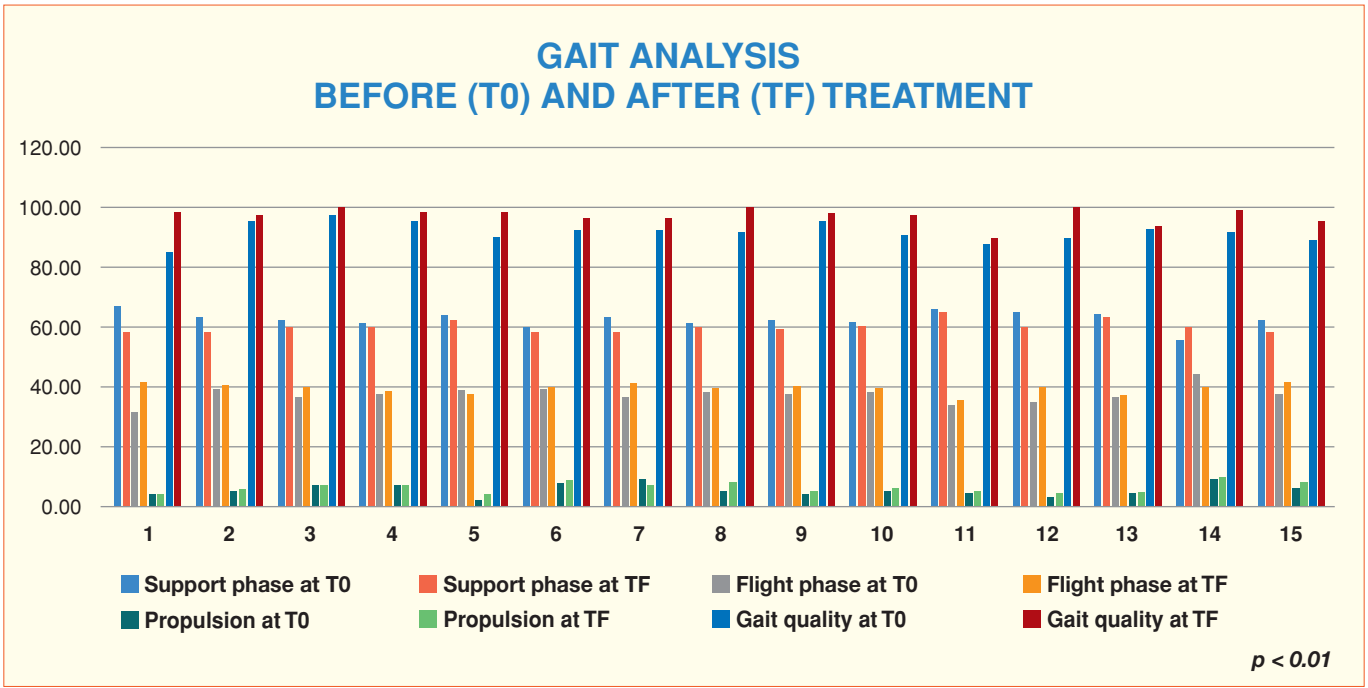
Hip OA is characterised by pain, decrease in the joint's range of motion lameness and gait defects that, in the most severe cases, requires joint replacement surgery.

Conventional treatments aim to increase the range of motion of the joint and reduce pain and they rely mainly on the use of anti-inflammatory drugs and physical therapies.

In our trial, we only injected a medical device containing collagen (MD-HIP) via the subcutaneous route.
The injection sites were periarticular and peritrochanteric.

The former (periarticular sites), because

TAB. 4



MD- HIP contains an active substance that provides specific trophism for the acetabulofemoral joint.
The latter (peritrochanteric sites), because we noticed that, in order to compensate, these patients develop a tendinopathy of the peritrochanteric and gluteus medius muscles that exacerbates the symptoms experienced.

– The results obtained show a clear improvement in the clinical and functional status.

As regards the primary outcome, there was a significant reduction in pain as well as an increase in the joint's range of motion.

The functional improvement was also evident, as rated by both patients and the WOMAC Scale, as well as by means of gait analysis, with an improvement in the support phase and speed.

CONCLUSIONS

The purpose of our study was to evaluate the treatment of hip OA using Collagen Medical Device-HIP (MD-HIP).

All patients were evaluated using reference clinical and functional scales and with a highly-innovative gait analyser.

– The data showed a significant improvement in the values after 4 consecutive weeks of treatment with MD-HIP, injected via the subcutaneous route.

These variations achieved statistical significance.

– Gait analysis represents an optimum system for evaluating the results achieved.

References

1. Qvistgaard E. *et* Al. – Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage. **2006** Feb;14(2):163-70. Epub 2005 Nov 14.

2. AA.VV. – EULAR Recommendations **2003**: an evidence-based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies *Including*: Jordan K.M. *et* Al. – Therapeutic Trials (ESCISIT). Ann Rheum Dis **2003**; 62:1145-1155.

3. Bellamy N. *et* Al. – Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. **2006** Apr 19.

4. Migliore A. *et* Al. – Efficacy and safety of viscosupplementation by ultrasound-guided intra-articular injection in osteoarthritis of the hip. Osteoarthritis Cartilage. **2003** Apr; 11(4): 305-6.

5. Reshkova V. *et* Al. – Efficacy and safety evaluation of Guna Collagen MDs injections in knee osteoarthritis – A case series of 30 patients. Physiological Regulating Medicine, **2017**; 27-29.

6. Paoloni M. *et* Al. – Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid. Clin Biomech (Bristol, Avon). **2012** Aug;27(7):661-5. doi: 10.1016/j.clinbiomech.2012.02.004. Epub 2012 Mar 11.

7. Kelgrenn J.H., Lawrence J.S. – Radiological Assessment of osteoarthrosis. Ann. Reum. Dis. **1957**; 16:494-502.

8. Salaffi F. *et* Al. – Reliability and validity of the WOMAC Osteoarthritis Index in Italian patients with osteoarthritis of the knee. Osteoarthritis Cartilage. **2003**; 11: 551-60.

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CLINICAL

C. Supino

LOW-DOSE BDNF AND SPECIFIC LEARNING DISABILITIES – A POSSIBLE INDICATION

SUMMARY

Specific Learning Disabilities (SLD) are conditions that present a discrepancy between the levels of academic performance and the potential deduced from the subject's actual intellectual abilities.
Learning disorders involve difficulty in concentration or attention, in language development, or in processing visual and auditory information.
Diagnosis includes intellectual, educational and language assessments as well as medical and psychological assessments.
Treatment consists, first of all, in educational management and in medical, behavioral and psychological therapy.
– In a group of 9 patients Guna-BDNF was added to these treatments with an evident improvement (+50%) vs the control group in test performance and an increase in self-esteem.

KEY WORDS

LOW DOSE MEDICINE, BDNF, NEUROTROPHINS, SPECIFIC LEARNING DISABILITIES

https://d2m3czf6fvb8bh.cloudfront.net/site_content/files/images/categories/children/dyslexia_in_children_750.jpeg

INTRODUCTION

The acronym **SLD** (Specific Learning Disabilities) refers to a diagnostic category regarding specific developmental learning difficulties pertaining to neurodevelopmental disorders according to the DSM 5 (1,2).

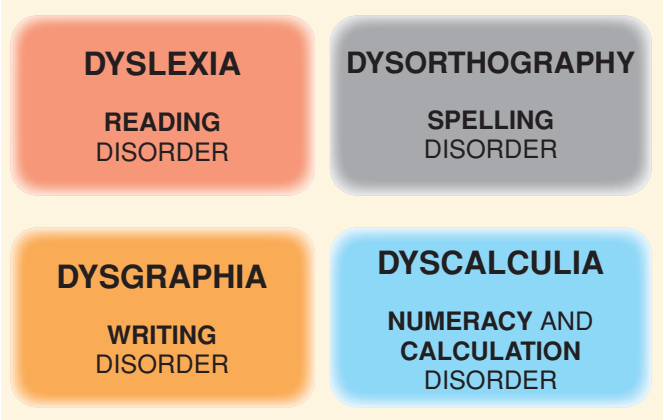
– Neurodevelopmental disorders are neurological conditions that present in early infancy, usually before the start of primary school.

SLDs impair personal, social, scholastic and/or professional development and entail difficulties in the acquisition, retention and application of skills or specific sets of information.
Although these disorders affect children and teenagers who do not usually present particular disabilities or difficulties, without adequate support, they can make scholastic activities difficult.

SLDs are, therefore, a series of disabilities that are relatively common during the developmental age, that can be attributed to a primarily constitutional neurobiological origin, and that regard the acquisition of scholastic skills, intended as tools that make it possible to obtain the formal knowledge proposed through educational processes.

– Each of these disorders concerns different functions and abilities: speech, motor skills, reading, writing, and arithmetic.
The characteristic that is common to them all is the specificity of the deficit, which can be attributed to consistent

FIG. 1



and recognisable areas that are independent of the subject's cognitive level.

– The term 'specific' regards the fact that the disability presents in an individual who does not present neurological conditions (e.g. epilepsy), or secondary defects (hearing or sight impairments), who is of adequate intelligence and does not present any particular cultural disadvantage conditions.

Depending on the type of difficulty, different conditions are identified regarding the specific skills of reading, intended as the ability to decode a text **(dyslexia)**, writing, intended as the ability of phonographic encoding and spelling **(dysorthography)**, graphomotor skills **(dysgraphia)** and arithmetic, disorder affecting numeracy and calculation skills, intended as the ability to understand and work with numbers **(dyscalculia)** (FIG. 1).

The Istituto Superiore di Sanità [Italian National Institute of Health] Consensus Conference (Cc-ISS, 2011) defines SLDs *"disorders that affect a specific area of abilities, without affecting general intellectual functioning. They involve the instrumental skills of scholastic learning"* (TAB. 1).

It is important to stress that children with SLDs are of normal or higher than normal intelligence and they find it easy to obtain an overview, to see the bigger picture.
They are able to grasp the fundamental elements of a discussion or situation, they reason in a dynamic manner and create unusual associations that others find it difficult to develop.
They learn readily from experience and tend to remember facts not in an abstract way but as life experiences, stories and examples.
They think primarily in images, visualising words and concepts in a three-dimensional manner, and memorise things far more readily by pictures.

– They are able *to see things* from different perspectives and they process information in a global manner rather than sequentially.

TAB. 1

SLDs involve a specific area of skills	**Reading Spelling Writing Calculation**
Intact general intellectual function	**QI >70**
SLDs involve the instrumental skills of scholastic learning	**Compensatory tools**

This matter has a considerable social importance, as SLDs are disorders that, from an epidemiological point of view, have an incidence in the general population of **2-3%** of all scholastic difficulties, in most subjects with non-specific learning disabilities or difficulties (about **20%**) (TABS. 2, 3).

At the current time, children and teenagers with SLDs are not entitled to a special needs teacher.
Pursuant to Law 170/2010 (TAB. 3), they are entitled to compensatory learning and technological aids (speech synthesis, recorders, word processing software and programmes with spelling correction functions, calculators) and dispensatory measures that allow them to replace certain types of assessment with equivalent, more suitable ones.

– An analysis of the available literature reveals that the disorders most commonly associated with LSDs are attention deficit and hyperactivity disorder (ADHD) and specific language impairment (SLI).
The 2007 Consensus Conference revealed that in clinical practice, there is a high presence of comorbidities among SLDs and between SLDs and other disorders (dyspraxia, behavioural and mood disorders, anxiety disorders, etc.).
– This high comorbidity results in a great diversity in the functional and expressive profiles with which SLDs present, which has considerable implications on the diagnostic investigation front (CC-2007) (FIG. 2).

DIAGNOSIS

Diagnosis can be difficult.
– As a matter of fact, until the diagnosis is clearly defined, the children, their parents and the school are confused regarding the poor scholastic performance, without understanding the reason for it.

In this initial stage, teachers tend to question the child's effort, and family

conditions, they complain of laziness and lack of commitment, and frequent problems regarding conduct in the classroom.
Teachers also encounter difficulties in understanding why the child, who does not appear to have any particular difficulties within his/her peer group, objects, refuses or is reluctant when asked to read and/or write (3).
– This generates confusion and disarray in the parents, who tend to alternate between strict and punitive behaviour with continuous encouragements to make a greater effort and long periods of waiting, hoping the situation will improve spontaneously.

During this phase, the child feels misunderstood by everyone and starts to question his/her own abilities, which in turn results in lower self-esteem, psycho-affective problems, a feeling of inferiority and even guilt, especially if he/she feels that judged to be lazy and unwilling.
– In these cases, the interpretations and actions of the adults tend to make matters worse.

When a SLD is diagnosed and if the disorder is not adequately treated, the psychological symptoms of the distress can take various, and sometimes opposing, forms: on the one hand the child may have a withdrawn attitude, be introverted and avoid confrontation; this set of reactions can be defined of a depressive or inhibitory type.
On the other hand, the child may demonstrate feelings of anger resulting in disruptive behaviour, challenging teachers and showing aggression towards academic staff and their peers, which inevitably triggers a vicious cycle within the class.

The same child can often present both types of behaviour at different times (4).

Statistically, the diagnosis is most often formulated by teachers at the end of the **second year** of **primary school**, due to the greater exposure to reading and writing; they then notify the parents and a diagnostic pathway is undertaken with the involvement of paediatric neuropsychiatry facilities (FIG. 3).
Primary-care paediatricians can also play a role in identifying a child with SLD by administering a checklist (TABS. 4, 5, 6).
SLDs affect males more commonly than females, with a ratio of **5:1**.

SLDs have a neurobiological origin.

In infants, the symptoms are practically inexistent, as SLDs affect cognitive areas that infants have not yet developed; warning signs may be observed in preschool children (e.g. speech problems or difficulties learning nursery rhymes).
– The disorder becomes fully evident in school-age children.

Although it is recognised that SLDs have a genetic cause, the cerebral processes involved are yet to be clearly defined, despite the active research in this field.
– The genetic origin is demonstrated by the high familiarity of SLDs; children of parents with SLDs are more likely to have the same disorder than children whose parents do not have SLDs.

Indeed, it is not uncommon for the parents of children with SLDs to report encountering the same difficulties as their child, although it is likely that no specific diagnosis was formulated at the time.
– The neurobiological origin underlying cognitive abnormalities is associated with behavioural symptoms of the disorder, which include an interaction between genetic, epigenetic and environ-

DISABILITIES law 104/1992
«Framework law regarding the assistance, social integration and rights of persons with disabilities»
Assessments are usually carried out by the Local Health Authorities, through medical commissions including a social worker and an expert on the cases to be reviewed, established within the various Local Health Authorities.

TAB. 2

SLDs law 170/2010
«New regulations for specific learning disabilities in the scholastic setting»
SLDs are diagnosed within the specialist care provided by the Italian National Health Service or accredited specialists or facilities.
Use of individualised and personalised teaching, with effective and flexible forms of schoolwork that also take into account the particular characteristics of the subjects involved.
– Incidence 2-3% of all disabilities.

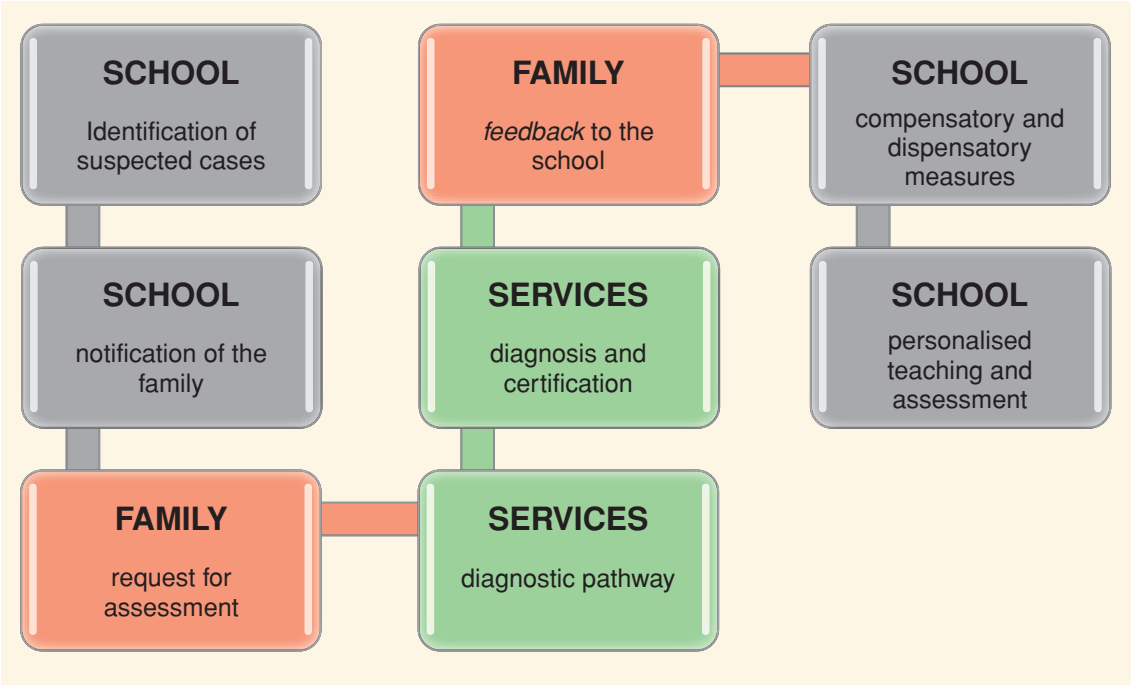
TAB. 3

FIG. 2

SLDs – COMORBIDITIES

OTHER NEUROPSYCHOLOGICAL DISORDERS (e.g. ADHD – Attention Deficit and Hyperactivity Disorder)	SEVERAL CONCOMITANT SLDs	OTHER MENTAL HEALTH DISORDERS (anxiety, depression, behavioural disorders)

FIG. 3



mental factors involving the cerebral capacity to perceive or process verbal or nonverbal information effectively and precisely (DSM-5, 2014).

Other potential causes include:

- maternal illness or substance abuse during pregnancy
- complications during pregnancy or delivery (e.g. blood loss or spotting, septicaemia, prolonged delivery or emergency delivery)
- neonatal problems (prematurity, low birth weight, severe jaundice, perinatal asphyxia, post-term birth, breathing difficulties).

Postnatal risk factors include **1)** exposure to environmental toxins (e.g. lead, heavy metals, pesticides, endocrine-disrupting chemicals), **2)** Central Nervous System infections, **3)** cancers and their treatments, **4)** trauma, **5)** malnourishment, **6)** severe social isolation, and **7)** affection deprivation.

It is important to remember that certain studies have identified a relationship between SLDs and **the dysfunctional aspects** of cerebral mechanisms that **do not** in any way affect intelligence.

When a psychological trauma interferes with normal pyschobiological development in children and adolescents, there is a shift from a brain (and body) focused on learning and a brain (and body) focused on survival.

- The **learning brain** is engaged in exploring (acquisition of new knowledge and of new neuronal synaptic connections), the **survival brain** tries to anticipate, prevent and protect against the damage caused by potential or actual dangers; it identifies threats and activates bodily resources to achieve hyperalertness and deploy defensive adjustments.
- The **survival brain** surrenders to rapid automatic processes that involve the more primitive parts of the brain [brainstem (especially the midbrain), limbic system structures, such as the amygdala], largely bypassing the areas of the brain involved in more complex adjust-

TAB. 4

PAEDIATRICIAN CHECKLIST
– PRE-SCHOOL AGE AND YEAR 1 OF PRIMARY SCHOOL

The **child**:

- struggles to understand verbal instructions and messages
- has difficulties expressing him/herself clearly when recounting an episode he/she was involved in or witnessed
- has difficulties making him/herself understood to strangers
- has difficulties holding pencils or pens
- struggles to draw a person whose head, body, arms and legs are recognisable
- is clumsy and lacks dexterity
- has difficulties perceiving new words and repeating them immediately after hearing them
- has difficulties understanding the quantities the numbers 1 to 4 correspond to; counting to 5; recognising which of two sets of objects (maximum of five objects) is larger and which is smaller.

Source: C. Toso, **2009**. Associazione Culturale Pediatri.

ments to the environment (anterior cingulate cortex, insula, prefrontal cortex, etc.) (5,6).

Prolonged corticosteroid activation and the hyperadrenergic state induced by constant alarm states result in the inhibition of neurogenesis, thereby hindering dendritic development and the formation of synapses, they induce "pruning" actions on existing nervous connections and induce cell death processes that result in the shrinking of the hippocampus (7).

As mentioned previously, the neurobiological bases of SLDs have been consolidated.
In the case of **dyslexia**, the best known of these disorders, the neurobiological origin was already suspected more than a century ago.
– In 1891-2, the French neurologist Jules Déjerine (8,9) suggested that the reading problems, defined by Hinshelwood (10) as "reading blindness", were due to anatomical lesions present in the left posterior region of the brain, which plays a critical role in reading processes.
The decisive turning point in the knowledge of the pathogenetic bases of dyslexia came with the advent of dynamic neuroimaging techniques such as PET or Functional Magnetic Resonance.
– These methods are able to show changes in the activation of cerebral areas as a consequence of given tasks and – therefore – make it possible to define the differences in functioning of areas of the cerebral cortex in dyslexic individuals.

It is known that both acute and chronic stress reduce the production of **BDNF** - Brain Derived Neurotrophic Factor in the hippocampus, where they also cause structural changes and neuronal damage, (11,12) and that BDNF tends to diminish in old age (13).

– Furthermore, BDNF protects against the toxicity of certain substances, by increasing the production of **glutathione reductase** (14).

PAEDIATRICIAN CHECKLIST
– HALFWAY THROUGH YEAR 1 AND YEAR 2 OF PRIMARY SCHOOL

The **child**:
- has not yet learned to read simple words (year 1) or sentences and short passages (year 2)
- has not yet learned to write simple words (year 1); makes a lot of mistakes when writing (year 2)
- has handwriting that is not legible to strangers
- has difficulties counting forwards to 20
- is unable to establish whether a number up to 20 is greater than another
- is poorly motivated in his/her schoolwork and frequently presents avoidance behaviour in relation to studying.

Source: C. Toso, **2009**. Associazione Culturale Pediatri.

TAB. 5

PAEDIATRICIAN CHECKLIST
– FROM YEAR 3 OF PRIMARY SCHOOL ONWARDS

The **child**:
- has obvious difficulties reading and writing correctly
- has difficulties writing in joined-up writing
- has difficulties reading books or other material on his/her own (e.g. toy assembly instructions)
- has difficulties reading to him/herself (is still only able to read out loud or whispering)
- has difficulties understanding what he/she is reading
- has difficulties learning the multiplication tables
- has difficulties arranging numbers in columns correctly.

Source: C. Toso, **2009**. Associazione Culturale Pediatri.

TAB. 6

It is therefore reasonable to presume that patients with SLDs have a **deficiency** of **BDNF** due to exposure to acute and/or chronic, psychological and physical stress.

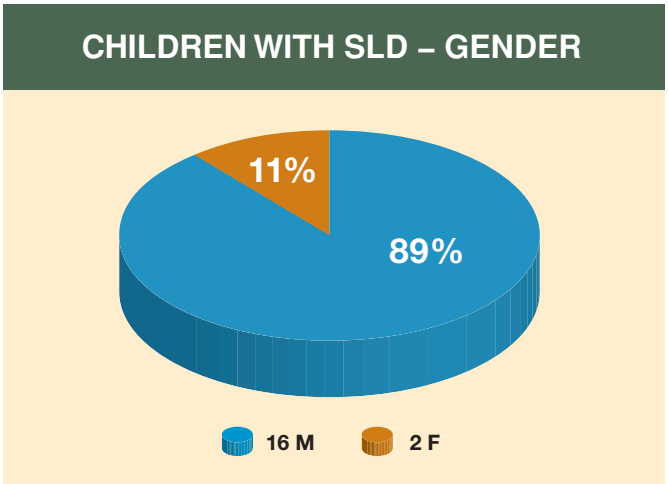
CURRENT TREATMENT

Although the treatment of Learning Disorders hinges primarily on scholastic management, it may also include medical, behavioural and psychological treatment.

– The effectiveness of teaching programmes may require a curative, compensatory, rehabilitative or strategic approach (i.e. teaching the child how to learn).
Some children require special teaching in just one subject and can continue to attend their classes normally.
Others require individual and intensive educational programmes.

– Medicinal products have a mild effect on scholastic performance, intelligence and learning abilities in general, although certain psychostimulants, like methylphenidate and certain amphetamine preparations, can improve the degree of attention and concentration, and therefore allow the child to perform assignments more effectively.

FIG. 4



MATERIALS AND METHODS

This study enrolled a total of **18 patients** (16 M; 2 F) (FIG. 4) aged between 6 and 9 years diagnosed with SLD in paediatric neuropsychiatry hub centres who were administered:
– the WISC-IV (Wechsler Intelligence Scale for Children), the gold-standard clinical tool for assessing cognitive abilities in children of between 6 years and 16 years and 11 months of age.
The WISC-IV makes it possible to calculate 5 composite scores: total intelligence quotient (TIQ) representing the overall cognitive abilities of the child and 4 additional scores, namely 4 Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and the Processing Speed Index (PSI)
– writing and spelling tests pertaining to the assessment battery for writing and spelling skills (BVSCO)
– MT reading tests.

Lastly, in order to obtain a personality profile, each parent was separately administered the *Child Behaviour Checklist* (FIG. 5).

Patients who, at the time of diagnosis, also presented other types of current or known comorbidities were excluded from the study.
– The children were split *random* into 2 groups (A, B).
Both groups were assigned compensatory learning and technological aids and dispensatory measures at school and speech therapy in an outpatient setting.

Patients in **Group A** were also administered **Guna-BDNF**, 20 drops via the sublingual route, morning and evening before meals (TAB. 7).

Patients in **Group B** were not administered Guna-BDNF.

• BDNF, which was isolated in 1982 by Yves- Alain Barde *et* Al. (15), is a 25 kDa homodimeric protein produced by the Central and Peripheral Nervous System, and particularly in the hypothalamus, hippocampus, cerebral cortex (frontal lobe, occipital lobe, insula, sensory and motor cortex), amygdala, salivary glands, kidney, prostate, retina, endothelial cells and in the follicular fluid.

BDNF acts by activating the receptors p75 and Trk.

During development, the neuropeptide plays a key role in neuronal survival, migration and phenotypical differentiation, as well as in axonal and dendritic growth and in the formation of synapses.
In adult life, its main function is to regulate synaptic plasticity and it is involved in learning, memory and behavioural processes.
BDNF has also been detected in serum with concentrations 10 time greater than those of plasma.

– BDNF is the most active of all neurotrophins in terms of neo-neurogenesis.

It has a protective action against injuries involving the dopaminergic brain structures.
It exerts its effect primarily on the serotonergic neurons (16).
Furthermore, in one *in vivo* study it was also demonstrated that Guna-BDNF reaches the brain within 24 hours of oral administration and reaches peak levels after 48 hours. It remains in the cerebral tissue for a long time even in the absence of further treatment , as it triggers the physiological production systems underlying good endogenous anti-ageing functioning (17).

During the treatment, no side effects were reported and there were no dropouts.

FIG. 5

CHILD BEHAVIOUR CHECKLIST

The first part acquires information on the various areas of personal and social functioning.

The second part consists of 118 items taking the form of statements regarding behaviour in various areas and emotional problems.

The scores are compared with reference value, to obtain two overall scores, one for skills (activity, social life, school) and one for behavioural and emotional problems, and two separate profiles; a skills profile and psychological and/or mental disease profile.

MEDICINAL PRODUCT	POSOLOGY
GUNA-BDNF	20 drops morning and evening

TAB. 7

– At the 1-year follow-up visit conducted at the paediatric neuropsychiatry centres, the same tests indicated above were re-administered and an improvement in performance was observed in both groups (A, B).

▶ **Group A** achieved a **50%** ≈ higher score than Group B in the various items.

DISCUSSION AND CONCLUSIONS

SLDs are changes in normal development with a neurobiological origin and they affect the acquisition of certain scholastic skills. The characteristic common to this group of disorders is the specificity of the deficit.
SLDs cannot be cured, but they are susceptible to appropriate compensatory measures and neuropsychological training, especially as regards speech, memory, and attention.

At the current time, there is no specific pharmacological therapy that has a significant impact on these functions.

▶ The considerable result obtained by administering Guna-BDNF on the performance of subjects with SLDs allowed these young patients to obtain better scholastic performance and a more effective inclusion in their peer groups, thereby sparing them detrimental feelings of inadequacy and isolation.

– It would be appropriate to enrol further patients and for other studies to be conducted in order to confirm the validity of the low-dose treatment proposed. ■

References

1. Ammaniti M., Cornoldi C.,Vicari S. – Novità nell'approccio alla psicopatologia dello sviluppo del DSM-5. Psicologia clinica dello Sviluppo/ a. XIX, n. 2, agosto **2015**.
2. Linee Guida per I Disturbi Specifici di Apprendimento. Gior Neuropsich Età Evol **2004**: (Suppl. 1): 178-197.
3. Tressoldi P.E., Stella G., Faggella M. – The development of reading speed in Italians with dyslexia: a longitudinal study. J Learn Disabil. **2001** Sep-Oct;34(5):414-7.
4. Slaghuis W.L., Ryan J.F. – Directional motion contrast sensitivity in developmental dyslexia. Vision Res. **2006** Oct:46(20):3291-303.
5. Pearlman L.A, Courtois C.A. – Clinical applications of the attachment framework: Relational treatment of complex trauma. J Trauma Stress. **2005** Oct;18(5):449.59.
6. Cloitre M., Courtois C.A., Charuvastra A., Carapezza R., Stolbach B.C., Green B.L. – Treatment of complex PTSD: results of the ISTSS expert clinician survey on best practices. J Trauma Stress. **2011** Dec;24(6):615-27.
7. Liotti G., Farina B. – Sviluppi traumatici. Eziopatogenesi, clinica e terapia della dimensione dissociativa. Raffaello Cortina Ed., **2011**.
8. Déjerine J. – Sur un cas de cécité verbale avec agraphie suivi d'autopsie. *In* Mémoires de la Société de Biologie, III, **1891**, pp. 197-201.
9. Déjerine J. – Contribution à l'étude anatomopathologique et clinique des différentes variétés de cécité verbale. *In* Mémoires de la Société de Biologie, IV, **1892**, pp. 61- 90.
10. Hinshelwood J. – Word Blindness and Visual Memory. Lancet, vol. CXLVI, n. 3773, **1895**, pp. 1564-1570.
11. Murakami S., Imbe H., Morikawa Y., Kubo C., Senba E. – Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. Neurosci Res **2005** Oct;53(2):129-39.
12. Smith M.A., Makino S., Kvetnansky R., Post R.M. – Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci **1995** Mar;15(3 Pt 1):1768-77.
13. Shi S.S., Shao S.H., Yuan B.P, Pan F., Li Z.L. – Acute stress and Chronic stress change Brain-Derived Neurotrophic Factor (BDNF) and Tyrosine Kinase-Coupled Receptor (TrkB) expression in both young and aged rat hippocampus. Yonsei Med J. **2010** Sep 1; 51(5):661-671.
14. Spina M.B., Squinto S.P., Miller J., Lindsay R.M., Hyman C. – Brain-derived neurotrophic factor protects dopamine neurons against 6-hydroxydopamine and N-methyl-4-phenylpyridinium ion toxicity: involvement of the glutathione system. J Neurochem **1992** Jul;59(1):99-106.
15. Barde Y.A., Edgar D., Thoenen H. – Purification of a new neurotrophic factor from mammalian brain. EMBO J **1982**;1(5):549-53.
16. Milani L. – Revisione critica e nuove considerazioni clinico-terapeutiche su Ignatia-*Strychnos Ignatii* BERG. Integrazione ragionata tra medicinali omotossicologici e neurotrofine omeopatizzate. Seconda Parte. La Med. Biol. **2009**/3; 25-35.
17. Uberti F., Molinari C. – BDNF diluito e dinamizzato contro l'invecchiamento cerebrale. La Med. Biol. **2018**/4;13-23.

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Article

The Collagen-Based Medical Device MD-Tissue Acts as a Mechanical Scaffold Influencing Morpho-Functional Properties of Cultured Human Tenocytes

The Collagen-Based Medical Device MD-Tissue Acts as a Mechanical Scaffold Influencing Morpho-Functional Properties of Cultured Human Tenocytes

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– Authors - Operational sites

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1) Introduction
Tendinopathies are painful chronic conditions involving the tendons, characterised by histological changes such as hypercellularity, neovascularisation, loss of collagen fibril organisation, an increase in proteoglycan and glycosaminoglycan content and an increase in the non-collagen components of the extracellular matrix.
The therapeutic approach to tendinopathies involves rest, cold compresses, NSAIDs, physiotherapy, local corticosteroid injections or biological and regenerative therapies such as platelet-rich plasma (PRP) and hyaluronic acid. However, the treatments currently available have not shown high efficacy and no long-term benefits have been reported.

– Tenocytes are specialised fibroblasts of the tendinous connective tissue. It has been demonstrated that **MD-Tissue** is able to stimulate the biosynthesis, secretion and maturation of type I collagen and induce tenocyte proliferation and migration (see Milani L., La Med. Biol. 2019/2; 12-16).

Purpose of the study
To verify whether the effects produced by MD-Tissue are due to mechanisms associated with mechanotransduction.

2) Materials and Methods
2-1 – Samples
Specimens of the gluteus minimus muscle were obtained from 4 patients undergoing hip replacement surgery (written informed consent obtained). The part presenting the typical, dense and regular structure of the connective tissue was isolated from each specimen and analysed.
2-2 – Cell culture preparation
2-3 – Covering of the cell cultures with MD-Tissue (Collagen + Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamin hydrochloride, NaCl) (100 μg/2ml) or with collagen (COL) alone. 2-4 – To verify whether MD-Tissue produces effects on the tenocytes through mechanical stimulation, the tenocytes were treated with cytochalasin, which inhibits the polymerisation of the actin filaments.
2-5 – Electronic microscopy (SEM)
The covers of the cell cultures with MD-Tissue or COL were analysed under an electronic microscope to verify the presence and alignment of Collagen fibres/fibrils. 2-6 – Raman spectroscopy. 2-7 – Immunofluorescence. 2-8 – Real-time PCR. 2-9 – Western Blot. 2-10 – SDS-Zymography. 2-11 – Statistical analysis.

3) Authors' conclusions
[...] in particular, we demonstrated that MD-Tissue influences certain tenocytes involved in extracellular matrix homeostasis and improves their focal adhesion and migration capacities.
*– We can confirm that MD-Tissue, **by acting as a mechanical scaffold**, could be an efficacious medical device for a new regenerative and rehabilitative approach for favouring **tendon healing** in **tendinopathies**.*


Proceeding

Ultrasound-guided collagen injections for treatment of plantar fasciopathy in runners: A pilot study and case series

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ABSTRACT

Ultrasound-guided collagen injections for treatment of plantar fasciopathy in runners: A pilot study and case series

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1) Introduction

Plantar fasciopathy (PF) is a musculoskeletal condition involving the plantar fascia, a thick band of connective tissue that joins the tuberosity of the calcaneus to the heads of the metatarsal bones and helps maintain the stability of the arch of the foot. The plantar fascia consists of 3 bundles, of which the central is the thickest and most frequently affected. PF used to be known as “plantar fasciitis”, which is an improper term as the condition does not involve any inflammation.

PF is now considered a degenerative disease that is more similar to a tendinopathy, and it is a chronic condition affecting the insertion of the plantar fascia at the medial calcaneal tubercle. The peak incidence of this condition occurs between 45 and 65 years of age. The incidence of PF amongst runners is 4.5-10% and in this type of athlete it is the 3rd most common cause of musculoskeletal disease.

In runners, PF is associated with overuse, training errors and improper footwear use.

– The diagnosis of PF is primarily clinical: the main symptom is acute, intense pain that tends to be localised at the calcaneal insertion of the plantar fascia. Runners with PF describe pain on the sole of the foot that is more intense in the morning and improves during training.

This is also frequently associated with foot stiffness and swelling in the calcaneal region.

The therapies/treatments for PF include NSAIDs, specific physical exercises, removable insoles, splints to be worn at night, instructions to lose weight and avoidance of footwear without a heel.

– Other treatments consist of local injections of corticosteroids, local anaesthetics, botulinum toxin and hyaluronic acid, as well as shockwave therapy, prolotherapy, ozone therapy and platelet-rich plasma.

2) Aims of the study

1) To evaluate the efficacy of ultrasound-guided collagen injections (MD-Tissue) in the treatment of PF in a group of runners;
2) Feasibility of the treatment with a view to studies on a larger patient cohort.

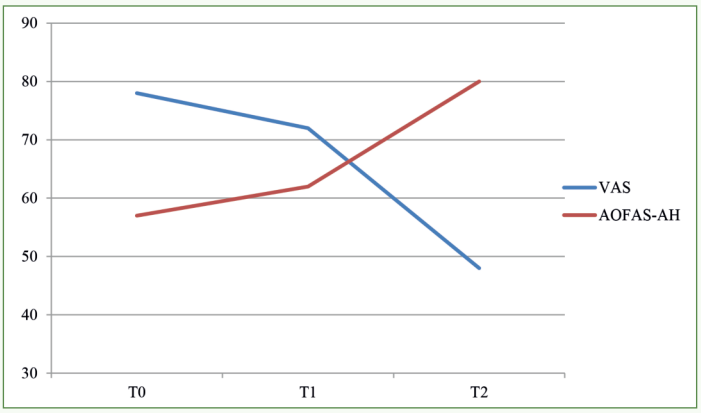
3) Materials and Methods

A total of 10 patients (7 M, 3 F) were enrolled; mean age: 34 ± 8 years, suffering from PF.
Each patient was administered, by the same practitioner, **4 injections** at 1-week intervals with **1 vial** (2 mL) of MD-Tissue, using a 22 G needle.
The ultrasound-guided injection was performed anteriorly to the calcaneal insertion of the plantar fascia, at the point where the fascia is thickest.
– The therapeutic effect was rated at enrolment **(T0)**, and one month **(T1)** and 3 months **(T2)** after the last treatment by means of 1) a 10 cm VAS; 2) pressure algometry (kg/cm^2); 3) AOFAS-AH (American Orthopaedic Foot and Ankle Society- Ankle-Hindfoot) score out of 100 points.

4) Results

The results were assessed as mean and standard deviation.
– At T1 = there were no significant differences compared to T0 in any of the 3 parameters considered.
– At T2 = **significant improvements in all 3 parameters considered**
(Fig. 1; Tab. 1).

Fig. 1 - VAS and AOFAS-AH scores at the various follow-up time-points.



N.B.: VAS = Visual Analogue Scale; AOFAS-AH = American Orthopaedic Foot and Ankle Society-Ankle-Hindfoot.

Tab. 1 - Mean and standard deviation values for VAS, pressure algometry and AOFAS-AH score at the various follow-up time-points.

Outcome measures	T0	T1	T2
VAS 0-10	7.8 ± 0.79	7.2 ± 0.63 Δ = 7.7% p = .98	4.8 ± 0.79 Δ = 38.5% p < .001
Pressure algometry kg/cm^2	4.45 ± 0.29	4.65 ± 0.26 Δ = 4.5% p = .11	5.2 ± 0.2 Δ = 16.9% p < .001
AOFAS-AH 0-100	57.4 ± 4.09	62.3 ± 3.74 Δ = 8.5% p = .19	80.8 ± 3.26 Δ = 40.8% p < .001

N.B.: VAS = Visual Analogue Scale; AOFAS-AH = American Orthopaedic Foot and Ankle Society-Ankle-Hindfoot. Δ = relative delta.

5) Authors' conclusions

[...] the preliminary results of this study suggest that injections of collagen (MD-Tissue) are useful in the treatment of PF.
As collagen is a structural protein of the plantar fascia, collagen for injection does not act merely on healing, but also on the recovery of original tissue function. The endogenous synthesis, maturation and secretion of collagen are also stimulated by the injected collagen, which therefore favours the repair of the plantar fascia.
The efficacy and absence of adverse effects can be rationalised on the basis of the factors indicated above.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CASE REPORT

Use of injectable collagen in partial-thickness tears of the supraspinatus tendon: a case report

Use of injectable collagen in partial-thickness tears of the supraspinatus tendon: a case report

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– Authors - Operational sites

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1) Introduction

Partial-thickness rotator cuff tear (PTRCT) is one of the most common shoulder conditions. The supraspinatus tendon is that most frequently involved in PTRCTs.
The treatment of PTRCTs is still controversial.
– A great many injective therapies (corticosteroids, hyaluronic acid, platelet-rich plasma, prolotherapy) have been proposed for the treatment of the condition; however, their efficacy is not always well-defined.
This is the first study to be conducted with ultrasound-guided injections of type I collagen of porcine origin in the treatment of PTRCTs.

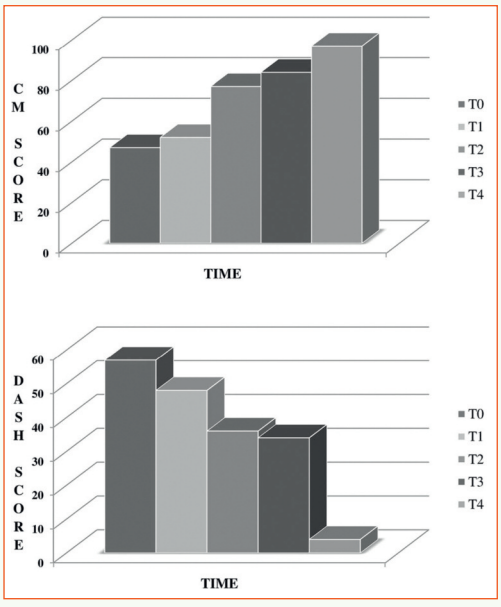
2) Case Report

55-year-old housewife complaining of pain and functional limitation of the left shoulder for two months. The ultrasound scan showed an Ellman grade II partial thickness tear on the articular surface of the supraspinatus tendon.
It was decided to treat the patient with US-guided intratendinous injections of type I collagen of porcine origin (**MD-Tissue**) (2 mL per treatment) for 4 consecutive treatments, one week apart + physiotherapy (3 times/week) consisting in motor re-education and proprioceptive exercises.
– The patient was assessed at enrolment (T0), immediately before the 3rd injection (T1), and one month (T2), 3 months (T3) and 18 months (T4) after the last injection using the Constant-Murley **(CM) score** and the **DASH** (Disability of the Arm, Shoulder and Hand) questionnaire (Fig. 1; Fig. 2)

3) Authors' conclusions

[...] the positive clinical and functional results obtained and the absence of adverse effects allow us to propose collagen injections as a valid option for the treatment of PTRCTs.
– The results obtained suggest that collagen injections have a ***regenerative effect*** *on the structure of the tendon.*

Fig. 1



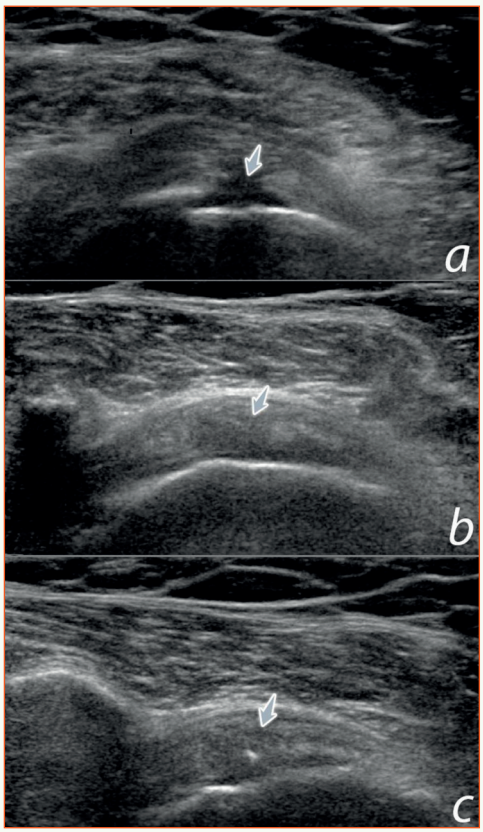


Fig. 2 - Ultrasound (US) images of the supraspinatus tendon at the various follow-up time-points.
a - The longitudinal US of the supraspinatus tendon at T0 shows a well-defined partial thickness tear on the articular surface of the tendon, without retraction (arrow).
b - Three months after the last injection, the tear has shrunk and is less clearly defined (arrow).
c - At the 18-month follow-up time-point, the tendon appears more regular and isoechoic, without signs of a tear (arrow).