*European Journal of Musculoskeletal Diseases*

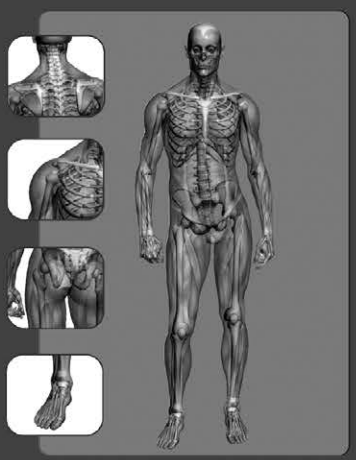
Volume 2, no.2 July-December 2013

# Collagen Medical Devices

INJECTABLE AMPOULES

MEDICAL DEVICE


## Description



A special characteristic of Collagen Medical Devices, which contain collagen and ancillary ingredients, is that they offer a refined and innovative approach to the treatment of painful diseases affecting the musculoskeletal system.
The ancillary ingredients of natural origin allow a better and more targeted positioning of Collagen in certain areas.
The collagen is of pig origin.
Injections are periarticular, intraarticular, intramuscular and intradermal. Collagen provides a mechanical support, which has a positive impact on stabilizing joint hypermobility, movement, pain, and life quality. Collagen Medical Devices have a structural function: replace, strengthen, protect and build the structure of cartilage, tendons, ligaments, joint capsules, etc, thus improving the histological structure of the collagen fibres of all the anatomical structures made up of collagen. This provides mechanical support to the affected areas.

## Key word:

**Collagen Medical Devices, 13 Medical Devices to treat different osteoarthro-myofascial pathologies**

## Composition

- **MD-HIP** (Hip):
  Collagene, Calcium phosphate
- **MD-ISCHIAL** (Sciatic nerve):
  Collagene, *Rhododendron*
- **MD-KNEE** (Knee):
  Collagene, *Arnica*
- **MD-LUMBAR** (Lumbar):
  Collagene, *Hamamelis*
- **MD-NECK** (Neck):
  Collagene, *Silica*
- **MD-SHOULDER** (Shoulder):
  Collagene, *Iris*
- **MD-SMALL JOINTS**
  (Small joints):
  Collagene, *Viola*
- **MD-THORACIC** (Torax):
  Collagene, *Cimicifuga*
- **MD-MATRIX** (Extracellulare matrix:
  Collagene, Citric acid, Nicotinamide
- **MD-MUSCLE** (Muscle):
  Collagene, *Hypericum*
- **MD-POLY** (Joints):
  Collagene, *Drosera*
- **MD-NEURAL** (Nerves):
  Collagene, *Colocynthis*
- **MD-TISSUE** (Soft tissues):
  Collagene, Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrocloride

## Therapeutic protocol

**MD-HIP**
**MD-ISCHIAL**
**MD-KNEE**
**MD-SMALL JOINTS**
1 treatment weekly
for 10 consecutive weeks.

**MD-MUSCLE**
**MD-NECK**
**MD-NEURAL**
**MD-POLY**
**MD-SHOULDER**
1-2 treatment/s weekly
for 10 consecutive weeks.

**MD-LUMBAR**
**MD-MATRIX**
**MD-THORACIC**
**MD-TISSUE**
2 treatments for the first 2 weeks; then, 1 treatment weekly until symptoms improve
(8-10 sessions on average).

## Packaging

- Box of 10 x 2ml ampoules.
- Box of 50 x 2ml ampoules.

CE 0373

GUNA LABORATORI
**GUNA S.p.a**
Via Palmanova, 71 - 20132 MILAN - ITALY
tel. +39 02 280181 - fax +39 02 28018449
export@guna.it www.gunainternational.com

COMPANY WITH
QUALITY MANAGEMENT SYSTEM
**UNI EN ISO 13485:2004**
CERTIFIED BY CERTIQUALITY

SCIENTIFIC DOCUMENTATION FOR THE EXCLUSIVE USE OF QUALIFIED STAFF

*EDITORIAL*

# EXPLORING SYNERGY BETWEEN VISCOSUPPLEMENTATION AND REHABILITATION EXERCISE IN SYMPTOMATIC OSTEOARTHRITIS

A. MIGLIORE

*Rheumatology Unit, S. Pietro Fatebenefratelli Hospital, Rome, Italy*

Osteoarthritis (OA) is the most frequent cause of joint pain and articular limitations. Current treatment options include analgesics, non-steroidal anti-inflammatory medication (NSAIDs), weight loss, physical therapy, exercise, activity modification, assistive devices, topical medication, intra-articular injections, and lastly surgery. Although many patients can be treated successfully with surgery in the end stage of disease, the majority of patients during the initial and intermediate stage of the disease requires non-surgical management before developing joint failure and a consequent arthroplasty.

Since OA is a long lasting disease, safe long-term treatments that may reduce pain and improve function avoiding the toxic effects of systemic medications, such as NSAIDs, should be fully exploited. Among these potential treatment options rehabilitation exercise and intra-articular injection of hyaluronate should be carefully evaluated. The use of viscosupplementation (intra-articular hyaluronic acid drug therapy) to treat OA is growing worldwide due to important results obtained from both randomized controlled trials and daily clinical practice reporting improvements in functional activity and pain management. However some disagreements appear in the recommendations for OA management due to the kind of control arm, length of follow-up, primary endpoints (if symptomatic or structural) and the influence of the 'placebo effect'. Despite this the use of HA in the treatment of OA should be encouraged because of its immediate bioavailability and the absence of systemic effects. Commonly the administration of HA is able to reduce symptoms by 30-50% for few months and repetition of injection every at least 8-12 months is needed in order to maintain a low level of symptoms. Patients and physicians are asking for something more effective and durable.

On the other hand rehabilitation exercise (both land-based and water-based and strength training), are commonly used in all individuals with knee OA, as well as therapies that can be prescribed according to individualized patient needs and preferences. Both land-based and aquatic exercise have been shown to decrease pain and improve function, and education has been associated with short-term pain relief. Unfortunately, the beneficial effects from exercise deteriorate and sooner or later disappear within three to nine months following cessation of the controlled exercise program.

Recently Svege L conducted a long-term follow-up of a randomised trial investigating the efficacy of exercise therapy and patient education versus patient education only on the 6-year cumulative survival of the native hip to THR in 109 patients with symptomatic and radiographic hip OA. The findings of this explanatory study suggest that exercise therapy in addition to patient education can reduce the need for THR by 44% in patients with hip OA.

Several trials exploring separately the efficacy of viscosupplementation and rehabilitation exercise have been carried out, on the contrary trials exploring together the effectiveness of viscosupplementation added to rehabilitation exercise have not been

*Corresponding author:*
Alberto Migliore
Rheumatology Unit
S. Pietro Fatebenefratelli Hospital
Via Cassia 600
00189 Rome, Italy
E-mail address: migliore.alberto60@gmail.com



2038-4106 (2013)

**DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.**

performed.

The credit of the Diracoglu paper published in this issue is to outline the rationale for combining both treatments in clinical practice. The best treatment for OA is not yet clear and probably never will be. For this reason the association of several treatments with different targets and potentially with additive and more favourable effects is a promising field of investigation.

# INTRA-ARTICULAR INJECTION AS A TOOL FOR SUCCESSFUL REHABILITATION PROGRAM

D. DİRACOGLU

*Istanbul University, Istanbul Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Pain Medicine*

**Rehabilitation is a goal-oriented treatment process intended to maximize independence of individuals with compromised function that results from primary pathological processes and resultant impairments. The main purpose of intra-articular treatments is to obtain painless joint motion and ambulation of the patient. With this respect, approaches of rehabilitation and intra-articular treatment share common goals. The main goal of rehabilitation applications is to increase the quality-of-life of the patients. Quality of life is the perception of a person's position in life related to his/her objectives, expectations, and standards in the context of his/her culture and system of values. It can be claimed that rehabilitation is certainly a team work. When planning the treatment, considering the main complaints of the patient, expectations from therapy, and the main goals of treatment may increase patient compliance and may result in a successful outcome. The physician should focus on the patient rather than the disease, and should conduct a team work together with other branch specialists. The amount of synergy provided by the combination of intra-articular therapy and rehabilitation can be demonstrated by well-designed studies.**

"Health" was defined by the World Health Organization (WHO) constitution as ''a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'' (1). The mission of rehabilitation specialists is to improve their patients' health status to the above-defined level. In general, medicine can be divided into three main areas: preventive, therapeutic and rehabilitation medicine. Today, medicine has been focused on therapeutic medicine more than the others. Yet these three domains of medicine carry equal importance in terms of public health. Rehabilitation is a goal-oriented treatment process intended to maximize independence of individuals with compromised function that results from primary pathological processes and resultant impairments (2). All approaches aiming to return patient to his/her condition before illness are under the scope of rehabilitation. Rehabilitation is a program jointly organized by a rehabilitation team in line with problems and goals and is a dynamic, mutual learning process (2). Obtaining optimal ambulation is one of the main purposes of physical rehabilitation. Yielding best function of weight bearing joints without pain may play a major role in getting functional activities. The main purpose of intra-articular treatments is to obtain painless joint motion and ambulation of the patient. With this respect, approaches of rehabilitation and intra-articular treatment share common goals. A lot of conditions can be considered under the scope of rehabilitation, such as neurological, rheumatic, orthopedic, cardiac, respiratory disorders, and pain management.

The International Classification of Functioning, Disability and Health (ICF) advanced the understanding and measurement of disability (3).

*Keywords: Intra-articular therapy, rehabilitation, quality of life*

*Corresponding Author:*
Prof. Demirhan Diracoglu,
Istanbul University, Istanbul Faculty of Medicine,
Department of Physical Medicine and Rehabilitation,
Division of Pain Medicine.
E-mail address: demirhan1@yahoo.com



2038-4106 (2013)

**DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.**

According to ICF, problems with human functioning are categorized in three inter-connected areas: impairments, activity limitations and participation restrictions (3). The ICF has two parts, each containing two separate components. Part one covers "*functioning and disability*" and includes the components "*body functions and structure*" and "*activities and participation*". Part two covers "*contextual factors*" and includes the components "*environmental factors*" and "*personal factors*" (4) (Fig. 1). A successful rehabilitation approach should consider all these factors.

The main goal of rehabilitation applications is to increase the quality-of-life of the patients. Quality of life is the perception of a person's position in life related to his/her objectives, expectations, and standards in the context of his/her culture and system of values. It is a complete physical, mental and social well-being status; it is not only lack of a disease. The evaluation of outcomes following a rehabilitation procedure requires the evaluation of patients' quality-of-life. There are many scales designed for measurement of quality of life such as generic scales like Short Form (SF)-36 Health Survey, Nottingham health profile, Euro-Quality of Life (QoL), Well-being scale and WHO-QoL (5,6). The patient's current health status, expectations, suitability and success of clinical interventions and compliance of the patient to treatment can affect quality of life. In a study, intra-articular hyaluronic acid injection was shown to have positive effects of SF-36 levels (7). Thus, it may be suggested that the main goal of rehabilitation, i.e. improvement in quality-of-life, may be obtained by intra-articular hyaluronic acid besides other modalities of rehabilitation such as exercise, physiotherapy and electrotherapy. In certain cases, the patient may benefit from combination of these methods. Physician should try to find the most convenient combination for his patient. When doing this, the most logical way to assess the success of treatment is to use quality-of-life scales.

Beyond the quality of life concept, rehabilitation tools are also useful in sports medicine. Togetherness of rehabilitation and intra-articular therapy may increase performance of athletes. Moreover, possible damage (related with excessive exercise load) of cartilage, capsule, ligaments, and periarticular soft tissues can be decreased in elite athletes with this integrative approach.

It can be claimed that rehabilitation is certainly a team work. A team is a group of people working together for reaching a common goal, willing to sacrifice their autonomy to the extent required for successful goal fulfillment (8). Medical team models can be classified into four groups. "Classical model" is the traditional method in which a physician supplies patient needs. In "multidisciplinary model" there is vertical relationship between team leader and other team members, whereas in "interdisciplinary model" patient is an active member of team and there is a horizontal relationship among team members. In "transdisciplinary model" borders among team members are indistinct. Interdisciplinary model seems to be the more convenient model for

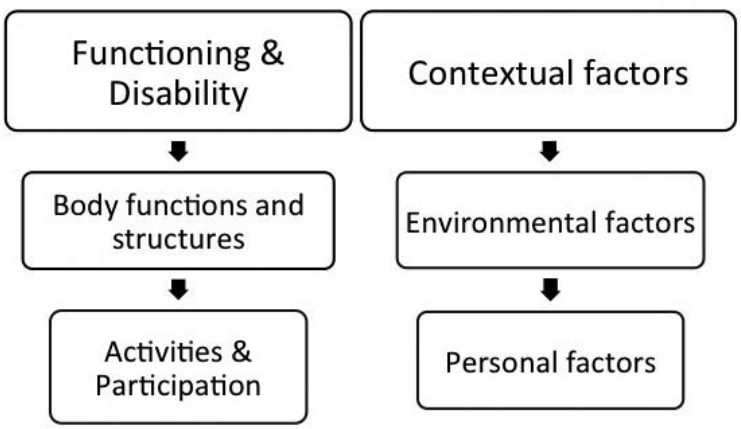



**Fig. 1.** *The items of International Classification of Functioning, Disability and Health.*

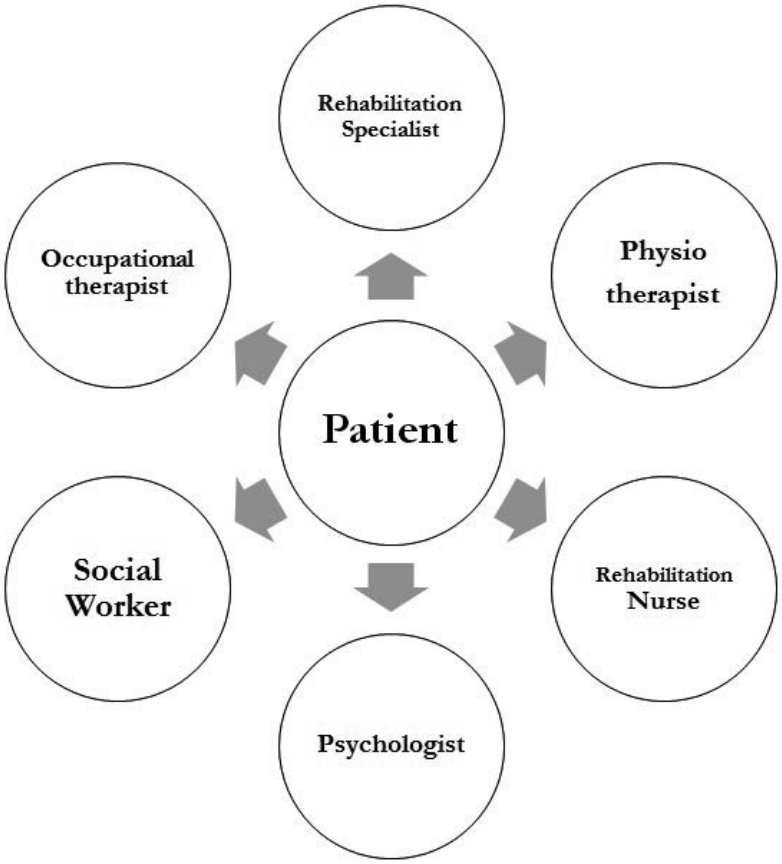



**Fig. 2.** *Core rehabilitation team.*

rehabilitation approach. Rehabilitation team should primarily focus on patient needs and demands. Core rehabilitation team consists of rehabilitation specialist, physiotherapist, rehabilitation nurse, psychologist, social worker and occupational therapist (Fig. 2). "Patient-oriented team approach" has been developed for problems encountered during adaptation of patients to rehabilitation process and the goal is to make patient needs as the main factor that directs rehabilitation team. Thus, the patient compliance gains importance and it is mainly affected by impairment in physician-patient relationship, discrepancy in targets of physician and patient, and difficulties in achieving of tasks. When planning the treatment, considering the main complaints of the patient, expectations from therapy, and the main goals of treatment may increase patient compliance and may result in a successful outcome. The physician should focus on the patient rather than the disease, and should conduct a team work together with other branch specialists. In daily practice, it may be difficult for patients to find many specialists at the same time. Therefore, the team leader should care about this and should guidance his/her patient according to that fact.

Rehabilitation program should be constructed after a detailed examination. When planning the program, data must be collected, goals should be defined, and re-evaluation should be performed (Fig. 3). The more frequent update of this circuit, the better compliance of the goals of the physician and of the patient.

Factors that affect rehabilitation results can be summarized as convenient medical treatment,

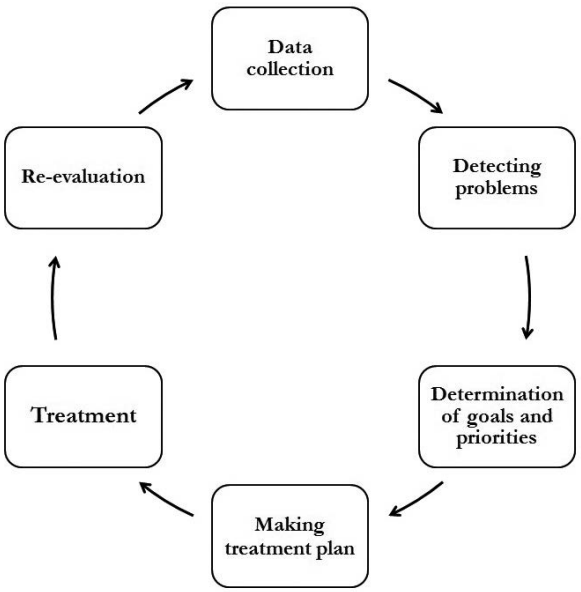



**Fig. 3.** *Rehabilitation planning and application cycle.*

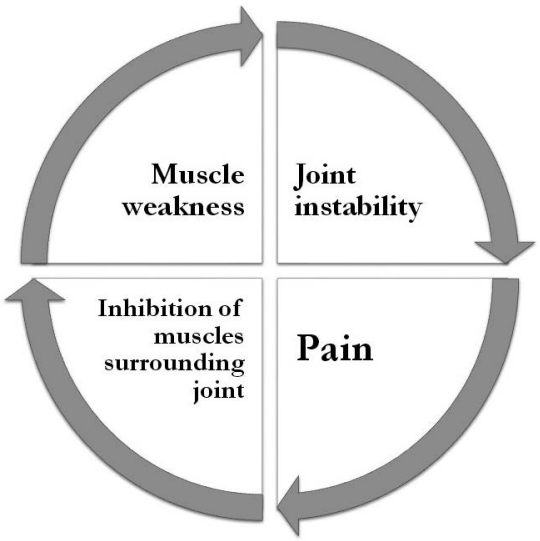



**Fig. 4.** *Muscle weakness and pain cycle.*

appropriate physiotherapy, good functional status of the joints, patient compliance, and family and social support. To achieve these conditions, mobilization of the patient is very important. In individuals without sufficient mobilization, both the pain sensation and the joint function are affected negatively. For a successful rehabilitation program, pain free mobilization of the patient should be increased (in both duration and distance). For this aim, many methods can be used. Exercise takes an important place among them. To obtain soft tissue mobilization, combination of physiotherapy and exercise can be used. Degenerative changes increasing with age, lead to problems especially in weight-bearing joints. Strengthening of muscles surrounding these joints can reduce the load of the joint and increase patient mobilization or ability to move. Stretching, strengthening and joint stabilization exercises are among the generally accepted exercise modalities (9). The reason of this preference is the interrelationship among muscle weakness, joint stability and pain. Exercise plays an essential role in OA management because muscle weakness creates joint instability, joint instability leads to pain and pain leads to inhibition of muscles surrounding joint (Fig. 4). Exercise decreases the failure and increases the functionality by decreasing pain, increasing range of joint motion, enhancing muscle strength, obtaining better walking and facilitating activities of daily living. Exercise prevents progressive joint damage by minimizing the stress that the joint is exposed to and correcting the biomechanics. Exercise also prevents from injury and improves overall health. In a previous study, we demonstrated that proprioceptive exercise added to strengthening exercise in patients with knee osteoarthritis provided a better outcome than strengthening exercise alone (10). As known, proprioception is ability to perceive body position in the three dimensional space. A corruption in proprioception poses a susceptibility of joints to the external stresses, as the body cannot maintain adequate position. Improving proprioception through a range of special exercises may increase endurance against traumatic conditions and retard joint degeneration. Hyaluronic acid injection was shown to increase proprioception of knee joint (11). As such, combination of proprioceptive exercises with injections may increase the effect of treatment. On the other hand, stabilization of central part of the body are critical to provide greater functional efficiency of the kinetic chain of the lower and upper limbs. The special exercise program created for this purpose is called to “core” stabilization exercise (12).

The major change in the public health in 21st century is the increase in elderly population. Diseases, which are seen more in elderly people, are become more important in terms of both economical and medical aspect. Pain, disability, loss of mobility and independence are the causes of reduced quality of life (13). Osteoarthritis, especially in the elderly, is an important problem that negatively affects the quality-of-life. The diagnosis of osteoarthritis is not difficult. But, too many treatment alternatives may lead to confusion time to time. For example, selection of patients suitable for intra-articular treatment may be problematic. According to the management pyramid in osteoarthritis, education, diet, weight loss, counseling, and exercises for the protection of range of motion and muscle strength should be given to all patients (14). In some patients short courses of non-steroidal anti-inflammatory drugs (NSAID's) or simple analgesics; shoe alterations, supportive devices, walking aids etc. due to biomechanical evaluation and teaching joint protection techniques will be adequate (14). Intra-articular injections can be seen in the upper part of the pyramid. The next-step should consider choices of joint lavage, debridement, and medical synovectomy. And at the top of the pyramid major surgical intervention, can be performed (14).

Intra-articular treatments are among distinguished therapies due to lack of systemic effects and specific administration to the site of pathology. They also can be repeated with the advantage of mechanical action. There are too many options in selecting material to intra-articular treatments, such as hyaluronic acids, corticosteroids, ozone- oxygen, platelet rich plasma (PRP), various NSAID's, sterilized natural anti-inflammatory extracts, joint lavage with physiologic saline, morphine, clodronate, interleukin 1 and the others. Among these, hyaluronic acids and corticosteroids are most commonly chosen preparations. For the purpose of increase joint mobility and decrease pain, hyaluronic acids can be used in non-inflammatory period. According to many studies, hyaluronic acid may affect intra-articularly with different ways: decreasing contact of cartilage with inflammatory mediators and degenerative enzymes, decreasing joint effusion, effect on nociceptors, participation to matrix structure, increasing joint lubrication, increasing Hsp72 expression, inhibition of free oxygen radicals and matrix metalloproteases (15-18). In a randomized and placebo-controlled study, we demonstrated that intra-articular injection of hyaluronan in patients with knee OA led to a short-term increase in proprioception and isokinetic muscle force, and also significant improvements in the functional status of patients (11). Based on these results, intra-articular hyaluronic acid injection exerts positive effects on the functional status of the patients. The main goal of rehabilitation practice is to increase functional capacity of the patients. Considering these results, utilization of rehabilitation methods and injection methods in combination seems to be logical.

Effects of corticosteroids' on inflammation is very well known. This strong anti-inflammatory effect can be used to support the rehabilitation process (19). On the contrary, it is possible to control inflammation and pain with convenient rehabilitation program accompanying to corticosteroid injections. Indeed, severe inflammation increases the level of pain perceived, and also limits joint range-of-motion, and eventually reduces the mobilization level of patients. The success of a rehabilitation program for a joint with severe inflammation is limited. Physician should first try to reduce and inhibit inflammation. If there is no complication, then rehabilitation program can be continued soon after intra-articular injection. For instance, shoulder problems are common in stroke patients. In a hemiplegic stroke patient, the most important reasons for shoulder pain are lack of muscle support of shoulder and inadequate posture. In many patients, shoulder pain has negative effects on stroke rehabilitation. In such cases, adding shoulder injections to the rehabilitation program may be a good choice. In case of frozen shoulder related with stroke or not, rehabilitation of shoulder joint is much more difficult. Because, both pain and motion limitation of the joint prevent administration of stretching/relaxing program. The number of treatment sessions increases and also the patient experience more pain during physical therapies. In such a condition, an intra-articular injection should be added to rehabilitation program. Thus, treatment sessions can be reduced besides increasing patient comfort. For this aim, both corticosteroids and hyaluronic acid can be used (20). In a study, authors suggested that the best outcome can be

obtained by a combination of exercise and injection in patients with subacromial adhesive bursitis (21). In another study, this approach was shown to be a cost-effective way. According to the results of this study, adding corticosteroid injections to the exercise and rehabilitation program conducted under the supervision of a therapist was more cost-effective than performing exercise alone (22). It has been shown that corticosteroid injections can be used safely and lead to desired results in diabetic patients with adhesive capsulitis (23). The adverse effects of systemic corticosteroids in long-term use is well-known. Systemic side effects are quite rare in intra-articular injections. This may affect positively the rehabilitation program.

In clinical progression of osteoarthritis, generally two consecutive phases can be noted. These are the inflammation (congestive) phase following an initial stress and the remission phase. Chondroresorption is especially seen in the inflammation phase. When planning rehabilitation of osteoarthritis, these phases should be taken into account. For example, in the inflammation phase, resting, decreasing joint load, passive mobilization, cold treatment, analgesic and anti-inflammatory treatment should be chosen. In the remission phase, strengthening exercises, aerobic exercises, proprioceptive exercises, hot treatments and hydrotherapy should take part in the rehabilitation program. Although anti-inflammatory effects of hyaluronic acid has been shown in some studies, intra-articular corticosteroids should be preferred in the inflammatory phase. During the remission phase, hyaluronic acid injections are more logical.

In conclusion, when the patients need rehabilitation and have degenerative joint problems to some extent or local joint inflammation, intra-articular injections may be extensively useful. On the contrary, rehabilitation can be facilitated with intra-articular treatments. Various studies showed complementary effects of injection and rehabilitation. The amount of synergy provided by the combination of these two methods can be demonstrated by well-designed studies.

## REFERENCES


1. Barbotte E, Guillemin F, Chau N; Lorhandicap Group. Prevalence of impairments, disabilities, handicaps and quality of life in the general population: a review of recent literature. Bull World Health Organ 2001; 79:1047-55.
2. Cameron MH. Introduction. Physical Rehabilitation. Evidence Based Examination, Evaluation and Intervention, Saunder-Elsevier, 2007, St. Louis, Missouri.
3. World Report on Disability, WHO, 2011. WHO Library Cataloguing-in-Publication Data. ISBN 9789240685215
4. Stucki A, Borchers M, Stucki G, Cieza A, Amann E, Ruof J. Content comparison of health status measures for obesity based on the international classification of functioning, disability and health. Int J Obes (Lond) 2006; 30:1791-9.
5. Bourré-Tessier J, Clarke AE, Mikolaitis-Preuss RA, Kosinski M, Bernatsky S, Block JA, Jolly M. Cross-cultural Validation of a Disease-specific Patient-reported Outcome Measure for Systemic Lupus Erythematosus in Canada. J Rheumatol 2013 Aug;40(8):1327-33.
6. Obradovic M, Lal A, Liedgens H. Validity and responsiveness of EuroQol-5 dimension (EQ-5D) versus Short Form-6 dimension (SF-6D) questionnaire in chronic pain. Health Qual Life Outcomes 2013; 11:110.
7. Rat AC, Baumann C, Guillemin F. National, multicentre, prospective study of quality of life in patients with osteoarthritis of the knee treated with hylane G-F 20. Clin Rheumatol 2011; 30:1285-93.
8. Nolan V: The Innovator's Handbook, Problem Solving, Communication and Teamwork, Penguin Books, 1989, Harmondsworth.
9. Knoop J, Dekker J, van der Leeden M, et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. Osteoarthritis Cartilage 2013 Aug;21(8):1025-34. Epub 2013 May 28.
10. Diracoglu D, Aydin R, Baskent A, Celik A. Effects of kinesthesia and balance exercises in knee osteoarthritis. J Clin Rheumatol 2005; 11:303-10.
11. Diracoglu D, Vural M, Baskent A, Dikici F, Aksoy C. The effect of viscosupplementation on

neuromuscular control of the knee in patients with osteoarthritis. J Back Musculoskelet Rehabil 2009; 22:1-9.
12. Kibler WB, Press J, Sciascia A. The role of core stability in athletic function. Sports Med 2006; 36:189-98.
13. Gigante A, Callegari L. The role of intra-articular hyaluronan (Sinovial) in the treatment of osteoarthritis. Rheumatol Int 2011; 31:427-44.
14. Dieppe P. Osteoarthritis and related disorders. In: Klippel JH, Dieppe PA (eds). Rheumatology Second Ed, Mosby, Philadephia, 1998; 8-1.1
15. Taka shi K, Goomer RS, Harwood F, Kubo T, Hirasawa Y, Amiel D. The effects of hyaluronan on matrix metalloproteinase-3 (MMP-3), interleukin-1beta(IL-1beta), and tissue inhibitor of metalloproteinase-1 (TIMP-1) gene expression during the development of osteoarthritis. Osteoarthritis Cartilage 1999; 7:182-90.
16. Kelly MA, Kurzweil PR, Moskowitz RW. Intra-articular hyaluronans in knee osteoarthritis: rationale and practical considerations. Am J Orthop 2004; 33(2 Suppl):15-22.
17. Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1-year placebo-controlled trial. Osteoarthritis Cartilage 1993; 1:97-103.
18. Asari A, Miyauchi S, Matsuzaka S, Ito T, Kominami E, Uchiyama Y. Molecular weight-dependent effects of hyaluronate on the arthritic synovium. Arch Histol Cytol 1998; 61:125-35.
19. Pekarek B, Osher L, Buck S, Bowen M. Intra-articular corticosteroid injections: A critical literature review with up-to-date findings. Foot (Edinb) 2011; 21:66-70.
20. Park KD, Nam HS, Lee JK, Kim YJ, Park Y. Treatment effects of ultrasound-guided capsular distension with hyaluronic acid in adhesive capsulitis of the shoulder. Arch Phys Med Rehabil 2013; 94:264-70.
21. Gasparre G, Fusaro I, Galletti S, Volini S, Benedetti MG. Effectiveness of ultrasound-guided injections combined with shoulder exercises in the treatment of subacromial adhesive bursitis. Musculoskelet Surg 2012; 96 Suppl 1:S57-61.
22. Jowett S, Crawshaw DP, Helliwell PS, Hensor EM, Hay EM, Conaghan PG. Cost-effectiveness of exercise therapy after corticosteroid injection for moderate to severe shoulder pain due to subacromial impingement syndrome: a trial-based analysis. Rheumatology (Oxford). 2013 Apr 28.
23. Roh YH, Yi SR, Noh JH, Lee SY, Oh JH, Gong HS, Baek GH. Intra-articular corticosteroid injection in diabetic patients with adhesive capsulitis: a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc 2012; 20:1947-52.


Oggi, il mondo di domani è l'impegno ad agire per un presente responsabile ed un futuro sostenibile. Per Bristol-Myers Squibb significa innanzitutto sviluppare farmaci che realmente possano fare la differenza nella vita delle persone per prolungare e migliorare la vita umana. Ma significa anche avere la piena consapevolezza degli obblighi verso la comunità locale e globale, trasformandoli in impegno concreto. Il nostro impegno guarda al futuro e alle realtà più lontane ma inizia nel presente e dai luoghi a noi più vicini. **Oggi, per il domani.**

www.bms.it

Bristol-Myers Squibb

# EFFECTS OF TOCILIZUMAB IN PATIENTS WITH POLYMIALGIA RHEUMATICA AND TYPE2 DIABETES: CASE SERIES OF 5 PATIENTS.

L.S. MARTIN-MARTIN[1], I. MISISCHI[2], C. LATINI[3], A. LATINI[1], A. SILVESTRI[1], A. RAGNO[1], and E. PAPINI[2]

*[1]Department of Internal Medicine, "Regina Apostolorum" Hospital – Albano Laziale (Rome-Italy)*
*[2]Department of Endocrinology, "Regina Apostolorum" Hospital – Albano Laziale (Rome-Italy)*
*[3]School of Medicine, University "La Sapienza" (Rome-Italy)*

**Polymyalgia Rheumatica (PMR) is a rheumatic disease characterised by inflammatory pain in the scapular and pelvic tracks and with elevated markers of inflammation as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The common treatment is steroid with consequent complications as: hypertension, osteoporosis, obesity and diabetes. Moreover, in diabetic patients treated with oral hypoglicemic agents the steroid therapy induces a rise of glycaemic values and, sometimes, a switch to insulin therapy. Tocilizumab (TCZ) is a monoclonal antibody that blocks the action of IL-6, currently used for Rheumatoid Arthritis. We proposed therapy with Tocilizumab and a low dose of steroid therapy in five patients with diabetes and onset PMR. At the end of the observation all patients have demonstrated a complete resolution of the clinical and serological picture and no change of the HbA1c value; none of the patients needed insulin therapy.**

Polymyalgia Rheumatica (PMR) is a common rheumatic disease that affects middle aged and older patients. Its incidence increases progressively after 50 years with a maximum peak between 70-80 years old (1). Polymyalgia Rheumatica is twice as common in women as in men and is related to giant cell arteritis (GCA), although the precise relationship between the two conditions remains unknown. While the aetiology of PMR remains elusive, both environmental and genetic risk factors are thought to contribute to its development (2).

In particular, the study of the allelic variants of the DR4 has revealed that some subtypes HLA-DRB1*04 (the allele HLA-DRB1*0404) are present in almost 50% of the patients (3). In the diagnosis of PMR distinguishing between GCA and PMR is important because GCA can lead to blindness and requires higher doses of medication. The onset of PMR usually is acute. However, symptoms generally are present for longer than one month before patients seek an evaluation. Polymyalgia rheumatica affects the shoulder and hip girdles causing aching and morning stiffness related to synovitis of proximal joints and inflammation of extra-articular synovial structures. (4) The most striking symptom is the functional impotence, sometimes so severe that the patient, must be helped to get dressed and undressed, and has difficulty getting up when he is sitting and/or raise the arms. Laboratory test findings in PMR are nonspecific and usually indicate the presence of inflammation with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). C-reactive protein is a more sensitive indicator of disease activity than ESR in PMR as it is less affected by extraneous factors such as increasing age (5). Patients with PMR may

*Key words: Polymyalgia Rheumatica, anti-IL-6 Antibodies, Diabetes mellitus.*

*Corresponding Author:*
Luis Severino Martin Martin,
Department of Internal Medicine,
"Regina Apostolorum" Hospital,
Albano Laziale (Rome-Italy).
E-mail addresss: severino.martin@gmail.com



2038-4106 (2013)

have a normochromic, normocytic anaemia and raised alkaline phosphatase but creatinine kinase is invariably normal (in contrast to elevated levels in polymyositis, hypothyroidism and other muscle diseases). Once the diagnosis is established, the steroids are the first-line therapy in the treatment of the PMR. The initial dose of prednisone is 15 mg a day, and it should be increased to no higher than 20 mg a day in the first two weeks of treatment and then gradually tapered over time. In general, the response to the therapy is excellent with the resolution of symptoms in a few days associated with a reduction of ESR and CPR. Glucocorticosteroid related adverse events are common and include osteoporosis, avascular necrosis, infections, diabetes, insufficiency fractures, steroid myopathies, hypertension, and cataracts, suggesting the need to improve the therapeutic options, mainly in patients at high risk related to steroid toxicity (6). Methotrexate or an anti-tumor necrosis factor drug is the most commonly used corticosteroid sparing agent but showed modest efficacy in this situation.

In the PMR, an increased plasma concentration of IL-6 has been demonstrated. In particular, the persistent increase of IL-6, after a successful steroid treatment, seems predictive of a relapse of the PMR (7). Tocilizumab (TCZ) is an anti-interleukin 6-receptor antibody that is being recently studied in the treatment of PMR patients who are intolerant or refractory to GCs, especially after failure of a second-line agent (8).

## PATIENTS AND METHODS

We selected 5 patients (3 females and 2 males, mean age 68 +/-3 years), with recent diagnosis of Polymyalgia Rheumatica with the onset of symptoms no more than one month previously and with well-controlled diabetes under oral therapy. All of them showed high CRP values at the baseline (Fig. 1), while the rheumatoid factor and the antibodies against cyclic citrullinated peptide (Ab-CCP) were negative.

The clinical aspects of the patients showed a typical clinical picture: a strong pain in the shoulder and hip girdles causing aching and morning stiffness of proximal joints and has difficulty getting up when he/she is sitting and/or raise the arms. Four out of five patients showed an important functional impotence, sometimes so severe that the patients, must be helped to get dressed and undressed. When the patients were visited, VAS pain average was 7. Four of five patients (3 males and 1 female) were affected by hypertension under good pharmacological control. 1 male was suffering from COPD and one female was treated with Levothyroxine for thyroid nodules. All patients underwent tests for hepatic, renal and bone marrow functions: AST, ALT, creatinine, complete blood count, protein electrophoresis, Na and K. Also, at the baseline, we excluded hepatitis, HIV infection and tuberculosis, their lipid profile was normal. Patients were well informed about the steroid therapy and the TCZ complications, Therefore, when their informed consent was obtained, all patients underwent a single infusion of TCZ at a dose of 8 mg/kg and steroid therapy at a weight based dose (5 mg/day if weight < 80 kg, or 7.5 mg/day if weight> 80 kg). After 30 and 60 days, all patients were checked for ESR, CRP, blood glucose, HbA1c, lipid profile, complete blood count, AST, ALT and creatinine and all patients filled out a self-report assessment of pain on VAS scale.

## RESULTS

At 30 and 60 days we showed a statistically significant reduction of CRP (from 40,2 mg/dl ± 15,2 to 4,1 mg/dl ± 4,9 and to 4,4 mg/dl ± 2 respectively p=0,001) (Fig. 1) and a complete disappear of pain. During the follow up all serological checks were normal and no complications were observed, but above all none of the patients needed to switch to therapy insulin because glycaemic control was maintained within the limits (Fig. 2).

We did not perform a statistical analysis due to the small sample size, since this is a pilot study exploring the efficacy and safety of Tocilizumab therapy in PMR patients affected also by type 2 diabetes and therefore with contraindications to high doses of steroids.

## DISCUSSION

Polymyalgia Rheumatica (PMR) is a common rheumatic disease that affects middle aged and older patients. The common treatment is oral prednisone resulting in a dramatic suppression of inflammation. The British Society for Rheumatology and the British

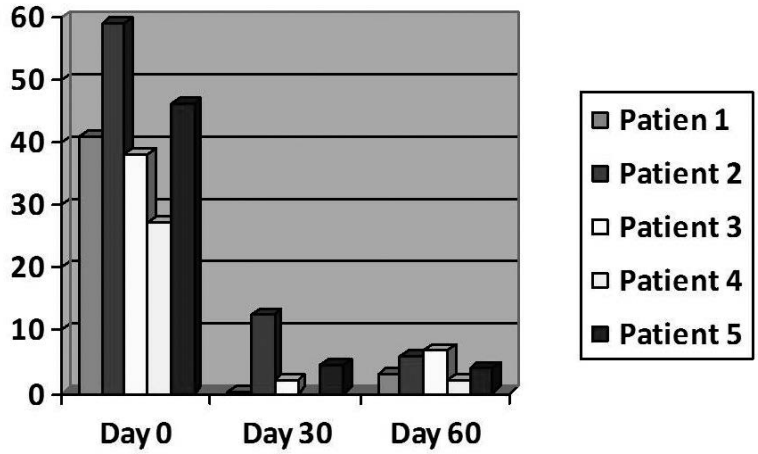



**Fig. 1.** *CRP values during follow-up (mg/dl).*

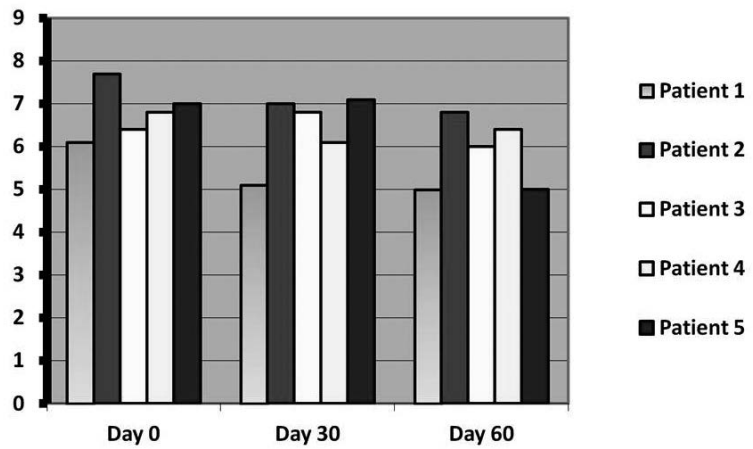



**Fig. 2.** *HbA1c values during follow-up (%).*

Health Professionals in Rheumatology consensus regimen suggests using: daily prednisolone: 15 mg for 3 weeks, then 12.5 mg for 3 weeks, then 10 mg for 4–6 weeks, then reduction by 1 mg every 4–8 weeks or alternate day reductions (eg. 10/7.5 mg alternate days) (9).

Unfortunately some concerns may arise in the steroid treatment of these Patients. Over 60% of patients have a disease relapse during the decrease of the steroid therapy, and many studies indicate that rarely the steroid treatment may be stopped before two years. Moreover elderly patients are often affected by several comorbidities contra-indicating the use of steroid treatments. Further the classical "steroid-saving" drugs have not been successful in PMR therapy, due to an insufficient production of endogenous glucocorticoids (10). Some evidences have suggested the involvement of IL-6 in the pathway of PMR, for this reason it has sparked interest in blocking IL-6 system to manage PMR. Recently two research groups have published positive clinical effects of Tocilizumab in the therapy of PMR (8,11).

In this pilot study we have explored a combined therapy with low dose of steroid and an inhibitor IL-6 Tocilizumab for diabetic patients affected by Polymialgia Rheumatica; our results showed a complete resolution of pain and inflammatory markers without requiring insulin therapy for a good glycaemic control. In addition it seems that TCZ has a positive effect against the insulin resistance; in fact other authors have found a normalization of HbA1c in patients treated with TCZ (12).Our findings could suggest the use of IL-6 inhibition at least in these kind of patients. Due to the cost of TCZ we cannot

propose IL-6 inhibition in all PMR patients, but it may be a suitable alternative treatment for patients with many comorbidities and especially in diabetic patients. This study is only a case series of 5 patients, it's necessary a RCT with a larger number of patients before drawing definitive conclusions.

## ACKNOWLEDGMENTS

We thank Monica Canto Martin, from Autonoma University - Madrid (Spain) for English traslation.

## BIBLIOGRAPHY

1. Cid MC, Font C, Coll-Vinent B, Grau JM. Large vessel vasculitides. Curr Opin Rheumathol 1998; 10:18-28.
2. Salvarani C, Cantini F, Hunder G. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008; 372:234–45.
3. Weyand CM, Hunder NH, Hicok K, Hunder G, Goronzy J. HLA-DRB1 alleles in polymyalgia rheumatica, giant cell arteritis and rheumatoid arthritis. Arthritis Rheum 1994; 37:514-520.
4. Salvarani C, Cantini F, olivieri i, et al. Polymyalgia rheumatica: a disorder of extra-articular synovial structures? J Rheumatol 1999; 26:517–21.
5. Cantini F, Salvarani C, Olivieri I, et al. Erythrocyte sedimentation rate and C-reactive protein in the evaluation of disease activity and severity in polymyalgia rheumatica: a prospective follow-up study. Semin Arthritis Rheum 2000; 30:17–24.
6. Ferraccioli GF, Di Poi E, Damato R. Steroid sparing therapeutic approaches to polymyalgia rheumatica/ giant cell arteritis. State of the art and perspectives. Clin Exp Rheumatol 2000; 18 (S 20):58-60.
7. Roche NE, Fulbright JW, Wagner AD et al. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum 1993; 36:1286-94.
8. Al Rashidi A, Hegazi MO, Mohammad SA, Varghese A. Effective control of polymyalgia rheumatica with tocilizumab. J Clin Rheumatol 2010; 19(7):400-1.
9. Dasgupta B, Borg F, Hassan N, et al. BSR and BHPR guidelines for the management of polymyalgia rheumatica. Oxford: Oxford University Press, 2009.
10. Cutolo M, Olivieri M, Secchi ME et al. Therapy of rheumatic polymyalgia: the pathophysiologic management. Reumatismo 2007; 59(4):271-279.
11. Hagihara K, Kawase I, Tanaka T, Kishimoto T. Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica. J Rheumatol 2010; 37(5):1075-6.
12. Ogata A, Morishima A, Hirano T et al. Improvement of HbA1c during treatment with humanised anti-interleukin 6 receptor antibody, tocilizumab. Ann Rheum Dis 2011; 70(6):1164-5.

# POWER DOPPLER ULTRASONOGRAPHY OF ACHILLES TENDON ENTHESES IN ATHLETES. CAN INTENSE PHYSICAL ACTIVITY INCREASE POWER DOPPLER SIGNAL AND SIMULATE ENTHESITIS AT ULTRASOUND EXAMINATION OF HEALTHY SUBJECTS?

G. FILIPPOU, A. ADINOLFI, I. BERTOLDI, V. DI SABATINO, V. PICERNO, M. GALEAZZI AND B. FREDIANI

*Department of Medicine, Surgery and Neurosciences, Section of Rheumatology, University of Siena.*

**A positive power Doppler (PD) signal on ultrasonographic examination (US) of entheses sites is generally considered a specific sign of inflammation. Some authors retain that intense physical activity may provoke increased blood flow at tendons, resulting in a positive PD signal. The objective of our study was to assess the effect of intense physical activity on ultrasonographic power Doppler analysis of Achilles tendon entheses in healthy subjects. We enrolled 8 professional basketball players in the study. All subjects underwent ultrasonographic power Doppler (USPD) examination of both Achilles tendons before and after a three hour training session. A patient with known Achilles tendon enthesopathy was used to optimize power Doppler settings. USPD analysis was negative before and after the training session in all subjects. Intense physical activity and mechanical stress of Achilles tendon entheses do not increase intratendinous power Doppler signal. A power Doppler signal at entheses sites should be considered specific for inflammation.**

The entheses are the sites at which tendons, muscles, ligaments and joint capsules are inserted into the bone. Inflammation involving entheses is considered as characteristic sign of spondyloarthritis, as entheses are the main anatomic target of inflammation in this type of arthritis (1). Joint ultrasonography is widely used to observe tendons and describe the alterations typical of enthesitis (2,3). The most characteristic ultrasonographic sign of entheseal inflammation is a positive power Doppler (PD) signal at the point of insertion of the tendon under examination. Although this sign is considered to be highly specific for inflammation, some authors claim that a positive PD signal can also occur following normal physical stimulation such as sport (9,10,11).

The aim of our study was to evaluate the presence of a PD signal in the tendons of healthy subjects following highly intensive physical activity.

## PATIENTS AND METHODS

Eight professional basketball players belonging to the "Società Costone" in Siena were recruited for the study. The inclusion criteria were absence of tendon pain or known tendinopathy, absence of other local or systemic pathologies and a negative history of non-steroidal anti-inflammatory drug or cortisone use. The mean age of the athletes examined was 23 years (range 18-29). All the athletes took part in 5 training sessions per week of approximately 3 hours each, as well as several hours of training in the gym and one basketball game. Power Doppler ultrasound evaluation was performed on both Achilles tendons

*Key Words: Power Doppler, enthesitis, sport, Achilles tendon, ultrasonography.*

*Corresponding author:*
Antonella Adinolfi
Department of Medicine, Surgery and Neurosciences,
Section of Rheumatology, University of Siena.
E-mail address: antonella.adinolfi986@gmail.com



2038-4106 (2013)

of all eight athletes immediately before and after a three hour training session. In order to carry out the analyses at the training ground, a portable device with multi-frequency probes was used (Esaote MyLab 25, Genoa, Italy) at a maximum frequency of 18 MHz.

Scans were performed with subjects lying on a bed in the prone position, with their feet slightly off the end of the bed. To optimize Power Doppler settings, a patient with known acute Achilles tendinopathy was examined immediately prior to evaluation of the eight study subjects, in the same conditions (Fig. 1). All ultrasound evaluations were performed by the same doctor, specialized in rheumatology and expert in muscoloskeletal ultrasonography.

## RESULTS

16 Achille's tendons were examined at the end of the training session. No significant alterations in grey scale US were noted after the training session. Similarly, Power Doppler ultrasound did not show the presence of intratendinous or entheseal vascular signals in any of the subjects examined, either before after physical exercise (Fig. 1).

## DISCUSSION

The ultrasound anatomy of normal entheses shows slow vascularization of the perientheseal tissues and the absence of a vascular signal in the entheses (2); the presence of an intratendinous PD signal is considered as a sign of inflammatory or degenerative tendon disease (2,3,4).

Inflammation of the entheses (enthesitis) is a characteristic of spondyloarthritis, the entheses being the main anatomic target of inflammation in seronegative arthritis (2,3).

Forms of tendon alteration associated with signs of neovascularization are also correlated with other tendinopathies caused by traumas or particularly accentuated mechanical stress: these include sports-related tendinopathies, which often show PD signals in symptomatic subjects (4).

Neovascularization seems to play a key role in the development of painful symptoms in tendinopathies (5,6,7). Vascular neoformation is related to altered VEGF (vascular endothelial growth factor) expression, which can be caused by various stimuli, such as hypoxia, mechanical stress, or the presence of inflammatory cytokines; the vessel walls are covered with a dense network of nerve structures, which are responsible for transmitting the sensation of pain as they are probably glutamate-mediated (6). To ascertain whether the presence of an ultrasound PD signal is specific to tendon inflammation, we focused our analysis on the tendons of professional athletes in direct relation to a training session. This allowed us to evaluate the effect of physical stress and related mechanical and metabolic factors on the vascularization of healthy and clinically normal entheses.

Previous studies have evaluated the ultrasonographic characteristics of entheses in direct connection to exercise (8-11) and some have suggested that increased vascularization in the tendons studied may represent a physiological response to exercise and increased functional demand. It should be pointed out, however, that these analyses provide no clear indication of the presence or lack of tendinopathy in the subjects studied, and in some of them the populations observed are mainly composed of symptomatic subjects suffering from chronic forms of tendinopathy. A study on patellar tendinopathy (jumper's knee) in badminton

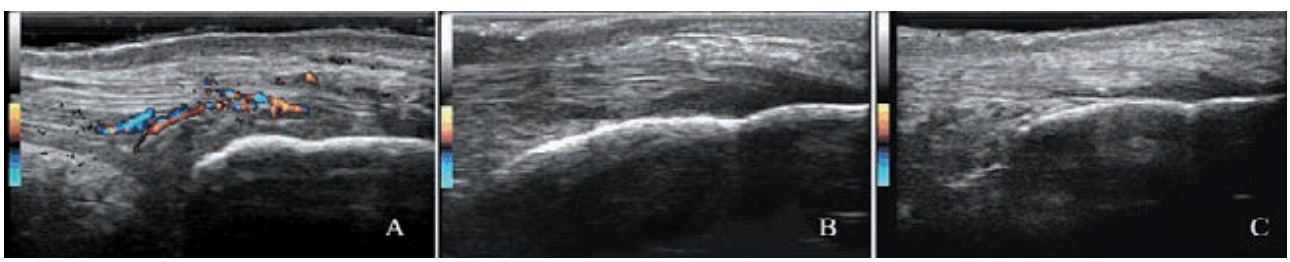



**Fig. 1.** *Longitudinal scan of the Achilles tendon entheses of our control subject (A) and of an athlete, before (B) and after (C) the training session. Power Doppler signal was not found at the healthy subject.*

players (8) revealed a high prevalence of painful tendinopathy in badminton players and an almost identical prevalence of PD signal at ultrasound examination, although the signal was also present in subjects without a recent or previous history of symptomatic tendinopathy. However, the authors confirmed a greater presence of vascularization in painful tendons compared to asymptomatic ones and found no increase in vascularization after the match as compared to before the match. A study conducted on the Achilles tendons of nonprofessional football players (9), on the other hand, concluded that tendon vascularization was frequent in the subjects observed (without giving details of any correlation with painful symptoms reported) and characteristically increased with physical exercise.

Boesen et al. (10) and van Snellenberg et al. (11), on the other hand, deny that there is a direct relationship between the presence of a vascular signal and tendinopathy of the affected area. Signs of neovascularization were found in both studies: in symptomatic subjects and asymptomatic populations of non-professional athletes in the former, and in healthy individuals with no athletic training in the latter. According to Boesen, while the PD signal is always positive in the study of symptomatic tendinopathies, Doppler activity should not always be interpreted as a pathological sign in itself. It can, however, be considered as a physiological sign in the tendons of asymptomatic volunteers not undergoing training that show a progressive increase following physical exercise, thus indicating a physiological response to increased functional demand (10).

These observations are in contrast with our results and those of other authors, which report the presence of vascularization as a pathological sign and have not found a vascular signal in asymptomatic subjects (7,12). Ohberg et al. (7), for example, found neovascularization in areas with other ultrasonographic and clinical signs of tendinosis, and especially in symptomatic areas, but not in the tendons of asymptomatic subjects.

Morel et al. (12) compared the vascularization of Achilles tendons and entheses in tissue samples from the cadavers of asymptomatic subjects with ultrasonographic scans of the healthy tendons of subjects without any symptoms of pain. Ultrasonographic analysis following the injection of a contrast medium did not show the presence of an intratendinous vascular signal in any case, nor did it identify the presence of the smaller vascular branches (capillaries) that histological examination had shown in the perientheseal regions, leading the authors to conclude that the presence of a more pronounced vascular component in the tendon structure should be considered as an indication of increased vascularization associated with inflammatory phenomena.

A study published in 2012 by Hirschmuller et al. (13), evaluated the role of ultrasonography of Achille's tendon as a prognostic tool for tendonitis. Based on the results obtained, the authors concluded that the neovascularization within the Achilles tendon should be considered the most important prognostic factor of early tendinosis, excluding its role as part of an adaptive process. This study was based on the evaluation of the whole tendon and not specifically at the entheses, but it is in accordance with our results that power Doppler signal is not present in normal tendons (entheses or main tendon).

In conclusion, none of the tendons observed in our study showed the presence of vascular signal following physical exercise, suggesting that entheseal vascularization does not reflect a condition of increased functional demand following muscular stress or due to mechanical factors. We can therefore conclude that the power Doppler signal is a highly specific ultrasonographic sign of entheseal inflammation.

## ACKNOWLEDGEMENT

The authors wish to thank the players and managers of "Associazione Sportiva Costone" for they kind participation at the study.

The authors declare no conflict of interest

## BIBLIOGRAPHY

1. Benjamin M, Mc Gonagle D. The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. J Anat 2001; 199:503-527.
2. Falsetti P, Acciai C, Lenzi L, Frediani B. Ultrasound of enthesopathy in rheumatic disease. Mod

Rheumatol 2009; 19:103-113.
3. D'Agostino MA, Said-Nahal R, Hacquard-Boudar C, Brasseur JL, Dougados M, Breban M. Assessment of peripheral enthesitis in the Spondyloarthropathies by Ultrasonography combined with Power Doppler. A cross-sectional study. Arthritis Rheum 2003; 48:523-533.
4. Benjamin M, Toumi M, Ralphs JR, Bydder G, Best TM, Milz S. Where tendons and ligaments meet bone: attachment sites (entheses) in relation to exercise and/or mechanical load. J Anat 2006; 208:471-490.
5. Zanetti M, Metzdorf A, Kundert HP, Zollinger H, Vienne P, Seifert B, et al. Achilles tendons: clinical relevance of neovascularization diagnosed with Power Doppler ultrasonography. Radiology 2003; 227:556-560.
6. Pufe T, Petersen WJ, Mentlein R, Tillmann BN. The role of vasculature and angiogenesis for the pathogenesis of degenerative tendon disease. Scand J Med Sci Sports 2005; 15:211-222.
7. Ohberg L, Lorentzon R, Alfredsn H. Neovascularization in Achilles tendons with painful tendinosis but not in normal tendons: an ultrasonographic investigation. Knee Surg Sports Traumatol Arthrosc 2001; 9:235-238.
8. Koenig MJ, Torp-Pedersen ST, Boesen MI, Holm CC, Bliddal H. Ultrasound Doppler of the anterior knee tendons in elite badminton players. Colour fraction before and after the match. Br J Sports Med 2010; 44(2):134-9.
9. Fahlstrom M, Alfredson H, () Ultrasound and Doppler findings in the Achilles tendon among middle-aged recreational floor-ball players in direct relation to a match. Br J Sports Med 2008; 10.1136/bjsm.2008.047316.
10. Boesen MI, Koenig MJ, Torp-Pedersen S, Bliddal H, Langberg H. Tendinopathy and Doppler activity: the vascular response of the Achilles tendon to exercise. Scand J Med Sci Sports 2006; 16:463-469.
11. Van Snellenberg W, Wiley JP, Brunet G. Achilles tendon pain intensity and level of neovascularization in athletes as determined by color Doppler ultrasound. Scand J Med Sci Sports 2007; 17:530-534.
12. Morel M, Boutry N, Demondion X, Legroux-Gerot I, Cotton H, Cotton A. Normal anatomy of the heel entheses: anatomical and ultrasonographic study of their blood supply. Surg Radiol Anat 2005; 27:176-183.
13. Hirschmuller A, Konstantinidis L, Frey V, Dickhuth HH, Baur H, Sudkamp NP, Helwig P, Prognostic Value of Achilles Tendon Doppler Sonography in Asymptomatic Runners. Med Sci Sports Exerc 2012; 44(2):199-205.

# KNEE LAVAGE VERSUS INTRA-ARTICULAR HYALURONAN IN ADVANCED KNEE OSTEOARTHRITIS.

M. MORTADA[1] and E.A. ELEWA[2]

*[1]Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University, Egypt.*
*[2]Assistant Professor of Rheumatology and Rehabilitation, Faculty of Medicine, Zagazig University, Egypt.*

**Many patients with advanced knee osteoarthritis (OA) who are indicted for total knee joint replacement (TKR) are unfit for operation or refuse it for different reasons. Palliative treatment for this group of patients may be important for decreasing pain and improving function. The aim of the study was to compare efficacy and safety of knee joint lavage[KJL] ( two 14 gauges needles and 2 liters of 0.9% saline) and intra-articular hyaluronic acid injections (HAIs) (3 x 2ml, 1 week apart).We performed a single-centre, single blind, randomized, parallel group trial comparing KJL and HAIs. Patients with advanced knee OA (Kellgren/Lawrence score 4) who are indicted for TKR and unfit or refuse to have TKR, were randomized to either knee lavage using the 2 needle technique or a weekly intra-articular injection of hyaluronic acid for 3 weeks. Patients were followed up for 12 months. The primary outcome measures were the Western Ontario and McMaster Universities OA Index total pain score WOMAC (a Likert scale) and patient global assessment (PGA) questionnaires. Seventy patients were recruited of whom 36 received KJL and 34 received HAIs. At the end of the 1st month, there was a reduction in the WOMAC pain score of 80% and 40% in KJL and HAIs groups respectively. At this time point just 88% (32 patients) and 50% (17 patients) of subjects in KJL and HAIs groups respectively felt that their knee pain had improved compared to baseline. At the end of the 6th month post injection, there was a reduction in the WOMAC pain score of 50% and 10% in KJL and HAIs groups respectively. At this time point just 88% (32 patients) and 50% (17 patients) of subjects in KJL and HAIs groups respectively felt that their knee pain had improved compared to baseline. At the end of the 9th month post injection, there was a reduction in the WOMAC pain score of 25% and 5% in KJL and HAIs groups respectively. At this time point just 27.7% (10 patients) and 5.9% (2 patients) of patients in KJL and HAIs groups respectively felt that their knee pain had improved compared to baseline. By the end of the 12th month, none of patients in both groups felt that his knee pain had improved compared to baseline and there was no reduction in WOMAC pain score. At the ends of 1st, 6th and 9th months, the improvement in WOMAC pain score and the number of subjects reporting an improvement in symptoms was significantly greater in the KJL group compared to the HAIs group. In patients with advanced OA, KJL improved pain better than HAIs and for a longer duration.**

Osteoarthritis (OA) is the most common joint disease and one of the most frequent causes of physical impairment (1). Osteoarthritis affects about 10% of the population over 55 years of age, of those one-quarter are severely disabled (2). Osteoarthritis of the knee has been associated with a decrease in the

*Key words: Osteoarthritis, joint lavage, hyaluronan.*

*Corresponding Author:*
Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University, Egypt.
E-mail address: m_a_mortada@yahoo.com



2038-4106 (2013)

elasticity and viscosity of the synovial fluid, which may alter the transmission of mechanical forces to the cartilage, possibly increasing its susceptibility to mechanical damage, or wear and tear (3). Hyaluronan, a high molecular mass polysaccharide produced by type B synovial cells, is one of the main components of synovial fluid. Within the joint cavity, hyaluronan plays a major role in joint lubrication and in maintaining homeostasis (4). Hyaluronic acid is frequently applied by intra-articular injection, but the evidence concerning its clinical relevance is conflicting. Although previous studies showed that viscosupplementation is an effective treatment for OA of the knee with beneficial effects (on pain, function and patient global assessment) (5), the guidelines of American college of rheumatology (ACR) about pharmacological treatment of knee osteoarthritis reported that there were no positive or negative recommendations about using hyaluronic acid injections in patients with Knee OA (6).

The use of joint lavage as a palliative treatment for OA of the knee was started around 1934, when Burman reported that diagnostic arthroscopies improved the symptoms of patients with this disease [10].The assessment of this therapeutic treatment suggested that joint lavage, whether alone or combined with arthroscopy, relieved pain in patients with gonarthrosis (7). Joint lavage as a treatment for the management of patients with some knee disease - particularly arthritis - is especially interesting as it is a relatively non-invasive, virtually painless technique with no side effects; it can be performed at the physician's clinic, is willingly accepted by patients, and is highly effective in relieving pain and improving function (8). The favorable effect of the JL treatment on OA relies on the following phenomena: cartilage debridement, joint distension, removal of microcrystals, joint cooling, dilution of degrading enzymes and various cytokines involved in chondrolysis, and distruption of intra-articular adhesion (9). However, the efficacy of JL in relation to alternative treatments remains to be demonstrated beyond doubt. Knee joint lavage did not addressed in 2012 guidelines of American college of rheumatology (ACR) about pharmacological treatment of knee osteoarthritis (6). In a review of available studies, the methodological quality and the quality of reporting was poor, identified a moderate to large degree of heterogeneity among the trials and concluded that Joint lavage does not result in a relevant benefit for patients with knee osteoarthritis in terms of pain relief or function improvement (10).

Taking in consideration the limited choices available for patients with advanced OA especially those who are unfit or refuse total knee joint replacement (TKR) surgery, we undertook the present study, in which we compared the benefits of the knee joint lavage (KJL) and intra-articular hyaluronic acid injections (HAIs) in patients with advanced OA of the knee.

## MATERIAL AND METHODS

*Patients*

Seventy consecutive patients with knee OA attending the outpatient Clinic of Rheumatology & Rehabilitation Department, Faculty of Medicine, Zagazig University were selected for the study.

*Inclusion criteria:*

Patients aged 40 years or greater, Fulfilling the American College of Rheumatology criteria for osteoarthritis (11), who had advanced OA grade IV radiographic stage osteoarthritis (Kellgren–Lawrence grading system) (12). Continued pain in the target knee despite conservative treatments and patients who indicted for total knee joint replacement TKR but unfit or refuse to have surgery.

*Exclusion criteria:*

Secondary OA in the target knee, viscosupplementation in any joint in the past 9 months, surgery in the knee within the past 6 months, intra-articular injection of corticosteroids in any joint within 3 months before screening.

Patients were randomly assigned to receive either hyaluronic acid injections or knee lavage in the target joint. Patients completed the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index Likert (13) and patient global assessment (PGA) questionnaires (14).

*Study design*

We performed a single-centre, single blind, randomized, parallel group trial comparing KJL and HAIs. Patients in both groups could only employ paracetamol as an analgesic in case of need, up to 4 mg/day. The ethics committee of the hospital approved the study protocol and all participants signed an informed consent.

*Treatment administration*

All treatments were given by the first author.

Hyaluronic acid injections were performed in the target knee, once a week for three weeks, using Hylan G-F 20 (Synvisc, Genzyme Corporation, Ridgefield, New Jersey, USA). Arthrocentesis was performed before injection. Knee lavage was done by the 2 needle technique described in previous reports (15). The procedure started with cleansing of the skin around the knee with iodine solution, after which a local anaesthetic (1% lidocaine) is injected intra-articularly (20 ml) and throughout the capsula, subcutaneous tissue and skin around the lateral superopatellar portal (10 ml). The first 14 gauge needle is introduced into the lateral superopatellar portal and connected to the infusion line of the 0.9% saline solution. The knee cavity is filled with saline, which helps with the introduction of the second 14 gauge needle just above the first needle into medial superopatellar portal. The saline infusion line is then connected to the second portal (inflow) and saline is evacuated through the first portal (outflow). Adequate lavage is ensured by transient stopping of the outflow needle, mobilisation of the joint (10–208 of flexion and extension combined with valgus and varus stress, in order to open and irrigate the tibiofemoral compartments) and manual compression of the distended joint. A total of 2 Liter of 0.9% saline is injected into and evacuated from the knee joint in 5–10 minutes. The total duration of the procedure is about 60-90 minutes.

*Follow up*

Patients were followed for 12 months. All patients competed the follow up and when a patient Missed his/her follow up date, he / she was contacted by telephone to attend in the nearest date to their missed date. The primary outcome measures were the Western Ontario and McMaster Universities OA Index total pain score WOMAC (a Likert scale) and patient global assessment (PGA). Efficacy of treatment was evaluated according to the Osteoarthritis Research Society International (OARSI) criteria (16). All of the variables were measured at baseline, at 1 month, at 3 months, and at 6 months, at 9 months and at 12 months. All follow ups were done by the second author who was blind to the method of interventional treatment.

*Statistical analysis*

Statistical analysis was done using SPSS software package, version 15.0, 2006, Ecosoft corporation, USA. The statistical analysis of data consisted in a descriptive analysis with the calculation of absolute and relative frequencies for qualitative variables and means (standard deviation [SD]) for quantitative variables. The inferential analysis compared the baseline values using the Student t test for quantitative variables and the $x^2$ test (dichotomic variables) for qualitative variables. A covariance analysis was performed, contrasting the WOMAC score at different timepoints. Significance was assumed at $p<0.05$.

## RESULTS

A total of seventy patients completed the study. Thirty six patients randomly assigned to knee joint lavage (KJL) and thirty four patients randomly assigned to intra-articular hyaluronic acid injection (HAIs). All patients were indicated for TKR surgery but either unfit for surgery (32 patients; 15 in KJL group and 17 in HAI group) or refuse surgery (38 patients; 21 in KJL group and 17 in HAI group). Of the 70 patients included in the study, 65% were women. Mean age was 57.3 years with a standard deviation (SD) of 3.9 for KJL group and 58.0 years with a standard deviation (SD) of 2.7 for HAIs group. The relatively younger mean age of patients in both groups may be due to that in our experience, younger patients with advanced OA usually accept interventional treatment more often than older patients. All patients complied with ACR criteria for knee OA. All patients had a radiologic stage IV accorfding with Kellgren-Lawrence classification. Table 1 reflects the clinical and demographic characteristics of patients included in each treatment group and baseline values are compared for each of the variables. There were no statistically significant, or clinically meaningful, differences between treatment groups in any baseline or demographic parameter.

At the end of the 1st month, there was a reduction in the WOMAC pain score of 80% and 40% in KJL and HAIs groups respectively. At the end of the 6th month, there was a reduction in the WOMAC pain score of 50% and 10% in KJL and HAIs groups respectively while, at the end of the 9th month, there was a reduction in the WOMAC pain score of 25% and 5% in each group respectively.

By comparing two treatment groups as regard reduction in WOMAC pain score, we found that there were significant difference between two groups at 1,6,9 months, but there was no significant difference between two groups at baseline or after 12 month (Table 2).

Efficacy of treatment was also evaluated by by Patient Global Assessment after 1 month then after 6, 9, and 12 months, we noticed the superiority of HAIs in improving function as there is no patients

**Table 1.** *Clinical and demographic characteristics and baseline values of patients in each treatment group.*

| | Group 1 (KJL)(N=36) | Group 2 (HAIs)(N=34) | t | P |
|---|---|---|---|---|
| Sex | Female: 25 (61.9%)<br>Male: 11 (30.6%) | Female: 21 (61.8%)<br>Male: 13 (38.2%) | 0.46* | 0.49 |
| Age,years (SD) | 57.36(3.9) | 58.0(2.7) | -0.91 | 0.37 |
| BMI (SD) | 31.6(2.9) | 31.9(2.7) | -0.45 | 0.66 |
| Disease duration years (SD) | 9.4 (3.1) | 8.4 (2.3) | 1.1 | 0.27 |
| Co morbidity: | | | | |
| No | 13 36.0% | 14 41.2% | 6.42 | 0.38 |
| Hypertension | 8 22.2% | 5 14.7% | | |
| Diabetis mellitus | 7 19.4% | 6 17.6% | | |
| Hypothyroidism | 1 2.8% | 5 14.7% | | |
| Gastritis | 4 11.1% | 4 11.4% | | |
| Combined | 3 8.4% | | | |

** significant difference using $x^2$ test.*

**Table 2.** *Western Ontario and McMaster University (WOMAC) Osteoarthritis Index (pain score) at each time point in the treatment groups.*

| | Group 1(KJL) | Group2 (HAIs) | T | P |
|---|---|---|---|---|
| **Month 0** | 17.4±1.7 | 17.1 ± 1.3 | 0.99 | 0.33 |
| **Month 1** | 9.8±3.8 | 14.2± 2.8 | -5.45 | 0.00* |
| **Month 6** | 13.2± 3.2 | 15.9± 1.8 | -4.37 | 0.00* |
| **Month 9** | 15.7 ± 2.5 | 17.2± 1.48 | -2.9 | 0.01* |
| **Month 12** | 18.1 ±1.67 | 17.6± 1.17 | 1.18 | 0.24 |

** significant difference measured through student t test.*

feeling worsen of condition with HAIs after 1, 6, 9 months while few number of patients getting worse after KJL, one patient after 1 month, 3 after 6 months and 4 after 9 months (Table 3).

Table 4 reflects the proportion of patients who presented improvement at different time-points during follow-up (1 month, 6 and 9 months) according to the OARSI criteria. Improvement in OA symptoms was observed during the first month and 6, 9 months in KJL group more than HAIs group and there were significant differences between the two groups.

## DISCUSSION

This study demonstrates that knee joint lavage is safe and effective in providing statistically

**Table 3.** *Results of Patient Global Assessment at each time point in the treatment groups.*

| | | No improvement | Worse | Good | Very Good | Better |
|---|---|---|---|---|---|---|
| **Month 1** | KJL n (%) | 4 (11%) | 1 (2.8%) | 12 (33.3%) | 9 (25%) | 10 (27.8%) |
| | HAIs n (%) | 18 (52.9%) | - | 6 (17.6%) | - | 10 (29.4% |
| **Month 6** | KJL n (%) | 12 (33.3%) | 3 (8.3%) | 10 (27.8%) | 2 (5.6%) | 9 (25%) |
| | HAIs n (%) | 30 (88.2%) | - | - | - | 4 (11.8%) |
| **Month 9** | KJL n (%) | 22 (61.1%) | 4 (11%) | 9 (25%) | - | 1 (2.8%) |
| | HAIs n (%) | 32 (94.1%) | - | - | - | 2 (5.9%) |
| **Month 12** | KJL n (%) | 31 (86.1%) | 5 (13.9%) | - | - | - |
| | HAIs n (%) | 32 (94.1%) | 2 (5.9%) | - | - | - |

**Table 4.** *Proportion of patients that showed improvement according to the International Society for Osteoarthritis Research.*

| | KJL group | HAIs group | P |
|---|---|---|---|
| 1 month. n (%) | 32 (88.9%) | 17 (50%) | 0.026 |
| 6 months. n (%) | 21 (58.3%) | 4 (11.8%) | 0.016 |
| 9 months. n (%) | 10 (27.7%) | 2 (5.9%) | 0.018 |

* *Statistical significance determined by* $x^2$ *test.*

significant, clinically relevant pain relief, according to the OARSI criteria, as well as measured by WOMAC A (walking pain) over 36 weeks (9 months), with a modest difference compared with intra-articular injection of hyaluronic acid. Pain while walking is particularly medically relevant for the assessment of symptomatic relief and has been selected as the primary efficacy measure in other studies (17-19). As can be proven by the obtained results there were no significant differences between KJL and HAIs treatment at the end of the study period, which has important repercussions because this can help to better limit the indications for JL treatment. Several studies have been performed to evaluate the therapeutic efficacy of JL and there has been great differences regarding their conclusions, probably due to methodological differences and also to the ethical and technical difficulties that "sham" interventions and patient blinding imply, which in many cases is impossible (20). Our results were consistent with Ike et al. (21) who performed a randomized, single-blind study comparing medical treatment and JL and proved that the latter was significantly beneficial for the pain produced by OA compared to the benefits found in patients who only received medical treatment. The possibility that the benefits of JL are due to a placebo effect induced by puncturing the knee cannot be excluded. In contrast

to our results Dawes et al (22) were incapable of showing any significant benefit of JL over intra-articular injection (IA) of saline and concluded that JL was not indicated in the management of knee OA. The size of the sample (20 patients) in this study may preclude a valid statistical analysis. It is important to point out the study published by Moseley et al (23) in which patients with knee OA were randomly assigned to one of 3 treatment groups: one in which only an arthroscopic lavage was performed; another in which debridement was performed after arthroscopic lavage; and the third one that simulated an arthroscopic lavage and served as placebo. The conclusion reached was that the response seen in the arthroscopic lavage as well as in debridement was not superior to placebo. The difference between our results and this study may be due to the difference efficacy of the procedure in each trial, only in our study were enrolled patients with advanced OA (KL score 4). However, Moseley study (23) can have a selection bias because it was performed in male subjects who refused to participate in the study in 44% of cases, because it was explained to them that they had a one in 3 chance of actually undergoing the procedure. In addition, this data is not applicable to the general population because most patients with OA are women. The results of our study concluded that KJL had significant improvement of pain but not joint function. Philippe Ravaud et al (24) performed a randomized trial with a relatively wide sample of patients, evaluating the efficacy of JL alone and JL associated to the use of IA steroids, using IA placebo as control group. Their study concluded that when compared to placebo, both procedures had significant improvements of pain but not joint function which agree with the present study.

## CONCLUSION

This study demonstrated that, in patients with advanced knee osteoarthritis, knee joint lavage is safe and effective in providing statistically significant, clinically relevant pain relief over 36 weeks, with significant difference compared with intra-articular hyaluronic acid injection. In addition, JL is a much cheaper therapeutic option than other medical treatment, because a single intervention leads to patient improvement than continuous treatment with another medication and much less side effects. It is necessary to point out that JL is a minimally invasive technique that can be performed on an outpatient basis and is widely accepted by the patient especially when other options for treatment are contraindicated. However, we recommended further studies that confirm these results and providing other resources to patients with advanced knee OA that may improve their quality of life.

Author contribution: The first author put the design of the study, did the maneuver of knee lavage and intra-articular hyaluronan, wrote abstract of paper and approved the final version to be submitted. The second author collected and examined the patients before treatment administration, wrote the main text of the paper including references, analyzed the data and approved the final version to be submitted.

Acknowledgements: The authors would like to thank Dr. Samar Amer Lecturer of Community Medicine who help us doing tests of statistics and planning for tables. Also, thank Dr. Enas Ibrahim residence of Rheumatology department who help us preparing patients before intra-articular treatment administration. No funding sources, and no funding source in publication.

Conflict of interest: No Conflict of interest

## REFERENCES

1. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. Clin Orthop Relat Res 2004; 427(Suppl):S6–15.
2. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001; 60:91-7.
3. Fam H, Bryant JT, Kontopoulou M. Rheological properties of synovial fluids. Biorheology 2007; 44:59–74.
4. Almond A. Hyaluronan. Cell Mol Life Sci 2007; 64:1591–96.
5. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006; 19(2):CD005321.

6. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012; 64(4):465-74.
7. Blackburn PM, Kramer J, Marcelis S . Arthroscopic evaluation of knee articular cartilage: a comparison with plain radiographs and magnetic resonance imaging. J Rheumatol 1994; 21:675– 679.
8. Frías G, Caracuel MA, Escudero A, Rumbao J, Pérez-Gujo V, Castro MC, et al. Assessment of the efficacy of joint lavage versus joint lavage plus corticoids in patients with osteoarthritis of the knee. Curr Med Res Opin 2004; 20(6):861–7.
9. Gibson JNA, White MC, Chapman VM, Strachan RK. Arthroscopic lavage and debridement for osteoarthritis of the knee. J Bone Jt Surg Ser B 1992; 74B:534-7.
10. Reichenbach S, Rutjes AW, Nüesch E, Trelle S, Jüni P. Joint lavage for osteoarthritis of the knee. Cochrane Database Syst Rev. 2010 May 12;(5).
11. Altman R, Asch E, Bloch D. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986; 29:1039–49.
12. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. Ann Rheum Dis 1957; 16:494–501.
13. Bellamy N, Buchanan WW, Goldsmith CH. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15:1833–40.
14. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005; 23(39):S14-8.
15. Ayral X. Arthroscopy and joint lavage. Best Practice & Research Clinical Rheumatology 2005; 19(3): 401–15.
16. Pham T,Van der Heijde D, Altman D,Anderson J,Bellamy N ,Hochberg M, etal. OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis and Cartilage 2004; 12:389–99.
17. Caborn D, Rush J, Lanzer W. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. J Rheumatol 2004; 31:333–43.
18. Waddell DD, Cefalu CA, Bricker DC. An open-label study of a second course of hylan G-F 20 for the treatment of pain associated with knee osteoarthritis. Curr Med Res Opin 2003; 19:499–507.
19. Altman R, Moskowitz R. The Hyalgan study group. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. J Rheumatol 1998; 25:2203–12. Extended report 118.
20. Frías G, Pilar F, Muñoz-Gomariz E, Caracuel M, Escudero A, Castro M, etal. Assessing the efficacy of non-arthroscopic joint lavage in patients with osteoarthritis of the knee. Reumatol Clin 2009; 5(5):189-193.
21. Ike RW, Arnold WJ, Rothschild EW, Shaw HL, Tidal Irrigation Cooperating Group. Tidal irrigation versus conservative medical management in patients with osteoarthritis of the knee. A prospective randomized study. J Rheumatol 1992; 19:772–9.
22. Dawes PT, Kirlew C, Haslock I. Saline washout for knee osteoarthritis: Results of a controlled study. Clin Rheumatol 1987; 6:61–3.
23. Moseley JB, O'Malley K, Petersen NJ. A controlled trial of arthroscopy surgery for osteoarthritis of the knee. N Engl J Med 2002; 347:81–8.
24. Ravaud P, Moulinier L, Giraudeau B. Effect of joint lavage and steroid injection in patients with osteoarthritis of the knee. Arthritis Rheum 1999; 42:475–82.

# EFFICACY AND SAFETY EVALUATION OF COLLAGEN INJECTION GUNA MDS IN KNEE OSTEOARTHITIS: A CASE SERIES OF 30 PATIENTS

V. RESHKOVA[1], R. RASHKOV[1] AND R. NESTOROVA[2]

*[1]Clinic of Rheumatology, Sofia, Bulgaria; [2] Medical Center "St. Irina, Sofia, Bulgaria*

**Collagen is the most abundant protein (structural protein-tissue; molecular weight 300 KDa) in mammalians' organism accounting for about 5-6% of an adult's body weight. In this case series we have evaluate the efficacy and safety of intra-articular injections of GUNA MD-KNEE + GUNA MD-MUSCLE in 30 patients (12 Male, 18 Women) affected by Radiological Knee Osteoarthritis (KL grade 2 or 3). 10 intra-articular injection with GUNA MD-KNEE + GUNA MD-MUSCLE were performed. Patients were evaluated at baseline and then at 8 and 12 weeks after treatment in term of VAS pain at rest and during movement, Lequesne index and patient and physician satisfaction. Intra-articular injection of GUNA-MDs show a significant improvement in pain at rest, pain during movement and functional activity in patients with knee oasteoarthrtis. GUNA-MDs show to be safe, no side effects were reported in all patients.**

Collagen is the most abundant protein in human body. ¼ of the whole protein mass of higher mammals is composed by collagen: bone and tendons, joint capsules and muscles, ligaments and fascia, teeth and serous membranes, skin and extracellular matrix. (1) One of the most frequent reasons of local joint pain is the slackening of intra-articular (ligaments and articular cartilage) and extra-articular structures (ligaments, joint capsule, tendons, muscles) causing joint hypermobility. This mobility leads to further and early consumption of these systems on one hand, on the other, promote progressive degeneration of cartilage. (2) A special characteristic of Collagen Medical Devices, which contain collagen and ancillary ingredients, is that they may offer an innovative approach to the treatment of painful diseases affecting the musculoskeletal system. The ancillary ingredients of natural origin are conjugated with collagen in order to allow a better and more targeted positioning of Collagen in certain areas. These collagen products may be used by periarticular, intra-articular, intramuscular and intradermal injections. Collagen provides a support, which may have a positive impact on stabilizing the function of joint avoiding hypermobility and ameliorating movement and pain. It is expected that intra-articular administration of Collagen Medical Devices could have a structural function: strengthen and protect the structure of cartilage and joint capsules. It is supposed to provide mechanical support to the affected areas. (3) Strengthen these structures, GUNA MDs might achieve regenerative and analgesic effect. (4) The purpose of this study is to confirm these hypothesis by evaluating the relief of localized pain or pain in movement.

## MATERIALS AND METHODS

30 outpatients (12 male and 18 female) with age between 55 and 70 years, affected by knee osteoarthritis [X-ray stage 2 or 3, according to Kellgren-Lawrence Classification (4)] were treated. The main exclusion criteria

*Key Wards: knee osteoarthritis, collagen intra-articular injection.*

*Corresponding author:*
Valentina Reshkova, PhD
Clinic of Rheumatology
Medical University of Sofia
13 Urvich Str.
1612 Sofia, Bulgaria
E-mail address: v_reshkova@abv.bg



2038-4106 (2013)

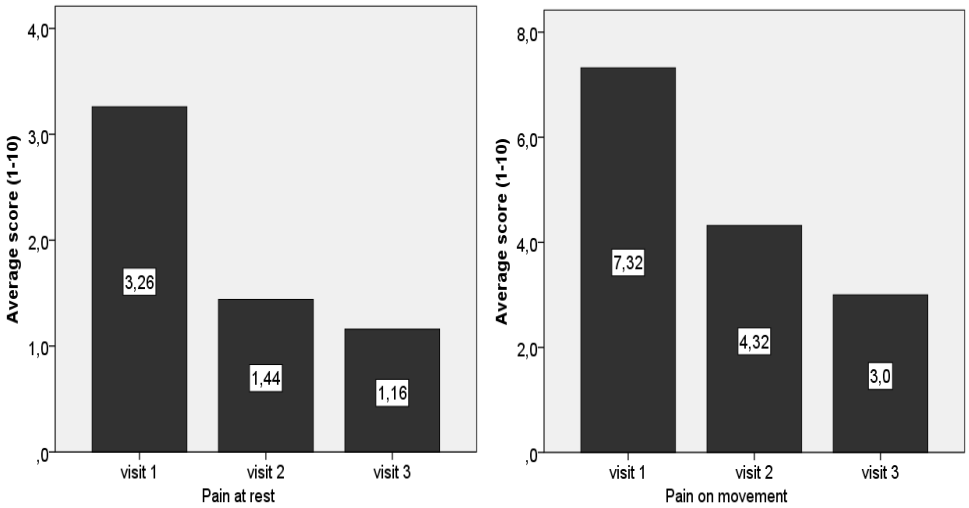



**Fig.1.** *Left size: Pain at rest, F (2,48) 35.871, p=0.000. Right size: Pain on movement F (2,48) 69.630, p=0.000*

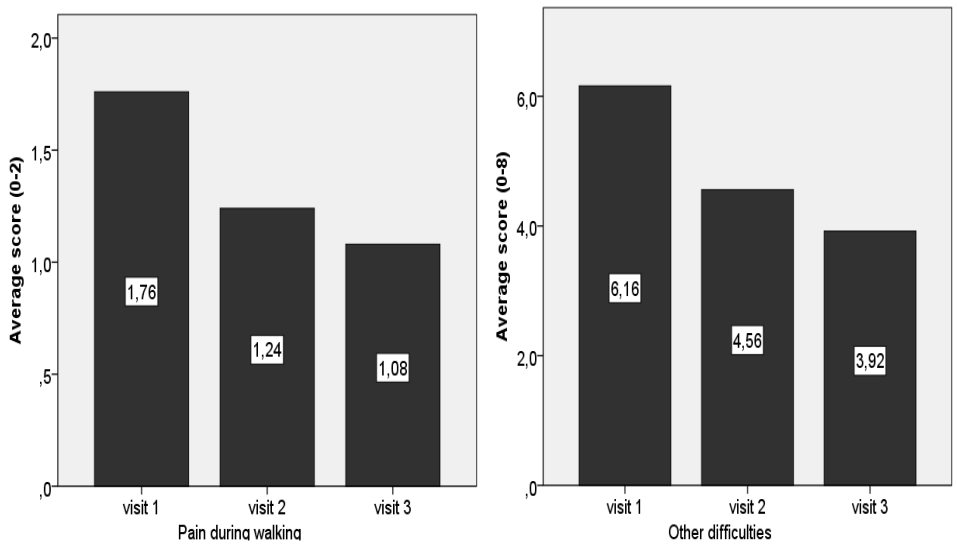



**Fig.2.** *Left size: Pain during walking F (2,48) 19.750, p=0.000. Right size: Other difficultes*

were: inflammatory diseases, gout, and malignancy. Intra-articular knee injections with GUNA MD-Knee (10 amp.) + GUNA MD-Muscle (10 amp.) were performed: 1 injections twice a week for 2 weeks and 1 injection weekly for 6 weeks (course of treatment: 8 weeks). Patients were evaluated before treatment (Visit 1) and at 8 (Visit 2, at the end of treatment) and 12 weeks (Visit 3, 30 days after treatment) in term of pain at rest (VAS and 5-point verbal scale) and during movement, algo-functional index of Lequesne, patient and physician efficacy assessment. (5)

## RESULTS

A significant reduction of VAS pain at rest was observed at Visit 2 and Visit 3 (Fig.1). Approximately 2-fold decreased of the average score for pain during movement was observed at Visit 3, if compared to baseline (Fig. 1). Pain at rest and during movement showed statistically significant decrease by application of

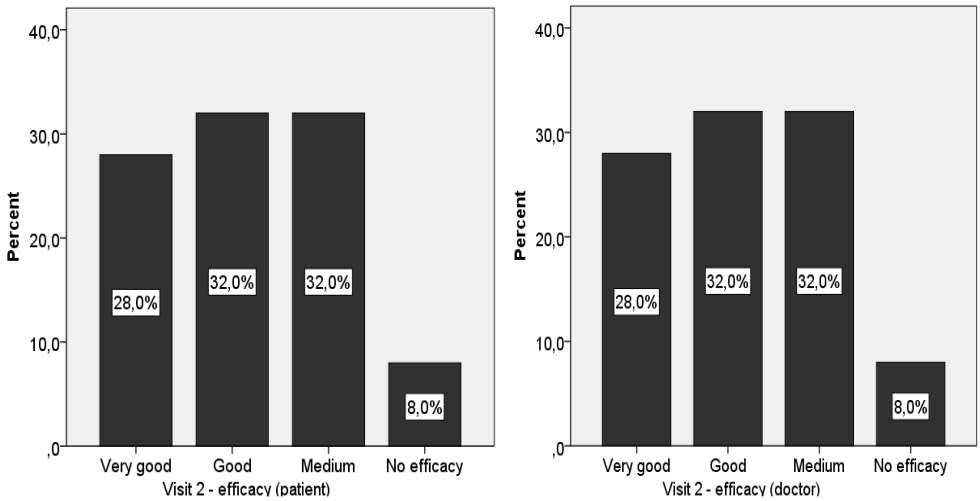



**Fig.3.** *Efficacy assessment by patient and by physician*

GUNA MDs. The reduction continued 30 days after the end of treatment. In terms of average score for pain during walking, we observed a reduction of 40% at Visit 3, if compared with baseline (Fig. 2). At Visit 3, the average score for other difficulties (Lequesne Index) decreased more than 2.5 times if compared with baseline (Fig. 2). At Visit 2, the assessment of patient satisfaction showed that 28% of patients felt very good satisfied, 32% good, 32% medium and only 8% did not consider the treatment effective (Fig. 3). On the third visit the percentages are even higher. The assessment of treatment efficacy at 8 and 12 weeks by patient ant by physician were similar (Fig. 3). No side effects were reported during the follow up.

## DISCUSSION

Current intra-articular treatment options for knee osteoarthritis (OA) include hyaluronic acid and corticosteroids. Viscosupplementation is a well-established treatment option in knee OA, and is included in the professional guidelines for treatment of the disease in this joint (6, 7). There are substantial data that exogenous HA may improve pain and function by non-mechanical, biologically based mechanisms within the synovial and articular environment (8). Hyaluronic acid (HA) is comparable in efficacy with intra-articular corticosteroids, which have a faster onset of action but a shorter duration (9, 10). The conclusions of a Cochrane meta-analysis seem to be in favor of higher efficacy of HA, both on pain and function, than any other form of systemic intervention or intra-articular corticosteroids (11, 12). Despite its good efficacy and safety Viscosupplementation is a not cheap treatment that limits its use considering also the lack of its reimbursement by the majority of countries.Also intra-articular placebo (saline solution) seems to be able to decrease pain in knee OA. (13, 14) Zhang et al., reported in a recent meta-analysis that IA placebo had effects above the average value of 0.51 ES (15). Even though placebo in OA appeared to be effective only for all patient-related subjective outcomes such as pain, stiffness and self-reported function, while not for structural modification outcomes. The results of this study seem to demonstrate that intra-articular administration of GUNA-MDs could be a safe and effective treatment in pain relief for patients affected by knee OA at stage 2 or 3, according to Kellgren-Lawrence Classification. This collagen product might be an adjunctive option to the actual available armamentarium in the IA management of knee OA.

The limitation of this study is the absence of comparative group; it would also be appropriate to carry out a comparative study firstly with placebo and then with the other products commonly used for IA injections (Hyaluronates, steroids, platelets rich plasma). It is also necessary to explain the

mechanism of action of collagen's intra-articular administration and whether it may have a structural beneficial effect. Further randomized controlled trials, with a larger sample size and longer-term follow-up, will be needed to demonstrate the real role played by GUNA-MDs injections in pain relief during knee OA.

## CONCLUSIONS

This case series suggest that intra-articular injection of GUNA-MDs in knee OA significantly affects pain at rest, pain during movement and functional activity of patients. Due to its safety and efficacy GUNA-MDs collagen products may be considered an interesting and promising option for the IA treatment of patients affected by mild knee OA. However, further studies will be needed to confirm these data.

## REFERENCES


1. Milani L. Prefazione a manuale di medicina biologica. Regolazione di base a matrice extracellulare. 3 Edizione. Guna ed., Milano; 2009.
2. Milani L. A new and refined injectable treatment for musculoskeletal disorders –bioscafold properties of collagen and its clinical use. Physiological Regulating Medicine 1;2010.
3. Urgelles-Lorie L A. Nociceptive pain- a new classification for pain control. Physiological regulating medicine 2008; 1.
4. Kellgren JH, Lawrence JS. Radiological Assessment of Osteo-Arthrosis. Ann Rheum Dis 1957; 16(4): 494–502.
5. Lequesne M, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee: Variation value in comparison with other assessment. Scand J Rheumatol 1987; suppl 65: 85-89.
6. Recommendations forthe medical management of osteoarthritis ofthe hip and knee: 2000 update. AmericanCollege of Rheumatology Subcommittee on OsteoartArthritis Guidelines. Arthritis Rheum. 2000; 43:1905–1915.
7. Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis: Report of a task force of the Standing Committee for International Clinical Studies including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2000;59:936–944.
8. Ghosh P, Guidolin D. Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects molecular weight dependent? Semin Arthritis Rheum 2002; 32(1):10–37.
9. Caborn D, Rush JL, Lanzer W, et al. A randomized single blind comparison of the efficacy and tolerability of hylan GF-20 and triancinolone hexacetonide in patients with osteoarthritis of the knee. J Rheumatol 2004; 31:333–343.
10. Leopold SS, Redd BB, Warme WJ, Wehrle PA, Pettis PD, Shott S. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. A prospective, randomized trial. J Bone Joint Surg Am 2003;85A:1197–1203.
11. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006;19:CD005321.
12. Campbell J, Bellamy N, Gee T. Differences between systematic reviews/meta-analyses of hyaluronic acid/hyaluronan/hylan in osteoarthritis of the knee. Osteoarthritis Cartilage 2007; 15: 1424–1436.
13. Karlsson J, Sjögren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford) 2002; 41:1240–1248.
14. Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006;26:325–330.
15. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 2008; 67:1716–1723.