



CLINICAL

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## SUMMARY

This article presents two studies, whose aim was to evaluate the efficacy of collagen injections of GUNA MDs regarding pain and functional activity of the shoulder in patients with clinically proved shoulder peri-arthritis by Musculoskeletal ultrasound (MSUS) assessment.

We randomized 20 patients with peri-arthritis and subacromial subdeltoid (SASD) bursitis in Study 1, and 22 patients with peri-arthritis and rotator cuff (RC) partial thickness tears (PTTs) in Study 2.

Combinations of GUNA MDs were applied in the subacromial space in the total course of treatment (8 weeks), respectively GUNA MD-Shoulder + GUNA MD-Matrix in Study 1 and GUNA MD-Shoulder + GUNA MD-Muscle in Study 2.

Clinical assessment included demographic and clinical data, a Visual Analog Scale (VAS) for pain (0-100), Shoulder Function Assessment (SFA) scale (0-70) and MSUS evaluation of the shoulder. Appraisal of the efficacy according to the patient and the physician were performed.

Results of both studies showed significant efficacy on pain and improvement of SFA index. 73 to 80% of all patients had a very good and good assessment of the efficacy, which coincided with the opinion of the physician in both trials.

We proved by MSUS evaluation reduction or absence of bursitis in 80% of patients in Study 1 and complete recovery or improved structure of the RC in 77% of patients in Study 2.

No adverse events were registered.

In conclusion, collagen injections of GUNA MDs significantly reduced pain, led to a lack or decrease of bursitis volume, repaired or improved RC tissues and increased functional activity of the shoulder, thereby increasing the quality of life.

## KEY WORDS

**COLLAGEN INJECTIONS GUNA MDs, SHOULDER PERI-ARTHRTIS, SUBACROMIAL SUBDELTOID BURISITIS, PARTIAL THICKNESS TEARS, ULTRASONOGRAPHY**

# BULGARIAN EXPERIENCE WITH INJECTABLE COLLAGEN GUNA MEDICAL DEVICES IN SHOULDER PERIARTHRTIS

## INTRODUCTION

About 20% of the world population have symptoms of pain and limited mobility of the shoulder (1). Shoulder pain correlates with age. Its frequency is between 6 and 11% up to 50 years of age and then increases more than twice, and ranges between 16 and 25% (2). RC is composed of collagen, proteoglycans (PG), glycosaminoglycans (GAG), water and cells. Light microscopy shows that the primary damage is the decreasing of collagen type I, in which fibers become thinner than normal. The extracellular matrix remodeling occurs by the impact of metalloproteinase enzymes which preceded clinical signs. Therefore, the only effective treatment would be a structural modifying treatment (3).

During the last years doctors have been

looking for medical products for local injections into the joints different from the traditional medicines, such as corticosteroids. Medical products that combine positive effects on joints with no side effects.

– Treatment with injectable collagen GUNA MDs presents a concept based on the synergistic effect of non conventional and conventional medicine. The purpose of the local administration of the collagen is essentially structural to provide mechanical support, replace, strengthen, structure and protect the zone where is injected. Due to its low dose (300 mcg), collagen acts signally, changing extracellular matrix and leading to the activation of cellular functions.

**GUNA MD-Shoulder** has analgesic effect on joint pain, reduces degenerative changes in the RC of the shoulder through the enhancement and strength-

ening of the collagen matrix in tendons, muscles, ligaments and joint capsule, which reduces pain. **GUNA MD-Matrix** has an antioxidant activity, improves the functions and regenerates the extracellular matrix, activating the cellular functions.

This results accelerate the healing process through faster resolution (drain effect) of swelling. **GUNA MD-Muscle** improves muscle tone by inhibiting the uptake of calcium and the enzyme phosphodiesterase (5,6).

Musculoskeletal ultrasonography (**MSUS**) is an approved imaging technique for diagnosis of RC pathology of the shoulder and monitoring of therapy (7-18). Sonographic assessment was performed according to OMERACT Group recommendations. All patients

were examined with commercial, real-time equipment Mindray M5 (China) using a 7.5-10 MHz linear phased array transducer. A standard scanning protocol including multiplanar, dynamic and bilateral evaluation was followed in order to avoid missing the assessment of one or more anatomic structures of the shoulder. Transverse and longitudinal planes from the Biceps tendon (**BT**), Subscapularis tendon (**SSC**), Supraspinatus tendon (**SSP**), **SASD bursa**, Infraspinatus tendon (**ISP**) and the Acromioclavicular joint (**ACJ**) were scanned.

The BT and ACJ were scanned in neutral position of the shoulder with flexed elbow at 90°.

The SSC tendon was assessed in full external rotation of the shoulder. Each patient's arm was put into full internal rotation with the hand placed posterior to

the spine for the assessment of SSP tendon. The ISP tendon was assessed in shoulder adduction with the hand on the opposite shoulder. A dynamic view of the SSP tendon was obtained by moving the patient's arm from a neutral position to a 90° abduction in order to detect encroachment of the acromion into the RC. The SASD bursa lies between the RC tendons and the Deltoid muscle, overlying the Bicipital groove and it is often invisible due to the small amount of fluid within it. Bursa can be visible as a thin hypo/anechoic band with thickness up to 2 mm under normal conditions. Bursitis consists in abnormal hypo/anechoic intrabursal material that is displaceable and compressible.

RC tendons are hyperechoic due to their fibrillar echotexture. PTT is discontinuity of fibres without signs of retraction. It can be visible as an anechoic focus inside the tendon. The tendon surface retains with normal convexity. PTTs could be classified as Bursal sided, Articular sided and Intra-substance tears according to their location within the tendon (10-17).

To objectify the MSUS evaluation, two trained and experienced sonographers with at least 5 years experience in MSUS scanned together each patient and reached consensus on the US findings.

Clinical assessment included demographic and clinical data, a Visual Analog Scale (VAS) for pain (0-100) and Shoulder Function Assessment (**SFA**) scale (0-70). Evaluation of the efficacy according to the patient and the physician were performed (19,20). The SFA test has 2 items concerning pain on motion and at rest; 4 items for shoulder function in daily activities; and 3 objective Range of Motion (ROM) measures. The SFA consists of two Visual Analogue Scales (pain at rest and during movement), four multiple choice questions about daily activities (dressing, combing hair, washing opposite axilla, and using the toilet), and three measures for ROM (total active abduction and two combined movements asking the patient to place the hand on the head with the el-

**TAB. 1**  
**Study 1**  
**- Inclusion and exclusion criteria.**

Inclusion criteria	Exclusion criteria
1 Age 18-80 years	1 Joint inflammatory and rheumatic auto-immune disease, infections
2 Clinical diagnosis: Shoulder periarthritis	2 Degenerative arthropathy, traumas, surgery in shoulder (incl. complete ruptures of the RC)
3 Duration of the symptoms up to <b>3 months</b>	3 Physiotherapy and topical corticosteroids application within a month before and during the monitoring
4 Pain by VAS over 25mm	4 Other diseases – diabetes mellitus, neurological diseases (incl. brachial plexitis, peripheral neuropathy)
5 <b>Bursitis of SASD bursa proven by MSUS</b>	5 Cancer, chemotherapy, radiotherapy

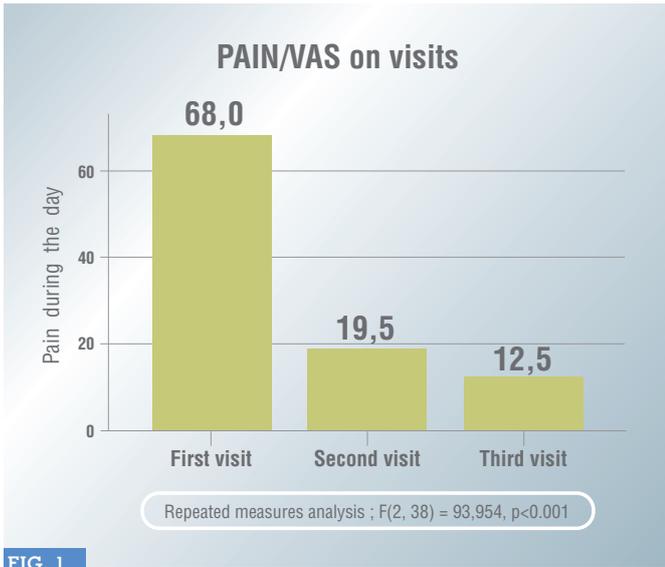


FIG. 1



FIG. 2

bow forward and backward). The overall score ranges from 0 (worst shoulder function) to 70 (best shoulder function).

### STUDY 1 – GUNA MDs EFFICACY IN SHOULDER PERIARTHROSIS WITH SUBACROMIAL SUBDELTOID (SASD) BURSITIS

The aim of this study was to evaluate the efficacy of Collagen injections of GUNA MDs regarding pain and functional activity of the shoulder in patients with periarthritis and bursitis of the SASD

Pain at rest	$F(2, 38) = 7,914, p = 0.001$
Pain during movement	$F(2, 38) = 74,078, p < 0.001$
Dressing	$F(2, 38) = 72,724, p < 0.001$
Combing hair	$F(2, 38) = 63,317, p < 0.001$
Washing opposite axilla	$F(2, 38) = 25,294, p < 0.001$
Using the toilet	$F(2, 38) = 14,256, p < 0.001$
Active abduction	$F(2, 38) = 64,373, p < 0.001$
Hand on the head with the elbow forward	$F(2, 38) = 33,496, p < 0.001$
Hand on the head with the elbow backward	$F(2, 38) = 53,451, p < 0.001$

TAB. 2

Results for each item in SFA.

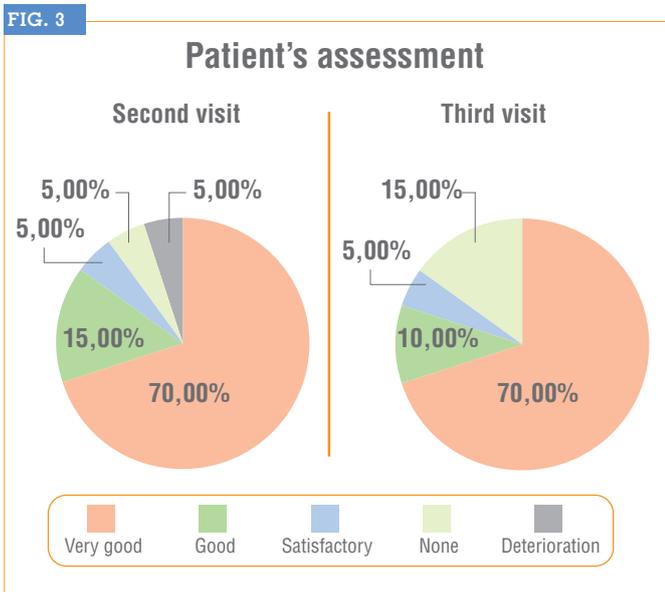


FIG. 3

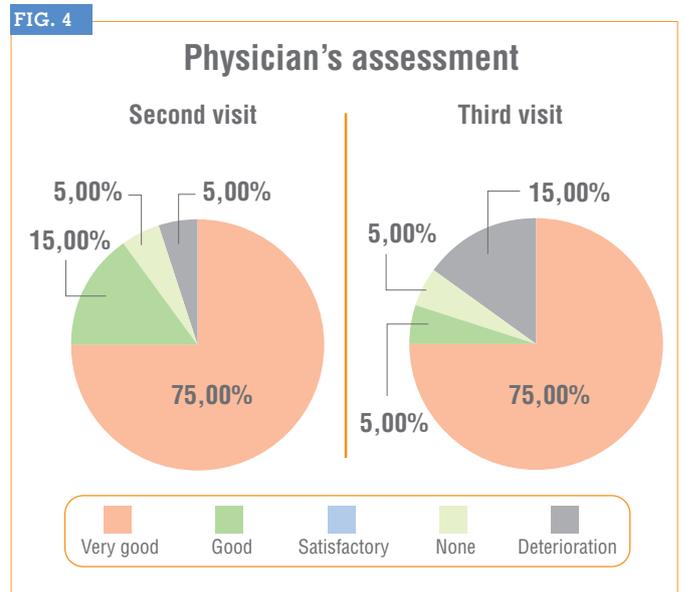


FIG. 4

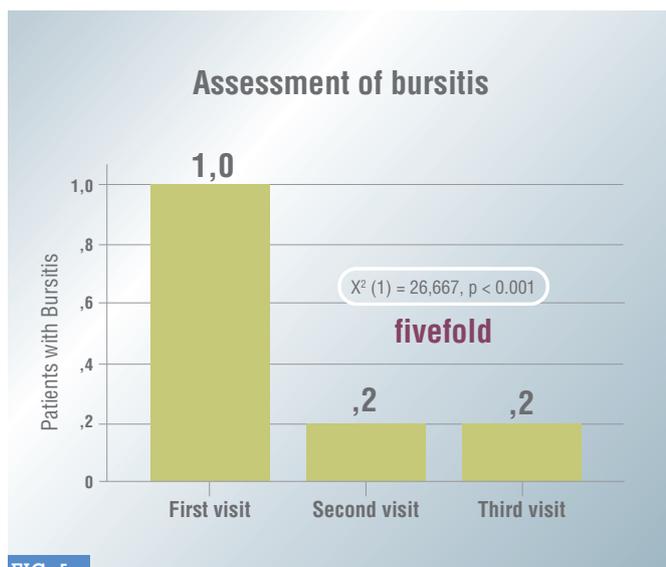


FIG. 5

bursa and duration of symptoms up to 3 months (21-24).

## MATERIALS AND METHODS

We enrolled **20 patients** with painful shoulder and proved by MSUS bursitis of the SASD bursa (TAB. 1).

At the baseline visit it was performed a standard X-Ray of the painful shoulder. Clinical assessment, VAS and SFA scale assessments (TAB. 2) were performed on the following visits: baseline (First visit), on 60<sup>th</sup> day (Second visit) and on 150<sup>th</sup> day (Third visit), as well as the evaluation of the efficacy according to the patient and the physician.

MSUS assessment was performed on all three visits (21-24).

– The combination of 1 vial of GUNA MD-Shoulder + 1 vial of GUNA MD-Matrix was applicated into the subacromial space of each patient, a total of 20 vials, 2 vials for each application, according to the scheme: first 2 weeks – 2 applications/weekly, followed by 6 weeks – 1 application/week in a general course of treatment (8 weeks) (21-24).

Collagen application technique: The applications were performed according to generally accepted rules.

The patient’s skin was sterilized with alcohol and Braunol. Access to the subacromial space was achieved with a lateral approach, inserting a 21-gauge (0.8X50 mm) needle under the anterolateral part of the acromion process, passing it through the Deltoid muscle, and directing it medially and slightly an-

terior to the SASD bursa, with care to avoid injection directly into the tendons of the RC (12, 24).

Statistical analysis:

For VAS and SFA assessment Repeated measures analysis was used. For assessment of Bursitis  $\chi^2$  analysis was used.

## RESULTS

**1.** VAS Pain during the day: on the second visit (60<sup>th</sup> day) the pain during the day reduced threefold and continued to reduce till the third visit (150<sup>th</sup> day) more than 5 times compared to the first visit (FIG. 1).

**2.** The index of SFA had a statistically significant improvement of all SFA criteria which correlated with increasing of the point number with 24.8 points. The improvement continued till the third visit too (FIG. 2).

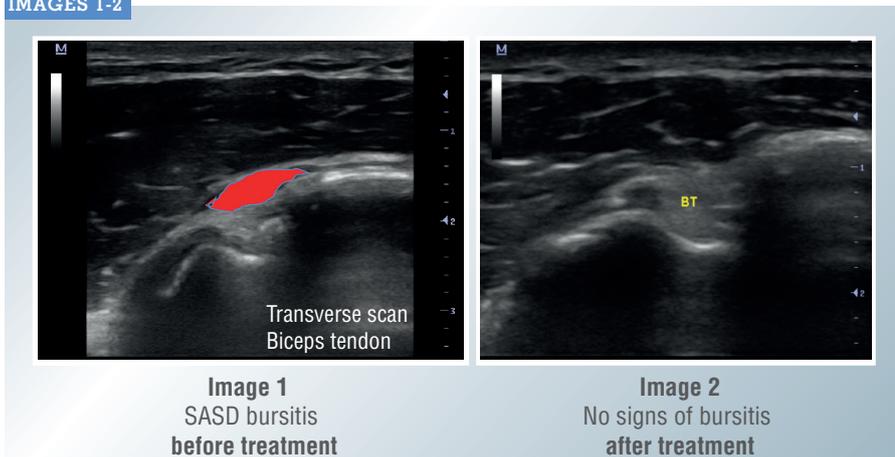
**3.** Patient Assessment: The scale had 5 levels of appraisal, from maximal (Very good) to minimal (Deterioration). Minimum **80%** of the patients gave a very good and good assessment of efficacy of Collagen Medical Devices (FIG. 3).

**4.** Physician’s Assessment: The scale was similar: Maximal evaluation (Very good) to minimal (Deterioration). Physicians gave very good and good evaluation of the efficacy of GUNA MDs treatment in at least **80%** of patients on the second and third visit (FIG. 4).

**5.** Bursitis: MSUS evaluation showed that **80%** of patients had reduction or lack of SASD bursitis on the second and third visit (FIG. 5).

We present sonographic images in transverse scan of BT showing SASD bursa before and after the treatment with GUNA MDs. **IMAGE 1** (baseline) shows the increasing quantity of fluid in the SASD bursa /hypoechoic distension of the bursa which is visible over the BT. At the second visit (after treatment) there is no sign of bursitis (**IMAGE 2**).

IMAGES 1-2



## STUDY 2 – GUNA MDs EFFICACY IN SHOULDER PERIARTHRITIS WITH PARTIAL THICKNESS OF THE ROTATOR CUFF TEARS OF THE SHOULDER

The aim of this study was to assess the effectiveness of the injectable collagen GUNA MDs regarding pain, functioning and recovery of periarticular tissues of the shoulder in patients with PTTs of the RC and duration of symptoms up to 7 days (25,26).

Based on cadaveric and imaging studies, the prevalence of PTTs ranges from 13% to 32%, in part related to its strong correlation to patient age. In one MRI study of asymptomatic individuals, the overall prevalence of PTTs was 20%. In patients under the age of 40, the prevalence was approximately 4%; whereas, in patients over the age of 60, the prevalence was 26% (27-28).

### MATERIALS AND METHODS

We enrolled **22 patients** with painful shoulder and PTTs of the RC proven by MSUS.

Standard X-Ray of the painful shoulder was made at the baseline visit.

Clinical assessment, VAS and SFA scale assessments were performed on the following visits: baseline (First visit), on 30-

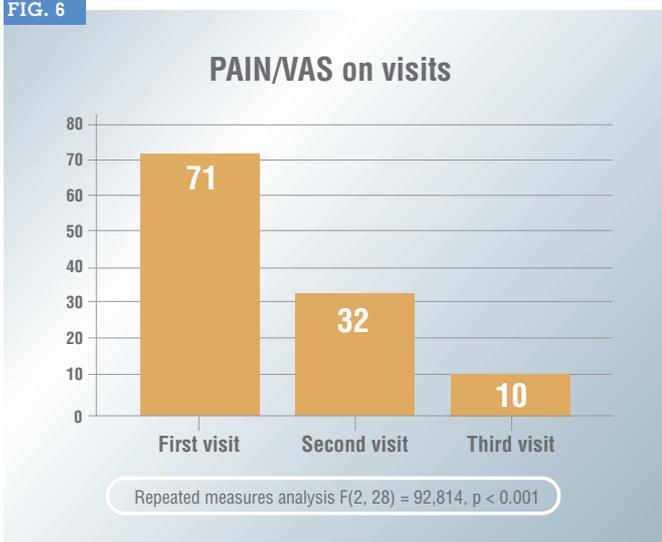
Inclusion criteria	Exclusion criteria
1 Age 18-80 years	1 Joint inflammatory and rheumatic auto-immune diseases, infections
2 Clinical diagnosis: Shoulder periartthritis	2 Degenerative arthropathy, traumas, shoulder surgery. Full thickness tears of the RC
3 Duration of the symptoms up to <b>7 days</b>	3 Physiotherapy and topical corticosteroids application within a month before and during the monitoring
4 Pain by VAS over 25mm	4 Other diseases – diabetes mellitus, neurological diseases (incl. brachial plexitis, peripheral neuropathy)
5 <b>PTTs of the RC proven by MSUS</b>	5 Cancer, chemotherapy, radiotherapy

**TAB. 3**  
**Study 2**  
– Inclusion and exclusion criteria.

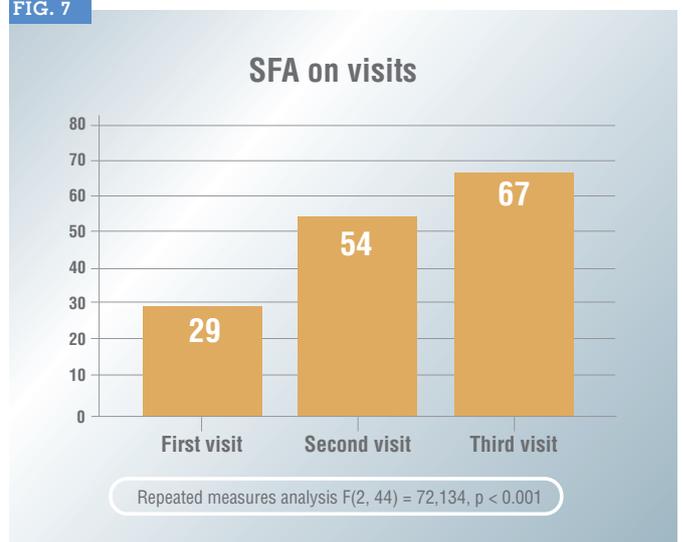
th day (Second visit) and on 60-th day (Third visit), as well as evaluation of the efficacy according to the patient and the

physician on 60-th day. MSUS assessment was performed on the baseline and on 60-th day (25,26).

**FIG. 6**



**FIG. 7**



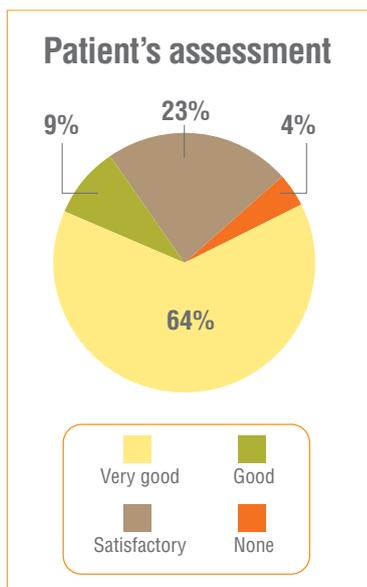


FIG. 8

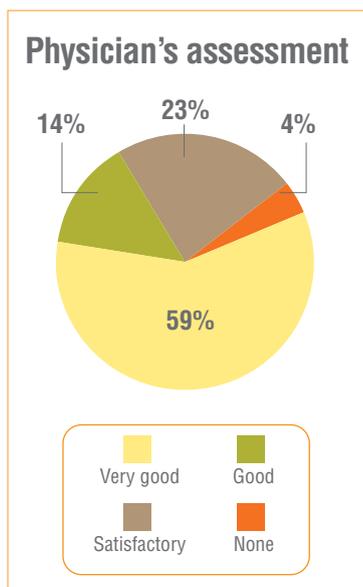


FIG. 9

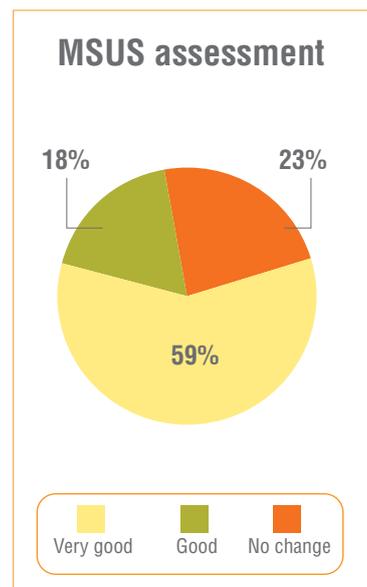


FIG. 10

– It was administered the combination of 1 vial **GUNA MD-Shoulder** + 1 vial **GUNA MD-Muscle** into the subacromial space of each patient, a total of 20 vials, 2 vials for each application, according to the scheme of Study 1, namely 2 applications weekly, for 2 weeks followed by 1 application weekly for 6 weeks (25,26).

Collagen application technique was identical to the one described above. Statistical analysis:

For VAS and SFA assessment Repeated measures analysis was used.

**RESULTS**

**1.** VAS for Pain was significantly reduced more than twofold on the second

visit and continued to reduce till the third visit, 7 times compared to the first visit (FIG. 6).

**2.** The SFA index had a statistically significant improvement of all criteria which correlated with an increasing of 25 points on the second visit. The improvement continued till the third visit with 38 points more compared to the first visit (FIG. 7).

**3.** Patient's and Physician's Assessments: **73%** of the patients gave a very good and good assessment of efficacy (FIG. 8), which coincided with the opinion of the Physician (FIG. 9).

**4.** MSUS evaluation: **77%** of patients

had a complete or improved structure of the RC at the third visit (FIG. 10).

We present sonographic images in transverse scan of SSP tendon before treatment showing PTT presented as anechoic band (Intra-substance lesion) on the background of tendinosis (IMAGE 3) and recovered tissue of the tendon after the treatment with GUNA MDs (IMAGE 4).

**CONCLUSIONS**

The GUNA MDs injections significantly affected pain, SASD bursitis, PTTs of the RC and functional activity of the shoulder. Efficacy assessment was high: **73%** to **80%** according to the patient and the same percentage according to the physician. **80%** of patients in the **First study** were without bursitis after treatment and they had full recovering of the RC on the second and third visit.

**77%** of patients with PTTs in the **Second study** had full recovery or significant sonographic improvement of the fibrillar echotexture of the RC tendons. All these data proved strengthening and restoring effect of GUNA MDs on collagen structures.

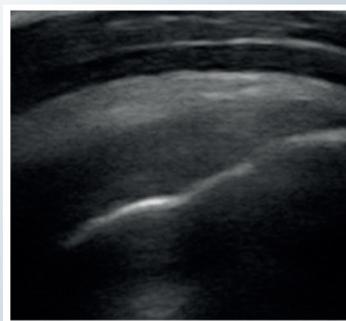
– Collagen Medical Devices GUNA in patients with Shoulder periarthrits and bursitis showed the following benefits:

**1.** High individual clinical response:

IMAGES 3-4



**Image 3**  
PTT of SSP tendon before treatment



**Image 4**  
No signs of PTT after treatment

pain (VAS), movement (Likert), Patient's assessment

2. High objective clinical response: Tests, SFA, Sonographic assessment, Physicians's evaluation

3. Successful treatment of SASD bursitis

4. Strengthening and restoring effect on collagen structures of the RC tendons, recovery in cases of incomplete RC lesions

5. Maintenance of the result beyond the last injection

6. Increasing patient quality of life

7. Total absence of adverse side effects.

### GUNA MDs UNDER ULTRASOUND CONTROL IN RC PATHOLOGIES OF THE SHOULDER

In the past few years there has been an exponential growth of number of studies published in this field reflecting the growing interest to implement these technique as part of the standard clinical practice (28).

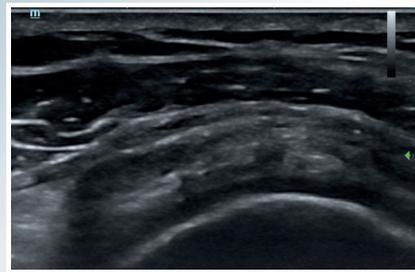
This method of drug application is safe and efficacy is higher than blind injections.

Application technique under US control is performed after skin disinfection according to generally accepted rules.

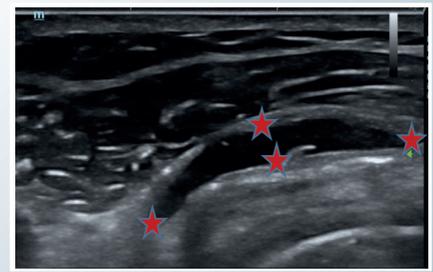
A 21-gauge (0.8X50 mm) needle penetration is "in plane" with angulation of 90°. After skin, subcutaneous tissue and Deltoid muscle penetration, the needle tip reaches the bursa. Real time injection can be rapidly carried out and drug deposition and dispersion can be checked immediately after finalizing the invasive procedure (28).

– We present some images of SSP tendinosis and GUNA MDs applications within the SASD bursa under US control:

**IMAGE 5** shows SSP tendinosis and not distended SASD bursa. Tendon is thickened and hypoechoic (tendon is swollen and its typical fibrillar echotexture is lost). In this case is better to apply GUNA MD injection within the SASD bursa and – this way – to avoid the risk of tendon lesion after the needle enter-



**Image 5**  
SSP tendonosis  
and not distended SASD bursa



**Image 6**  
SASD bursa is distended  
by GUNA MD-Shoulder

IMAGES 5-6



**Image 7**  
Hyperechoic profile of the needle (arrows)  
entering the bursa and filling it with MD-Shoulder  
and MD-Muscle

IMAGE 7

ing into the tendon tissue.

**IMAGE 6** shows distended SASD bursa by MDs Shoulder and Muscle. Note anechoic appearance of the MDs within the bursa.

In **IMAGE 7** is well visible the hyperechoic profile of the needle reaching the SASD bursa and injecting MD-Shoulder and MD-Muscle.

► In conclusion, the collagen injections of GUNA MDs are an innovative and effective approach with regenerative and analgesic effect in the treatment of Shoulder periarthritits with bursitis and/or PTTs.

Their easy application and total absence of side effects make them a modern device of choice in the physician's daily practice.

There is a new opportunity to apply GUNA MDs under US control which is a choice of the specialist. ■

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