International Orthopaedics
https://doi.org/10.1007/s00264-020-04870-w

ORIGINAL PAPER

Intra-articular gold induced cytokine (GOLDIC®) injection therapy in patients with osteoarthritis of knee joint: a clinical study

Ulrich Schneider[1] · Ashok Kumar[2] · William Murrell[3,4] · Agnes Ezekwesili[5] · Nagib A. Yurdi[3] · Nicola Maffulli[6,7]

Received: 13 June 2020 / Accepted: 3 November 2020

Abstract

Purpose To evaluate the safety and efficacy of a novel technique of preconditioning autologous blood with gold particles (GOLDIC®) and injection in patients with moderate to severe knee osteoarthritis (KOA).

Methods During this phase 2a, proof-of-concept (PoC) open label study, 83 consecutive patients that 64 patients met inclusion criteria (mean age: 64.8 years; 89 knees) with radiographically proven KOA, received four ultrasound guided intra-articular knee injections of GOLDIC® at three to six day intervals. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee injury and Osteoarthritis Outcome Score (KOOS) were evaluated at baseline, four weeks, three, six months, one, two and four years (T1–T6). The incidence of treatment related severe adverse events (SAEs) recorded. Intra-articular gelsolin level in patients with effusion was determined.

Results KOOS and WOMAC scores improved for the full duration of the study ($P < 0.05$), minimal clinically important difference (MCID) was observed at all time points in all KOOS subscores, with no reported SAEs. Intra-articular gelsolin level increased after treatment with reduction of effusion. No statistically significant evidence of an association between patient demographics and outcome were identified. Nine patients failed treatment, with 32 months mean time to failure and underwent total knee arthroplasty.

Conclusion PoC study of GOLDIC® as a novel device for conservative management of moderate to severe KOA was confirmed. GOLDIC® produces rapid and sustained improvements in all indices after treatment, with no SAEs.

Trial registration § 13 Abs.2b AMG Bavaria (Protokol Reg OBB 5-16) (Ref 53.2-2677.Ph_3-67-2)—Date 3/20/2010 retrospectively registered.

Keywords Stem cell therapy · Knee general · Goldic · Pain management · Platelet-rich plasma · Bone marrow aspirate concentrate

✉ William Murrell
doctormurrell@gmail.com

[1] iRegMed, Tegernsee, Germany

[2] My Doc Specialist Medical Centre DMCC, Fortune Executive Tower, JLT, Dubai, United Arab Emirates

[3] Abu Dhabi Knee and Sports Medicine, Healthpoint Hospital, Zayed Sports City, Abu Dhabi, United Arab Emirates

[4] Department of Orthopedic Surgery, Division of Surgery, William Beaumont Army Medical Center, Ft. Bliss, TX, USA

[5] Department of Nutrition, University of North Carolina, Chapel Hill, NC, USA

[6] Department of Musculoskeletal Disorders, University of Salerno School of Medicine and Dentistry, Salerno, Italy

[7] Barts and the London School of Medicine and Dentistry Centre for Sports and Exercise Medicine, Mile End Hospital, Queen Mary University of London, London, England, UK

Introduction

Osteoarthritis is one of the most common conditions of joints [1]. Greater numbers of people are developing symptomatic osteoarthritis of knee due to increased longevity [2]. Degenerative conditions pose treatment challenges not only for physicians but also for patients [3–5]. Patients with Kellgren-Lawrence (K-L) grades 2–3 knee osteoarthritis (KOA) can suffer due to pain and physical limitations for many decades [6]. Total knee replacement (TKR) is the last option for K-L grades 3–4 KOA [7]. TKRs are invasive, and can be associated with many direct complications and other medically related morbidities and in the rare instance, mortality [7]. Intra-articular (IA) injection therapy has generated increased interest [8]. IA hyaluronic acid (HA) and corticosteroids are commonly used, with short-term pain relief [9, 10].

Autologous blood–based products such as platelet rich plasma (PRP) and autologous conditioned serum (ACS), and stem cells are also utilized. However, they may not be effective long-term and in all K-L grades of KOA [11–15].

We developed an innovative technique of producing a conditioned serum rich in cytokines (Gold-IC) by utilizing specialized gold particles. Gold compounds (aurothiomalate) inhibit the production of nitric oxide (NO) from chondrocytes; Nitric oxide mediates the destructive effects of IL-1 and TNF-α which include reduced collagen and proteoglycan production, apoptosis of chondrocytes, and stimulation of matrix metalloproteases [16]. In vitro studies have shown that incubation with gold particles inhibit catabolic factors, increases anticatabolic and anabolic factors and also increases the level of gelsolin which is a key protein in cellular metabolism [17].

The exact mode of action of the GOLDIC® procedure is not well understood. In vitro studies have shown a significant increase in plasma gelsolin level in the autologous serum and increased gelsolin level in synovial fluid after every GOLDIC® injection. Both gelsolin and G-CSF have been shown to promote regeneration [18–21]. Gelsolin is an actin-binding protein and occurs in both cellular cytoskeleton and in the plasma [22]. The cytoskeleton is responsible for the viscoelasticity of cells. Gelsolin also regulates other important cell functions including cell motility, phagocytosis, apoptosis, and the activation of thrombocytes, and its plasma concentration is decreased in various tissue degenerative diseases. Experiments have shown decreased plasma gelsolin concentrations in animals with sepsis, and treatment with gelsolin had a positive effect on the survival rate in these animals [23]. Plasma gelsolin serves as a buffer to intercept inflammatory reactions of the body and was found to be decreased in rheumatoid arthritis [24]. Interestingly, the gelsolin level were found more reduced in the affected joints in comparison to plasma level.

The first GOLDIC® trial in horses showed significantly improved lameness [25]. The first human clinical trial investigated healing of tendoachilles, with significant follow-up clinical and MRI improvement. Compared to other blood-based biological methods, only the GOLDIC® procedure has been demonstrated upregulation of plasma gelsolin (pGSN) and granulocyte colony stimulation factor (G-CSF), both of which play an important role in tissue regeneration [26].

Encouraged by the results of these two GOLDIC® studies, we conducted this PoC open label trial to evaluate the safety and clinical effectiveness of GOLDIC® in patients with KOA.

Methods

Study design and treatment

This was a single-center phase 2a, PoC, open-label trial to assess the efficacy and safety of autologous intra-articular GOLDIC® therapy in patients with moderate to severe KOA. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidance for Good Clinical Practice. The clinical use and the study of autologous gold-induced serum (Goldic®) in KOA was approved by competent regional council in accordance with § 13 Abs.2b AMG Bavaria (Protokol Reg OBB 5-16) (Ref 53.2-2677.Ph_3-67-2), and all patients provided written informed consent in accordance with local requirements.

Treatment of 83 consecutive patients was investigated retrospectively from prospectively collected data. Of those who met the inclusion and exclusion criteria (Table 1) that yielded 64 patients (37 M and 27 F) and 89 knees enrolled during the period 2008–2015 at the Regenerative Medicine Centre Tegernsee,

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Study design	• Consecutive patients treated with intraarticular Goldic® injections. • Patients recruited • Minimum 4 year follow-up	• Patients surgically treated concomitantly with some other treatment platform or a part of another study. • Had knee surgery other than debridement. • Excluded surgical procedures included: ❖ Chondroplasty ❖ Marrow stimulation procedure ❖ Other cellular therapy ❖ Collagen implantation therapy ❖ Implanted simultaneously with scaffold device.
Participants	• Human subjects aged ≥ 18 years. • Chronic knee pain or symptoms for at least 3 months. • Radiographic confirmation of Kellgren-Lawrence Grades 2–4 osteoarthritis of knee joint.	• Active infection. • Pregnancy. • Neurological disorders. • Spondyloarthropathies. • Gout, hyperlipidemia. • Inflammatory arthritis • Metal sensitivity. • Pathologies of the lower limb which would interfere with the evaluation of osteoarthritis of knee joint. Patients were also excluded if they received in the two months prior to treatment: • Any intraarticular injections. • Had taken any symptomatic slow-acting drugs in osteoarthritis (SYSADOA): oral or topical steroids and/or non-steroidal antiinflammatories (NSAIDs).

Germany. All patients recruited for the trial were followed for a minimum of 4 years after the last GOLDIC® injection. Patients returned to the clinic at four weeks, three, six months, one, two and four years (T1–T6), and were assessed with WOMAC and KOOS by independent clinic nursing staff trained to administer the instrument with minimal intervention.

Patients

Patients with KOA with minimum three months of knee pain and/or swelling and a radiographic diagnosis of knee osteoarthritis K-L grades 2–4 as determined by independent musculoskeletal radiologists on plain radiographs or MRI were included in this study. Twenty-five patients underwent either simultaneous or staggered bilateral injections based on clinical symptomatology, see patient flow diagram (Fig. 1).

GOLDIC® therapy

For GOLDIC® therapy, 4 × 10 mL of blood was collected from each patient using four GOLDIC® BTS syringes (Arthrogen GmbH, Ringsee, Germany) at the time of initiating therapy. All four syringes were incubated at 37 °C for 24 hours. Incubation must be less than 28 hours or the chances of red blood cell lysis is increased and is not desirable as it changes the characteristics of the serum injectate negatively. Addition of anticlotting agent is not required as even if clot forms, it does not impact separating the cells and creation of the activated serum.

After the incubation process, the four tubes were centrifuged at 4000 rpm (2250*g*) for ten minutes. Then supernatant conditioned serum was collected and filtered through a 0.22-μM syringe tip filter (Millex GP, Merck Millipore, Tullagreen, Carrigtwohill, Cork, Ireland), and was then used for immediate IA injection or stored at − 20 °C for later use up to eight weeks from processing. All patients received four IA injections of approximately 3 ml. GOLDIC® serum every three to six days. In all cases, an ultrasound guided intra-articular injection was performed by superolateral approach under aseptic technique with a 22G spinal needle [27]. If a knee effusion was present, the synovial fluid was aspirated under aseptic condition, and the amount of aspirated fluid was documented and sent to an independent laboratory for

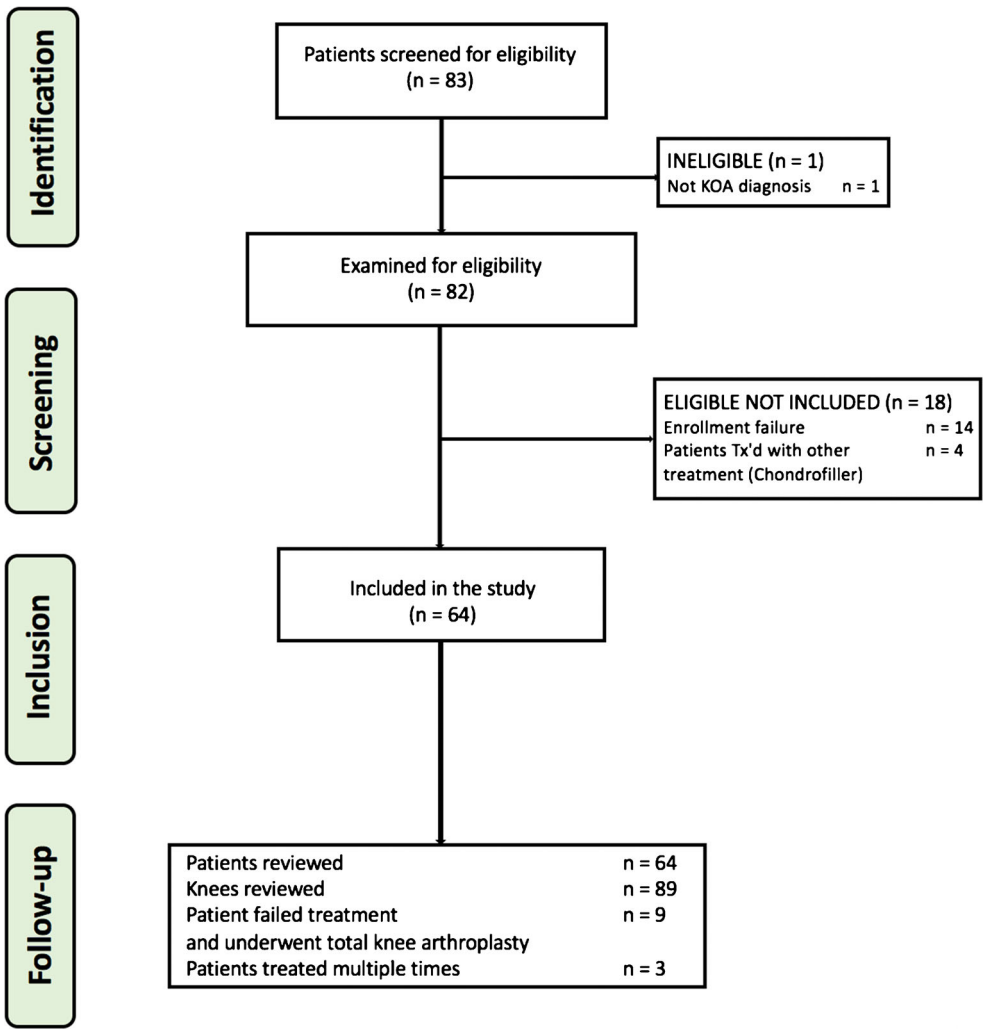


Fig. 1 Flow diagram

p-GSN analysis. Patients were advised to use ice pack/cold therapy for any knee pain at home and to avoid prolonged walking and standing for 24 hours after injection. Patients were also instructed to use only paracetamol (1 g up to four times per day) for post-injection pain and to strictly avoid NSAIDs. Post-injection rehabilitation, patients were asked to avoid strenuous exercise, were allowed only nonimpact exercises such as walking, cycling, and pool exercises; subsequently, gradual resumption of normal sport or recreational activities was allowed. Supervised physiotherapy and or knee supports were not required.

Assessments

The primary efficacy endpoint was change in WOMAC and KOOS before and at four weeks, three, six months, one, two and four years following the intervention [28, 29].

The WOMAC score was calculated out of the present study KOOS dataset. The primary safety endpoint was the incidence of SAEs during the entire treatment period.

Intra-articular gelsolin measurement

Joint fluid samples were obtained by direct aspiration before GOLDIC® injection, centrifuged at 800*g* for 15 minutes, separated and cryopreserved at − 80 °C. The individual biochemical parameters were determined following a standardized protocol using commercially available kits. Samples were analyzed in batches within eight weeks of collection (Department of Immunology, University of Heidelberg). After 1:5000 dilution, the concentrations of gelsolin (μg/ml) was measured using a human plasma gelsolin ELISA kit (SK00384-01, AVISCERA BIOSCIENCE, INC. Santa Clara, CA/USA). Based on the different dilution in the synovial fluid [30], the gelsolin values were corrected using urea concentration (Urea Assay Kit ab83362, Abcam plc, Cambridge/UK).

Statistical methods

Statistical analysis was performed by an independent statistician. The Kolmogorov-Smirnov-Test normality test showed no significant deviation compared to normal distribution in WOMAC and KOOS. Gelsolin evaluation data were analyzed by descriptive statistics only given the limited number of cases. Data were expressed as means and standard deviation.

We calculated a post hoc sample size based on the ability to detect an effect size of 1/3 with power of $b = 80\%$ and two-sided significance level $a = 5\%$, which showed that it was necessary to include at a minimum 71 knees.

Results

Patients

A total of 64 patients (89 knees) with KOA were included in the trial. There were 37 male and 27 female patients; mean age was 64.8 years (± 12.9 years); 47 patients had right and 42 had left knee involvement. Twenty-five patients had bilateral KOA (Table 2). The mean BMI was 28.2 (± 3.65 kg/m^2), and 17 patients had previously undergone knee surgery prior to treatment. Fourteen knees had grade 2, 36 had grade 3, and 39 knees had grade 4 K-L KOA.

Efficacy

KOOS and WOMAC scores showed statistically significant improvement in follow-up timepoints compared to T0, ($P < 0.05$) (Table 3). The best improvement in KOOS subgroups could be seen for the pain criterion (Fig. 2). The WOMAC subscale for function demonstrated the most significant improvement (Fig. 3). All KOOS and WOMAC subscores showed significant improvement in the mean for nearly all follow-up timepoints compared to T0 ($P < 0.05$) (Table 3). Concerning the grade of KOA, best results were seen in patients with grades 2 and 3 KL KOA (Supplementary Data, Fig. 2B and 3B), but significant improvement were seen also in patients with grade 4 KL KOA (Supplementary Data, Fig. 2C and 3C). Clinical results were not influenced by previous surgery, age or BMI. MCID was met KOOS (8–10 point change) (Table 3) for all timepoints and sub-scores. Nine patients failed treatment and underwent total knee replacement at mean of 32 months following procedure.

In the nine knees with an effusion that could be aspirated, the IA gelsolin (p-GSN) level showed a significant increase after the first GOLDIC® injection from 7.68 (± 4.68 mcg/mL) to 12.51 (± 6.78 mcg/mL). After the second and third injection, the p-GSN levels slightly increased to 13.74 (± 5.74 mcg/mL) and 15.18 (± 8.58 mcg/mL) respectively. The amount of effusion

Table 2 Baseline demographics and characteristics of the 64 patients (89 knees). *Mean given for all baseline characteristics except for gender and affected knee

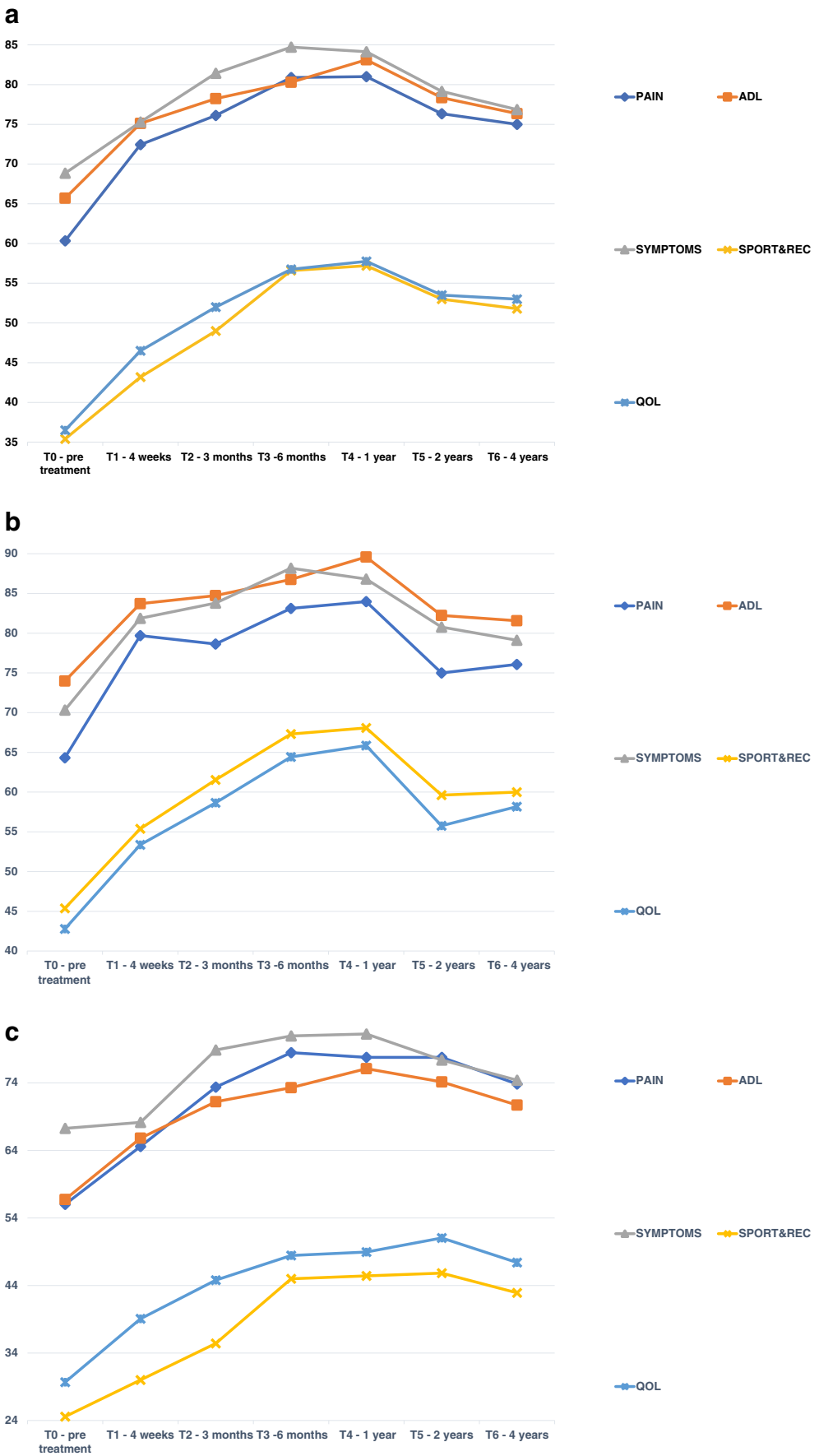
Baseline characteristics	Mean*	StdDev (+, −)
BMI (kg/m^2)	28.2	3.6
Age (years)	64.8	12.9
Gender (male/female)	37/27	
Side (right/left)	47/42	
OA grade II	$N = 14$	
OA grade III	$N = 36$	
OA grade IV	$N = 39$	

OA Osteoarthritis

Table 3 Mean KOOS and WOMAC scores at baseline data for all study participants, and follow-up at 4 weeks, 3, 6 months, 1, 2, and 4 years

SCORE	aspect	T0 - pre treatment	T1 - 4 weeks	T2 - 3 months	T3 - 6 months	T4 - 1 year	T5 - 2 years	T6 - 4 years
KOOS_ADL	Mean	65.7	75.1	78.2	80.3	83.1	78.4	76.4
	Std deviation	18.7	16.2	17.9	16.1	14.8	16.3	21.7
	Two way ANOVA Prob	0.000						
	Paired *t* test Prob (2-tail) vs T0		0.006	0.006	0.002	0.000	0.018	0.063
KOOS_PAIN	Mean	60.3	72.4	76.1	80.9	81.0	76.3	75.0
	Std deviation	18.4	18.0	16.9	14.4	13.3	15.4	19.9
	Two way ANOVA Prob	0.000						
	Paired *t* test Prob (2-tail) vs T0		0.001	0.001	0.000	0.000	0.004	0.012
KOOS_QOL	Mean	36.5	46.5	52.0	56.8	57.8	53.5	53.0
	Std deviation	20.9	25.3	27.2	24.2	23.1	22.9	26.2
	Two way ANOVA Prob	0.000						
	Paired *t* test Prob (2-tail) vs T0		0.013	0.002	0.000	0.000	0.002	0.005
KOOS_SPORT_REC	Mean	35.4	43.2	49.0	56.6	57.2	53.0	51.8
	Std deviation	26.6	30.6	28.3	28.9	30.8	29.2	34.6
	Two way ANOVA Prob	0.000						
	Paired *t* test Prob (2-tail) vs T0		0.070	0.007	0.001	0.001	0.014	0.027
KOOS_SYMPTOMS	Mean	68.9	75.3	81.4	84.7	84.1	79.1	76.9
	Std deviation	21.1	19.1	13.3	13.6	14.3	17.2	20.4
	Two way ANOVA Prob	0.000						
	Paired *t* test Prob (2-tail) vs T0		0.037	0.001	0.000	0.001	0.027	0.101
WOMAC_FUNCTION	Mean	23.3	16.9	14.8	13.4	11.5	14.7	16.1
	Std deviation	12.7	11.0	12.1	10.9	10.0	11.1	14.7
	Two way ANOVA Prob	0.000						
	Paired *t* test Prob (2-tail) vs T0		0.006	0.006	0.002	0.000	0.018	0.063
WOMAC_PAIN	Mean	7.0	4.5	3.7	3.1	3.0	4.0	4.3
	Std deviation	3.9	3.1	3.1	2.8	2.3	2.9	4.1
	Two way ANOVA Prob	0.000						
	Paired *t* test Prob (2-tail) vs T0		0.000	0.001	0.000	0.000	0.006	0.030
WOMAC_STIFFNESS	Mean	3.1	2.5	1.9	1.7	1.5	1.8	2.2
	Std deviation	2.5	2.5	1.9	1.9	1.8	2.0	2.3
	Two way ANOVA Prob	0.000						
	Paired *t* test Prob (2-tail) vs T0		0.074	0.002	0.002	0.001	0.006	0.078

Kolmogorov-Smirnov-Test shows no significant deviation compared to a normal distribution; red indicates significant mean differences ($\alpha < 0.05$)


a
85
80
75
70
65
60
55
50
45
40
35
T0 - pre treatment
T1 - 4 weeks
T2 - 3 months
T3 -6 months
T4 - 1 year
T5 - 2 years
T6 - 4 years
PAIN
ADL
SYMPTOMS
SPORT&REC
QOL
b
90
85
80
75
70
65
60
55
50
45
40
T0 - pre treatment
T1 - 4 weeks
T2 - 3 months
T3 -6 months
T4 - 1 year
T5 - 2 years
T6 - 4 years
PAIN
ADL
SYMPTOMS
SPORT&REC
QOL
c
74
64
54
44
34
24
T0 - pre treatment
T1 - 4 weeks
T2 - 3 months
T3 -6 months
T4 - 1 year
T5 - 2 years
T6 - 4 years
PAIN
ADL
SYMPTOMS
SPORT&REC
QOL

◀ **Fig. 2** **a** KOOS scores for baseline, 4 weeks, 3, 6 months, 1, 2, and 4 years after treatment with GOLDIC injections. S = symptoms, P = pain, ADL = activity in daily living, Sp = sports, QOL = quality of life. **b** KOOS mean scores for K-L grades 2 and 3 at baseline 4 weeks, 3, 6 months, 1, 2, and 4 years after treatment with GOLDIC injections. **c** KOOS mean scores for K-L grade 4 at baseline, 4 weeks, 3, 6 months, 1, 2, and 4 years after treatment with GOLDIC injections

decreased from 12.6 (± 3.8 mL) to 4.6 (± 2.4 mL) after the first aspiration and injection, to 1.8 (± 1.1 mL) after the second injection and finally to 1.2 (± 0.7 mL). After the third GOLDIC® injection, five of the nine patients showed no effusion.

Safety

Other than prolonged pain and swelling in four patients, no other adverse, or severe adverse events observed in this study.

Discussion

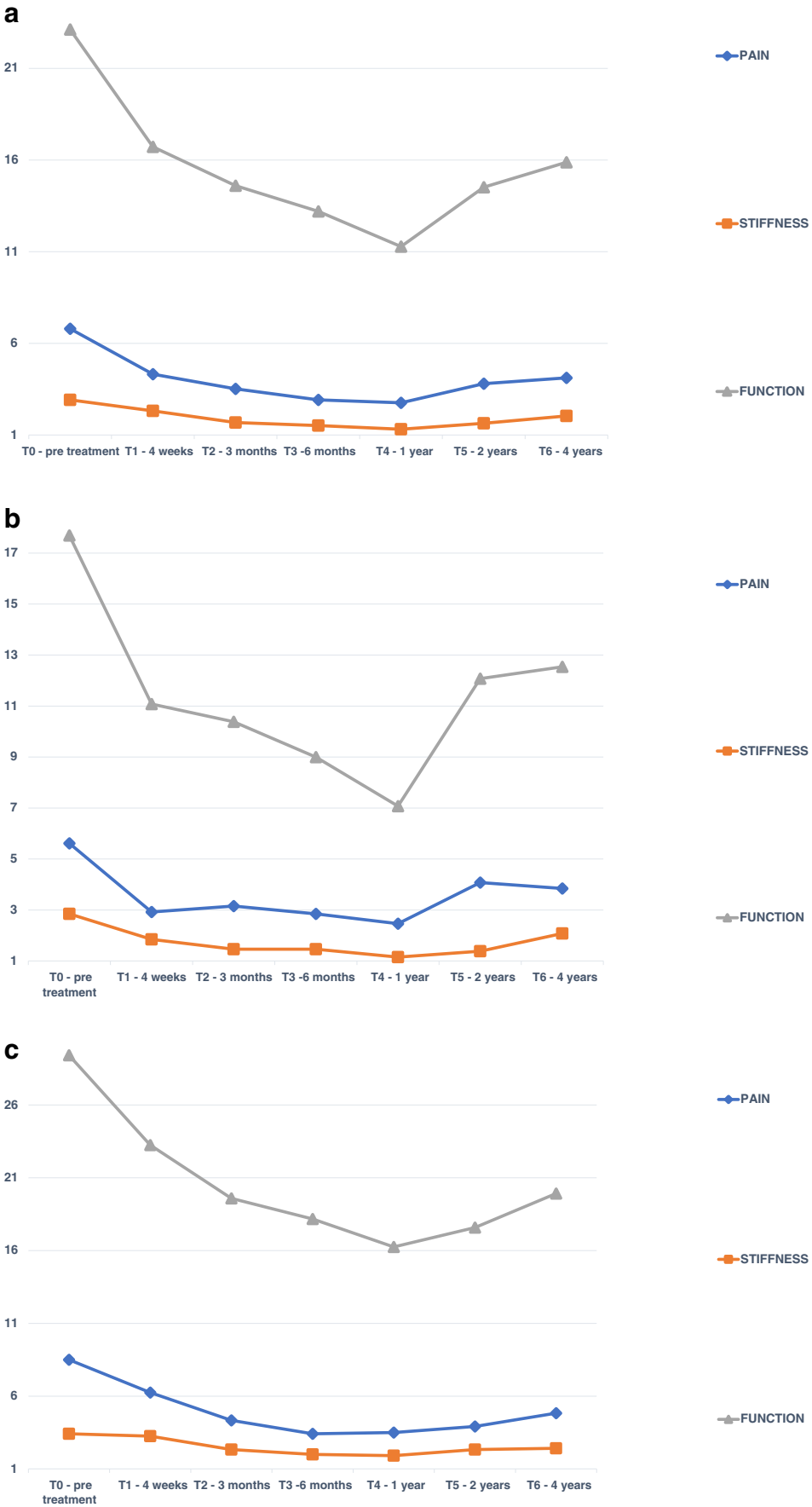
To our knowledge, this is the first investigation to report the efficacy of a novel biological device using gold particles as inducer of autologous proteins production (GOLDIC® method) for the treatment of KOA. The use of autologous blood products for the treatment of osteoarthritis is not new. For a few decades, preparations such as PRP, ACS, or autologous conditioned plasma (ACP) have been used with varying degrees of success [11–15, 31]. Alpha granules of platelet are rich sources of various growth factors like platelet-derived growth factor, transforming growth factor-beta, and vascular endothelial growth factor [32]. PRP use in the treatment of KOA is often debatable and conflicting in the current literature; studies reports PRP as better, having same effect or worse than hyaluronic acid in relieving pain in KOA [11–15]. Duration of effect of PRP has also been shown to be variable lasting for six months to one year [11–15]. The variable results could be explained by a lack of standardized technique of PRP preparation; variable types, other factors like gamma interferon, the number and site(s) of PRP injections [11–15]. In comparison to PRP, the technique of GOLDIC® preparation is standardized and uniform, so content and quality of the GOLDIC® serum is consistent. Another autologous blood product used in osteoarthritis is autologous conditioned serum (ACS); In this procedure, the patient's blood is taken up and cultured in special syringes containing special glass beads that stimulate peripheral leukocytes to produce antiinflammatory cytokines such as interleukin-1 receptor antagonist (IL-1ra) [13]. Conditioned autologous serum (CAS) like GOLDIC® also has IL-1ra that inhibit intra-articular destructive effects of interleukin-1 (IL-1) along with other factors that are present in the PRP (platelet-derived growth factor, insulin like growth factor and vascular endothelial growth factor) [26]. But in comparison, ACS requires multiple blood harvests for six injections, to be given at a widely spread and lengthy injection (0, 7, 14, 90, 180, 270 days) schedule [13]. It does not seem to promote long-lasting restoration of joint homeostasis as multiple injections over a nine month period are required. Treatment regimens for GOLDIC were designed to ensure that in the hands of the general practitioner the results of treatment will be uniform across different patient groups who may use the platform. Initial subjects for treatment were lame race horses, and jumpers, as animals cannot communicate their level of improvement, we can only ascertain response to treatment by the functional improvement. Up to ten injections were administered to animal subjects; however after years of experience, no additional benefit was seen after four injections. There is also some scientific basis of the treatment as well, seen in humans, before the trial began, in patients with swelling prior to treatment. Ninety-four percent of effusions were eliminated after the fourth injection, whereas 67% of effusions ceased after the third injection, therefore four injection series were selected for treatment standardization and to ensure optimal outcome. Additionally, as illustrated in the study, p-GSN levels significantly improved after the second injection, but only 55% of patients had eliminated their effusion at the completion of three injections. This point will continue to be observed in future investigations.

Although, in vivo studies demonstrate that ACS indeed improves pain and function in humans having KOA, however one in vitro study showed that ACS has increased levels of both anti-inflammatory and pro-inflammatory cytokines—tumor necrosis factor-alpha (TNF-α) when it was applied to osteoarthritis explant tissue, additionally, it did not have any direct effect on cartilage metabolism [13].

The first GOLDIC® trial in horses showed a significant improvement in clinical symptoms of horse joint disease and lameness [25]. First human clinical trial in tendoachilles showed a promising clinic results and impressive healing demonstrated on follow-up MRI [26]. Good results of these two GOLDIC® studies encouraged us to conduct this prospective trial to evaluate effectiveness in patients with KOA. Other objectives of this study were to evaluate its safety profile influencing the result of treatment of KOA.

In Germany, where the study took place, we were very stringent in the selection of patients who were administered the treatment, as most medical treatments are fully covered by the health system whereas, novel treatments although allowed by regulatory authorities when administered by the inventor, the cost of administration was covered by patients. Currently an ongoing investigation is examining cost-benefit analysis of GOLDIC® comparing other common injectable treatments.

A total of 64 patients (89 knees) with KOA were included in the trial. Sixty-four patients with affected 89 knees had statistically significant improvement in the global WOMAC and KOOS score at nearly all timepoints compared to baseline


a
21
16
11
6
1
T0 - pre treatment
T1 - 4 weeks
T2 - 3 months
T3 -6 months
T4 - 1 year
T5 - 2 years
T6 - 4 years
PAIN
STIFFNESS
FUNCTION
b
17
15
13
11
9
7
5
3
1
T0 - pre treatment
T1 - 4 weeks
T2 - 3 months
T3 -6 months
T4 - 1 year
T5 - 2 years
T6 - 4 years
PAIN
STIFFNESS
FUNCTION
c
26
21
16
11
6
1
T0 - pre treatment
T1 - 4 weeks
T2 - 3 months
T3 -6 months
T4 - 1 year
T5 - 2 years
T6 - 4 years
PAIN
STIFFNESS
FUNCTION

◀ **Fig. 3** **a** WOMAC scores for baseline, 4 weeks, 3, 6 months, 1, 2, and 4 years after treatment with GOLDIC injections. **b** WOMAC mean scores for K-L grades 2–3 at baseline, 4 weeks, 3, 6 months, 1, 2, and 4 years after treatment with GOLDIC injections. **c** WOMAC mean scores for K-L grade 4 at baseline, 4 weeks, 3, 6 months, 1, 2, and 4 years after treatment with GOLDIC injections

($P < 0.05$). The best improvement in KOOS subgroups could be seen for the criterion activity in pain. The WOMAC subscale for function the score showed the most impressive improvement. Best results were seen in younger patients with grades 2–3 K-L KOA, but good results were also seen in elderly patients with severe osteoarthritis. A good response in K-L grade 4 KOA showed that injected GOLDIC® is likely, not just working on promoting anabolism and preventing catabolism but is also helping in restoring the overall joint homeostasis. The best results in K-L grade 2 KOA show that the problem is more biological, and good results in K-L grades 3–4 KOA demonstrate that other mechanical factors such as osteophytes, bone loss, instability, and deformity may be partially affecting the outcome of GOLDIC® therapy. Besides grade of osteoarthritis, other variables such as previous surgery, sex, age, and BMI did not seem to influence the clinical outcome. With the improvement plateauing after two years, redosing is a possibility and may lead to an additive and disease modifying effect; however, this will be better evaluated within the confines of a randomized controlled trial with sham or saline comparison.

Another objective of this study was to evaluate the intra-articular gelsolin concentration during follow-up period. There was a significant elevation of intra-articular gelsolin concentration after the 1st injection in patients with effusion. Interestingly, the increased gelsolin level was accompanied by the reduction of the amount of synovial fluid production. Therefore, we can postulate that GOLDIC® may influence the overall joint homeostasis and reduce synovial effusion modulating the cytokine level, thus leading to an improvement in the clinical outcome. A subsequent study would be required to attempt to establish the disease modifying role of GOLDIC® therapy.

We also intended to evaluate the safety profile of GOLDIC® therapy by documenting any SAEs during the treatment and follow-up periods. No severe complications, or other SAEs occurred among the study subjects. Only minor adverse events were detected, such as a mild pain and effusion after the injections, which persisted for not more than two days in a few patients. Only one elderly patient with bilateral osteoarthritis of knee joint had diffuse swelling and pain which persisted for five days. Compared to other blood-based biological methods, only the GOLDIC® procedure has shown upregulation of plasma gelsolin (pGSN) and granulocyte colony stimulation factor (G-CSF) which both play an important role in tissue regeneration [18–21]. The results of the present study documented significant long-lasting benefits of the GOLDIC® method which have not been seen in other blood-based platforms such as PRP, ACS, or ACP with effects peaking at the two year mark instead of at three months for HA and six months for PRP, thus opening the possibility of repeat dosing and lengthening the period of symptomatic improvement; however, this will need to be investigated directly within new trials [9–15, 31].

The exact mode of action of the GOLDIC® procedure is not well understood. In vitro studies have shown a significant increase in plasma gelsolin level in the autologous serum and increased gelsolin level in synovial fluid after every GOLDIC® injection. Both gelsolin and G-CSF have been shown to promote regeneration [18–21]. Therefore, it is an important finding that GOLDIC® injections resulted in a significant increase of gelsolin in the synovial fluid.

Two of the major limitations of this investigation are the lack of randomization and blinding. Additionally, the design of this study did not include a control arm; limiting the conclusions, we can draw about the independent regenerative impact of the GOLDIC®therapy. Although the data were collected prospectively, and the investigation had been registered in a recognized trial registered, our data were analyzed retrospectively. The standard to introduce novel treatments should obviously be appropriately powered randomized controlled trials with robust outcome measures and adequately long follow-up. Nevertheless, we were stringent in the selection of patients who were administered the treatment under study, and patients were accurately followed up for at least four years after the index procedure. To ameliorate this shortcoming, the next step in this investigation would be to conduct blinded randomized control trials, with long-term follow-up, assessing the effectiveness of GOLDIC® therapy in KOA. This would allow the results of this body of research to be more generalizable to larger bodies of patients. Another limitation of this study is the evaluation of knee health and improvement primarily using patient-reported outcome measures. While this is common practice and was paired with measures of pGSN, imaging of the knee joint at sequential time points pretreatment and follow-up could help quantify the regenerative properties of GOLDIC® therapy.

The goal of the study should establish appropriate feasibility, and rationale for organizing a multicentric randomized placebo-controlled trial. Such a trial could also identify subgroups of patients that will benefit more from this treatment platform. In future investigations, PROMs, PROMs relation to PASS (patient acceptable symptom state), and objective measures such as functional tests such as isometric/isokinetic strength, as well as JSW (joint space width) on plain weight bearing radiographs, as well as qualitative and quantitative MRI results are planned to evaluate the outcomes of treatment more thoroughly.

Conclusion

PoC study of GOLDIC® as a novel device for conservative management of moderate to severe KOA was confirmed. GOLDIC® produces rapid and sustained improvements in all indices after treatment, with no SAEs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00264-020-04870-w.

Acknowledgments The authors would like to thank Eduard Collier, Nico Nagelkerk PhD, Pam Jackson PhD, Lisa Jackson PhD for their contributions to this scientific work. Contributors US was the coordinating investigator, WDM contributed to the study conduct and/or data collection.

Authors' contributions All authors analyzed and/or interpreted data. All authors collaborated in the drafting and critical revision of the manuscript. All authors approved the final version of the manuscript and vouch for the accuracy of the analysis and the fidelity of the study to the protocol.

Data availability Underlying data from this manuscript may be requested by qualified researchers upon request. Investigators may request access to deidentified patient data and redacted study documents which may include raw datasets, analysis-ready data sets, and blank data forms. Prior to the use of data, proposals need to be approved by an independent review panel at www.clinicalstudyrequest.com and a signed data sharing agreement will need to be executed. Some documents are available in German and others English.

Compliance with ethical standards

Ethics approval Competent authority of Bavaria authorized the study.

Consent to participate All patients were approved for treatment by written informed consent.

Consent for publication Written informed consent was obtained from all patients.

References

1. Garner M, Alshameeri Z, Khanduja V (2013) Osteoarthritis: genes, nature-nuture interaction and the role of leptin. Int Orthop 37:2499–2505
2. Hootman JM, Helmick CG (2006) Projections of us prevalence of arthritis and associated activity limitations. Arthritis Rheum 54:226–229
3. Alford JW, Cole BJ (2005) Cartilage restoration, part 1: basic science, historical perspective, patient evaluation, and treatment options. Am J Sports Med 33:295–306
4. Buckwalter JA, Brown TD (2004) Joint injury, repair, and remodeling: roles in post-traumatic osteoarthritis. Clin Orthop Relat Res 423:7–16
5. Trzeciak T, Richter M, Suchorska W et al (2016) Application of cell and biomaterial-based tissue engineering methods in the treatment of cartilage, menisci and ligament injuries. Int Orthop 40:615–624
6. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteoarthrosis. Ann Rheum Dis 16:494–502
7. Healy WL, Della Valle DJ, Lorio R et al (2013) Complications of total knee arthroplasty: Standardized list and definitions of the Knee Society. Clin Orthop Relat Res 471:215–220
8. Hochberg MC, Altman RD, Brandt KD et al (1995) Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee: American College of Rheumatology. Arthritis Rheum 38:1541–1546
9. Navarro-Sarabia F, Coronel P, Collantes E et al (2011) A 40-month multicenter, randomized placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injection of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 70:1957–1962
10. Creamer P (1997) Intra-articular corticosteroid injections in osteoarthritis: do they work and if so, how? Ann Rheum Dis 56:634–636
11. Filardo G, Di Matteo B, Di Martino A et al (2015) Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. Am J Sports Med 43:1575–1582
12. Betancourt JP, Murrell WD (2016) Leukocyte-poor platelet-rich plasma to treat degenerative meniscal tear: a case report. J Clin Orthop Trauma 7:106–109
13. Baltzer AW, Moser C, Jansen SA et al (2012) Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthr Cartil 17:152–160
14. Andia I, Maffulli N (2019) New biotechnologies for musculoskeletal injuries. Surgeon 17:244–255
15. Anz AW, Bapat A, Murrell WD (2016) Concepts in regenerative medicine: Past, present, and future in articular cartilage treatment. J Clin Orthop Trauma 7:137–144
16. Vuolteenaho K, Kujala P, Moilanen T et al (2005) Aurothiomalate and hydroxychloroquine inhibit nitric oxide production chondrocytes and in human arthritic cartilage. Scand J Rheumatol 34:475–479
17. Silacci P, Mazzolai L, Gauci C et al (2004) Gelsolin superfamily proteins: key regulators of cellular functions. Cell Mol Life Sci 61:2614–2623
18. Suhler E, Lin W, Yin HL et al (1997) Decreased plasma gelsolin concentrations in acute liver failure, myocardial infarction, septic shock, and myonecrosis. Crit Care Med 25:594–598
19. Li GH, Arora PD, Chen Y et al (2012) Multifunctional roles of gelsolin in health and disease. Med Res Rev 32:999–1025
20. Okano T, Mera H, Itokazu M et al (2014) Systemic administration of granulocyte colony-stimulating factor for osteochondral defect repair in a rat experimental model. Cartilage 5:107–113
21. Piktel E, Levental I, Durnaś B et al (2018) Plasma gelsolin: indicator of inflammation and its potential as a diagnostic tool and therapeutic target. Int J Mol Sci 19:E2516
22. Kopecki Z, Cowin AJ The role of actin remodeling proteins in wound healing and tissue regeneration. In: Alexandrescu VA (ed) Wound Healing - New insights into Ancient Challenges. IntechOpen. https://doi.org/10.5772/64673 (date assessed Apr 2020) from: https://www.intechopen.com/books/wound-healing-new-insights-into-ancient-challenges/the-role-of-actin-remodelling-proteins-in-wound-healing-and-tissue-regeneration
23. DiNubile MJ (2008) Plasma gelsolin as a biomarker of inflammation. Arthritis Res Ther 10:124
24. Lee PS, Waxman AB, Cotich KL et al (2007) Plasma gelsolin is a marker and therapeutic agent in animal sepsis. Crit Care Med 35:849–855
25. Schneider U, Veith G (2013) First results on the outcome of gold-induced, autologous-conditioned serum (GOLDIC) in the treatment of different lameness-associated equine diseases. J Cell Sci Ther 5:151
26. Schneider U, Wallich R, Felmet G et al (2017) Gold-induced autologous cytokine treatment in Achilles tendinopathy. In: Canata G,

d'Hooghe P, Hunt K (eds) Muscle and Tendon Injuries. Springer Berlin, Heidelberg: ISAKOS, pp 411–420
27. Ulasli AM, Ozcakar L, Murrell WD (2019) Ultrasound imaging and guidance in the management of knee osteoarthritis in regenerative medicine field. J Clin Orthop Trauma 10:24–31
28. Bellamy N, Buchanan WW, Goldsmith CH et al (1988) Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 15:1833–1840
29. Roos EM, Lohmander LS (2003) The Knee Injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 1:64
30. Kraus VB, Huebner JL, Fink C et al (2002) Urea as a passive transport marker for arthritis biomarker studies. Arthritis Rheum 46:420–427
31. Smith PA (2016) Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: an FDA-sanctioned, randomized, double-blind, placebo-controlled clinical trial. Am J Sports Med 44:884–891
32. Anitua E, Andia I, Ardanza B et al (2004) Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 91:4–15