ORIGINAL ARTICLE

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AUTOLOGOUS CONDITIONED SERUM IN THE THERAPY OF OBESITY-RELATED KNEE OSTEOARTHRITIS

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Abstract. Introduction: *Knee osteoarthritis (KOA) is a common joint disorder affecting the elderly population. Conservative treatment includes lifestyle modifications, weight loss, physiotherapy, nonsteroidal anti-inflammatory drugs, chondroprotective agents, intra-articular application of steroids, hyaluronic acid, and autologous blood component injections. Obesity-related KOA has recently been extensively studied as a separate disease, and there are currently no explicit guidelines regarding its treatment. Currently, there is only a few literature data on the intra-articular administration of autologous conditioned serum (ACS) in subjects with KOA, which suggests an improvement in pain management and functional impairment. However, no separate studies have been performed for obesity-related KOA. Therefore, the aim of our study was to evaluate the efficacy and safety of ACS in the treatment of obesity-related KOA.* ***Materials and methods:*** *A total of 20 patients with Kellgren-Lawrence (KL) grade 2-3 obesity-related KOA were included in the present study, all of whom received intra-articular ACS. Demographic data and routine laboratory examinations were performed and musculoskeletal ultrasound was used to assess for synovitis prior to intervention. Pain and functional impairment were assessed through visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) prior to intervention, 1 week and 6 months post-treatment.* ***Results:*** *We reported a statistically significant decrease in pain and functional improvement 1 week post-treatment, which persisted up to 6 months post-treatment. Better improvement was noted in KL grade 2 and in subjects with synovitis. There were no major adverse events reported.* ***Conclusions:*** *The intra-articular administration of ACS provides rapid improvement of pain and functional impairment in obesity-related KOA, which persists up to 6 months post-treatment.*

Key words: *obesity-related knee osteoarthritis, autologous conditioned serum, intra-articular injection, pain, knee function, treatment*

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INTRODUCTION

Osteoarthritis (OA) is among the most common joint disorders worldwide and is associated with chronic joint pain, impaired mobility, and reduced quality of life [1, 2]. The incidence of OA has been increasing in recent decades, as has its global burden, mainly due to the aging population and prevalence of obesity across the globe [3, 4]. The knee is the most often involved joint, followed by the interphalangeal joints of the hand and the hip joint [5]. Risk factors implicated in the development of knee osteoarthritis (KOA) can be divided into person-level factors, such as age, sex, obesity, genetic predisposition, dietary habits, etc., and joint-level factors, including previous injury, abnormal axis loading, joint instability, muscle weakness, and sarcopenia [1, 6]. The main symptoms of KOA include pain, swelling, stiffness, and reduced range of motion [7, 8]. The conservative treatment of KOA includes oral paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, intra-articular application of steroids, hyaluronic acid (HA), platelet-rich plasma (PRP) and other autologous products, physical therapy, kinesiotherapy, lifestyle modifications, exercise, weight loss, and the use of gait aids [9-12]. End-stage KOA with persistent pain and restricted mobility is treated by partial or total knee replacement [4].

Obesity-related KOA, or metabolic syndrome-associated KOA, has recently been highlighted as a separate disease phenotype [2, 13, 14]. Obesity impacts the development of KOA not only by increased mechanical load on weight-bearing joints such as the knee, but also by creating a state of chronic micro-inflammation within the tissues, an impaired secretion of adipokines, and the development of sarcopenia [2, 13, 14]. Higher body mass index (BMI) has been associated with higher pain score, reduced physical activity, and impaired mobility [14]. In addition, hypertriglyceridemia and low levels of high-density lipoproteins (HDL) have been correlated with more severe knee pain, while an increase in low-density lipoproteins (LDL) appears to contribute to synovial inflammation and osteophyte formation through lipotoxicity, generation of pro-inflammatory cytokines, and mitochondrial dysfunction in chondrocytes [15, 16]. Currently, there are no specific treatment guidelines on the management of obesity-related KOA, and some widely-used conservative treatment modalities may be contraindicated for other manifestations of metabolic syndrome, such as hypertension, impaired glucose tolerance, or diabetes [17, 18].

The clinical benefit of products derived from autologous blood components in the reduction of pain and joint inflammation is attributed to the anti-inflammatory cytokines and proregenerative factors released by blood cells [19]. These elements, present in plasma or serum, are delivered via intra-articular injections [4, 20]. In recent years, PRP and autologous conditioned serum (ACS) have been investigated as therapeutic alternatives in the pain management of KOA after failure of other conservative treatment options or contraindications for their use, yet their cartilage regeneration potential remains to be fully elucidated [4]. A number of studies have reported a positive impact of the use of PRP in KOA. However, controversial results have also been presented [8, 21-23]. The use of ACS in the treatment of KOA has been the subject of expanding research in recent years, yet there is little available data [4]. Furthermore, no separate studies on ACS application in obesity-related KOA have been published yet. Therefore, the aim of the present research was to evaluate the impact of intra-articular injections of ACS on pain management and functional improvement in subjects with obesity-related KOA.

MATERIALS AND METHODS

The present study was a prospective open-label trial of the clinical efficacy and safety of intra-articular injections of ACS in subjects with obesity-related KOA. The study was conducted at the Clinic of Rheumatology at "Sv. Ivan Rilski" University Hospital from 2023-2025. A total of 20 subjects – 13 females and 7 males, ranging from 40 to 77 years of age – were included in the present study. All of them matched the clinical criteria for KOA of the American College of Rheumatology (ACR) and the criteria for metabolic syndrome of the International Diabetes Federation. Both knees were evaluated in 4 patients, making for a total of 24 knee joints. All patients provided written informed consent before study interventions. Height, weight, systolic and diastolic blood pressure, and waist circumference were measured, and BMI was calculated and recorded. Laboratory blood samples were obtained, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipid profile, glucose, insulin, glycated hemoglobin, and uric acid. The Homeostatic Model Assessment (HOMA) index was derived. Conventional standing anteroposterior joint radiographs were obtained by disease grading according to the Kellgren-Lawrence (KL) scale, and musculoskeletal ultrasound examination was performed to detect and grade synovial inflammation by the presence of synovial fluid and synovial hypertrophy. All patients conformed to the following

inclusion criteria: age ≥18 years, BMI ≥ 18.5 kg/m^2, unilateral or bilateral KOA with a KL score ranging from 1 to 3. The exclusion criteria included KL score 4, other previously diagnosed rheumatic diseases, such as rheumatoid arthritis, spondyloarthritis, gout, fibromyalgia, etc., joint infection, previous partial or total knee replacement, pregnancy, malignancy, uncontrolled heart, liver, or kidney failure, and psychiatric disorders.

Withdrawal, incubation, preparation, and administration of ACS adhered to well-established protocols [4, 24, 25]. 10-12 ml of blood was collected and transferred to a dedicated tube with glass beads serving as contact surfaces for aggregation and activation of blood cells (Sanakin®, Sanakin BioScience SA, Switzerland). Blood samples were incubated at 37 °C for 3 hours, then centrifuged at 4,000 rpm for 5 min, and 3-5 ml of serum was withdrawn into a sterile syringe. The ACS was then injected within 15 min through a medial approach into the knee joint, with the patient in a supine position. A total of 5 weekly injections of ACS were administered to each patient. In two female patients, ACS was administered in both knees at each visit according to the above procedure. The use of topical and oral NSAIDs, topical, oral, and/or intra-articular steroids was prohibited from 3 weeks before the first ACS application, throughout the 5 weeks of ACS application, and further 3 weeks after the last intra-articular injection. Patients were allowed to use paracetamol (acetaminophen).

Pain and functional impairment were assessed through a visual analogue scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) before the first application of ACS and at 1 week and 6 months after completion of the 5-week treatment course. Statistical analysis was performed using Kolmogorov-Smirnov's test, one-way analysis of variance (ANOVA), and Tukey's honestly significant difference (HSD) post-hoc test.

RESULTS

Descriptive statistics of patients' demographics and laboratory values are presented in Table 1.

Notably, the mean BMI was 30.35, indicating overall obesity of the cohort rather than overweight. Mean ESR and CRP levels were normal. Total cholesterol and LDL levels were slightly elevated, and the mean HOMA index was above the standard reference range of 2.5. KL grade 2 was reported in 10 (41.7%) knees, and KL grade 3 – in 14 (58.3%) knees. Synovial inflammation was reported in 15 (62.5%) knees.

A statistically significant improvement in patient assessment of pain measured through VAS was reported in 17 out of 20 subjects at 1 week after completion of the 5-week course of ACS, including the 4 patients who received bilateral knee injections, which was maintained at the 6-month interval in 15 patients (Table 2, 3; Fig. 1).

Table 1. Descriptive statistics of patients' demographics and laboratory values. N = 20

Parameter	Min	Max	Mean	Median	SD
Age	40	77	63.2	62.5	9.698616
Height	158	183	167.4	166.5	6.612588
Weight	57	108	85.2	83	13.41091
BMI	21.2	38.3	30.35	30	4.130821
Waist circumference	72	126	106.15	107.5	13.14404
Systolic blood pressure	124	158	135.35	133	8.71342
Diastolic blood pressure	68	118	87.05	86.5	10.71877
ESR	3	31	11.25	9.5	7.765477
CRP	0.1	11.5	2.505	1.5	2.944975
Total cholesterol	2.54	8.03	5.6485	5.4	1.358282
HDL	1.03	2.63	1.6525	1.47	0.510942
LDL	0.8	5.45	3.3085	3.055	1.178024
Triglycerides	0.62	2.8	1.471	1.235	0.666719
Glucose	4.48	8.31	5.7385	5.41	1.093215
Glycated hemoglobin	4.4	7.9	5.895	5.75	0.817876
Insulin	2.2	39.6	12.5035	12.1	8.498746
HOMA index	0.43	10	3.212	2.84	2.216378
Uric acid	186	504	342.4	325.5	87.72349

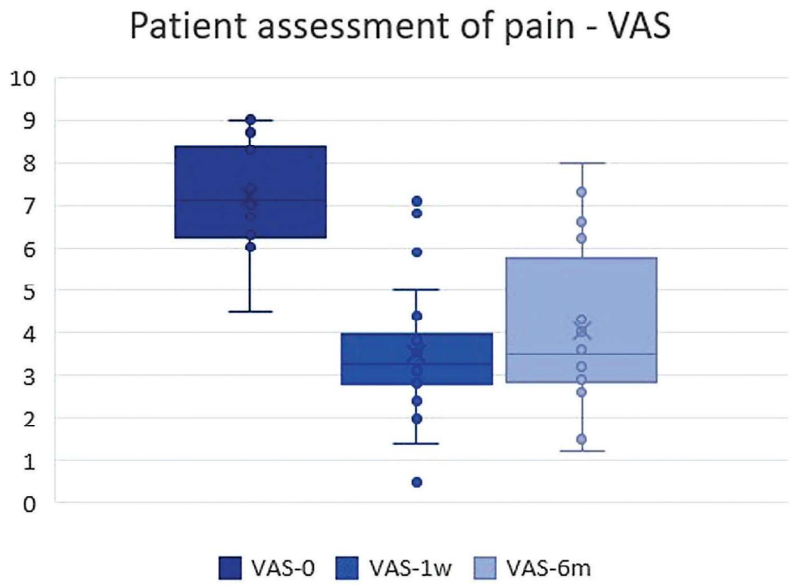

Fig. 1. Box plot displaying the results of the statistical analysis of patient assessment of pain on a visual analogue scale (VAS) ranging from 0 to 10 before treatment (VAS-0), 1 week post treatment (VAS-1w), and 6 months post treatment (VAS-6 m). N = 20

Table 2. Descriptive statistics of the parameter 'patient assessment of pain' by visual analogue scale, the minimal score being 0 – "complete lack of pain", and the maximum score being 10 – "worst possible pain". N = 20

Parameter	Min	Max	Mean	Median	SD
Patient assessment of pain – VAS, before treatment	4.5	9	7.18333	7.1	1.148786
Patient assessment of pain – VAS, 1 week post-treatment	0.5	7.1	3.49583	3.25	1.535232
Patient assessment of pain – VAS, 6 months post-treatment	1.2	8	4.04583	3.5	1.88287

Table 3. Tukey's honestly significant difference (HSD) test for multiple comparisons between patient assessment of pain before treatment (A), 1 week post-treatment (B) and 6 months post-treatment (C). N = 20

Treatments pair	Tukey HSD Q statistic	Tukey HSD p-value	Tukey HSD inference
A vs B	11.6432	0.0010053	significant
A vs C	9.9066	0.0010053	significant
B vs C	1.7366	0.4427591	insignificant

A similar tendency was noted in the WOMAC score (Table 4, 5; Fig. 2), indicating a significant impact on joint function.

Improvement was better in patients with lower KL scores and in those with associated synovial inflammation. Of the three subjects who did not improve, all had KL grade 3 KOA, and only one had associated synovial inflammation on musculoskeletal ultrasound. Of the two subjects who improved initially at week 1 and relapsed at 6 months, one was a patient who had received bilateral injections and relapsed in the right knee, which was scored as KL grade 3 and had no synovial inflammation, while the other was scored as KL grade 3 and had associated synovitis.

In all subjects, the intra-articular administration of ACS was well tolerated. Common mild adverse events included a slight but transient increase in pain after the first intra-articular administration of the serum, warmth, and redness in the injected joint, which rarely necessitated local application of ice, rest, or use of paracetamol.

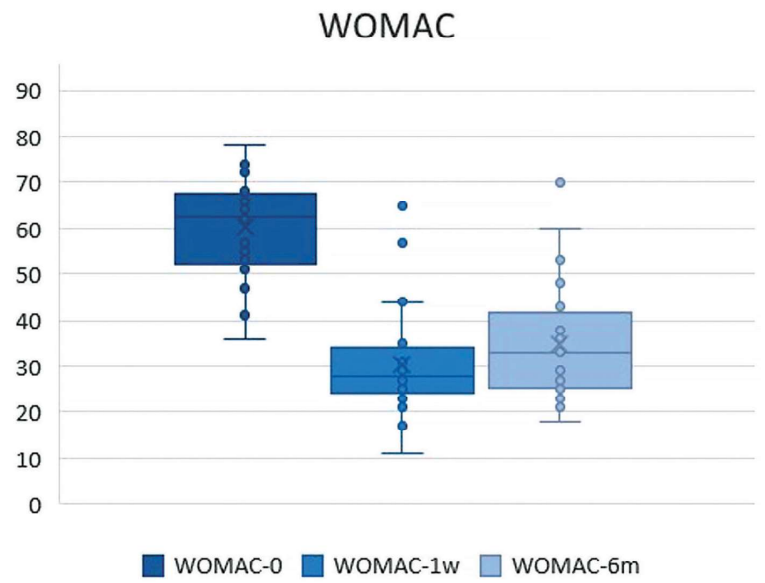

Fig. 2. Box plot displaying the results of the statistical analysis of knee pain and functional impairment assessed hrough WOMAC score, ranging from 0 to 96 before treatment (WOMAC-0), 1 week post-treatment (WOMAC-1w), and 6 months post-treatment (WOMAC-6m). N = 20

Table 4. Descriptive statistics of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) assessment of knee pain and functional impairment, the minimal score being 0 – "no symptoms at all", the maximum score being 96 – "worst possible symptoms". N = 20

Parameter	Min	Max	Mean	Median	SD
WOMAC, before treatment	36	78	60.45833	62.5	10.790411
WOMAC, 1 week post-treatment	11	65	30.20833	28	12.136826
WOMAC, 6 months post-treatment	18	70	34.91667	33	13.144404

Table 5. Tukey's honestly significant difference (HSD) test for multiple comparisons between Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) assessment of knee pain and functional impairment before treatment (A), 1 week post-treatment (B) and 6 months post-treatment (C). N = 20

Treatments pair	Tukey HSD Q statistic	Tukey HSD p-value	Tukey HSD inference
A vs B	12.2855	0.0010053	significant
A vs C	10.3733	0.0010053	significant
B vs C	1.9122	0.3727897	insignificant

DISCUSSION

In recent years, the role of obesity and metabolic syndrome in the pathogenesis of KOA has been extensively studied, leading to the proposal of a separate disease – obesity-related KOA. Obesity not only enhances the mechanical load on knees as weight-bearing joints, which promotes cartilage degradation, but also leads to an altered secretion of adipokines, generation of free fatty acids and reactive oxygen species, which ultimately create an inflammatory environment through up-regulation of a plethora of pro-inflammatory cytokines [26]. Furthermore, KOA has now been widely considered a "whole joint disease", which indicates no single involvement of the cartilage, but also of the synovium, subchondral bone, ligaments, and muscles [2]. This raises the question about the complex treatment of KOA in patients with obesity or metabolic syndrome.

ACS is a blood product rich in cytokines and growth factors released by blood cells upon stimulation with glass beads [18, 24]. Its main anti-inflammatory effect is attributed to the presence of interleukin-1 (IL-1) receptor antagonist (IL-1Ra) [8, 24, 25, 27]. IL-1 and especially its isoform IL-1β is a major driver of KOA pathogenesis by promoting cartilage degradation through the release of proteolytic enzymes by osteoblasts and synovial fibroblasts, mediating synovial inflammation and subchondral bone remodeling, and directly increasing joint pain by stimulating the production of neural growth factor (NGF) by synovial fibroblasts [28]. Incubation time in the preparation of ACS appears to be of crucial significance and varies between 1 and 24 h in published studies.

However, it has recently been suggested that an incubation time of 3 h provides the optimal ratio between IL-1Ra, growth factors such as platelet-derived growth factor (PDGF), and pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNFα), despite their concentrations all rising with longer incubation [8]. The ACS used herein, Sanakin®, was also incubated for 3 h. The concentration of IL-1Ra and PDGF also appears to be higher in ACS compared to PRP, which suggests better clinical efficacy [8].

The first system for ACS processing, branded as Orthokine®, was introduced in the late 1990s. The investigators established that incubation of blood with glass beads for 24 h at 37 °C significantly increased IL-1Ra production by macrophages, monocytes, and platelets [8, 29]. Auw Yang et al. [30] evaluated the efficacy of Orthokine® for the treatment of symptomatic KOA but found no difference in the WOMAC score compared to saline and, subsequently, did not recommend its use. Baltzer et al. [24] compared intra-articular injections of Orthokine® to hyaluronan (HA) and placebo in patients with KOA. In all three groups, the authors reported a reduction of pain and improvement of quality of life. However, ACS was superior in pain relief to both HA and saline. In conclusion, the authors proposed the use of ACS for the treatment of low- to moderate-grade, painful KOA. Another study by Vitali et al. [25] reported a statistically significant reduction in VAS pain and WOMAC score 6 months after a course of 4 weekly injections of ACS, with no major adverse events. A recent paper by Leone et al. [4] on 30 patients with KOA KL grade 1 to 3 who had failed PRP treatment showed an improvement in VAS and Lequesne scales in 67% of patients treated with intra-articular administration of ACS in the first month, which persisted till the first year of follow-up. Furthermore, the study established no relationship between the treatment outcome and KL grade. Finally, Shirokova et al. [31] and Cheng et al. [8] also suggested a higher pain management potential and better impact on moderate synovitis with ACS compared to PRP, thus highlighting a possible therapeutic "niche".

A recent paper by Lv et al. [32] suggested that KOA may be divided into four subtypes based on the predominant pathophysiological mechanism: 1) cartilage degradation-driven; 2) bone remodeling-driven; 3) pain-driven; 4) inflammation-driven. The authors suggested that different treatment modalities may have a superior clinical efficacy in a particular subtype and suggested that IL-1Ra may be beneficial in the inflammation-driven subtype. As outlined above, obesity and metabolic syndrome create a pro-inflammatory environment, while the increased levels of "harmful" adipokines, such as leptin and visfatin, directly upregulate IL-1β, thus promoting subsequent cartilage degradation, synovitis, subchondral bone remodeling, and increasing pain sensation [18]. In addition, subjects with obesity-related KOA usually suffer from concomitant cardiovascular, endocrinological, and renal pathologies, which may provide serious limitations to often-used treatment modalities such as NSAIDs and steroids. ACS, therefore, may be beneficial in obesity-related KOA, but no studies of its clinical efficacy and safety in this separate entity have been published so far.

In the present study, a statistically significant improvement in knee pain and function measured through VAS and WOMAC was reported in a cohort of patients with obesity-related KOA, which was already evident 1 week post-treatment and persisted for 6 months post-treatment. The treatment was well tolerated, and no major adverse events were reported. Better improvement was noted in patients with lower KL grade and in those with associated synovial inflammation. These results are on par with those previously reported in patients with KOA [8, 31] and are further supported by a study by Li et al. [33], who found that IL-1β levels in synovial fluid were elevated in patients with early compared to late stage KOA. Therefore, we propose that ACS is an effective and safe therapeutic alternative in subjects with obesity-related KOA, particularly in early stages (KL grade 2) and in cases of associated synovial inflammation, including in cases where traditional physical therapy may have failed [34].

Limitations of the present study exist and should be acknowledged. First, this was a prospective, open-label trial that did not include a placebo group for ethical reasons. Second, the therapeutic effect of ACS is directly proportional to the concentration of IL-1Ra in the serum; patients with lower concentrations may experience a less pronounced improvement and vice versa. No measurements of IL-1Ra concentration in the ACS were conducted prior to application. Third, we did not measure synovial levels of IL-1β, which may be beneficial before choosing which patients may be suitable for ACS therapy. Finally, the impact of ACS on the hyaline cartilage and any possible cartilage regeneration and/or decrease of cartilage degradation was not studied herein.

CONCLUSIONS

The intra-articular administration of ACS provides rapid improvement of pain and functional impairment in obesity-related KOA, which persists up to 6 months post-treatment. Patients who did not improve had a higher KL grade and usually no synovial inflammation, which supports the role of IL-1Ra found in ACS in improving inflammation-related symptoms of KOA. No major adverse events were

reported. Further research is needed to evaluate the potential role of ACS in promoting cartilage regeneration or decreasing the rate of its degradation.

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

Informed Consent from Participants: *Informed consent was obtained from all participants included in the study.*

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