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Prospective Short-Term Observational Study of Glucosamine Complex with Chondroprotectors Effect in Adults with Diagnosed Knee and/or Hip Osteoarthritis

Maija Puce[1*], Anna Medne-Simsone[2], Klinta Luize Sprudza[3]

[1]Dinas Puhartes Family Doctors Practice Ltd., Sigulda, Latvia
[2]Annas Mednes-Simsones Family Doctors Practice Ltd., Bauska, Latvia
[3]Faculty of Medicine, Riga Stradins University, Riga, Latvia
Email: *maija.viskere@gmail.com

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Abstract

Objective: Osteoarthritis (OA) of the knee and/or hip is a chronic degenerative disease that severely impacts quality of life. Current treatments, such as NSAIDs, provide only symptomatic relief and are associated with significant side effects. This study evaluates whether short-term supplementation with a glucosamine complex (glucosamine, chondroitin, hyaluronic acid, omega-3, type II collagen) can improve OA symptoms. Methods: A prospective observational study recruited 200 OA patients from family physician practices in Latvia. Patients were divided into 1) Study group (n = 100) receiving Artroveron® 5in1 COMPLEX WITH OMEGA-3 (Glucosamine hydrochloride 300 mg, Omega-3 fatty acids 100 mg, Chondroitin sulfate 50 mg, Hyaluronic acid 20 mg, Type II collagen 20 mg); 2) Control group (n = 100) receiving no chondroprotectors. Pain levels were assessed at baseline and after 30 days using: Western Ontario and McMaster Universities Arthritis Index (WOMAC), Visual Analogue Scale (VAS). Results: Study group (glucosamine complex) had a statistically significant reduction in pain scores compared to the control group ($p < 0.001$). WOMAC pain score decreased from 7.3 ± 3.8 to 6.0 ± 3.6 ($p < 0.001$). WOMAC stiffness score improved from 3.4 ± 1.7 to 2.6 ± 1.8 ($p < 0.001$). WOMAC difficulty score reduced from 26.6 ± 11.3 to 21.0 ± 11.5 ($p < 0.001$). VAS pain score decreased from 5.8 ± 1.6 to 4.9 ± 1.5 in the study group, compared to 4.8 ± 1.8 to 4.2 ± 2.0 in controls ($p < 0.001$). Conclusion: Short-term supplementation with Artroveron® 5in1 COMPLEX WITH OMEGA-3 significantly reduced OA pain and stiffness compared to untreated control group. These findings suggest that glucosamine supplementation may serve as

an effective alternative for OA symptom management.

Keywords

Knee Osteoarthritis, Chondroprotection, Glucosamine, Chondroitin, Omega-3 Fatty Acids, Hyaluronic Acid, Collagen Type 2

1. Introduction

Osteoarthritis (OA) is globally the most common form of arthritis and the leading cause of chronic disability among elderly [1]. The incidence of the disease is expected to increase with an aging population and obesity numbers that are constantly rising [2].

OA is the most prevalent joint disease characterized by progressive cartilage degeneration, changes in the subchondral bone, and chronic synovitis [3]. The progression of OA is slow and occurs over years and even decades. The prevalence of OA, particularly of the large weight-bearing joints such as the knee and hip, is predicted to grow therefore it is necessary to find a new approach to prevent or slow down the progression of OA [4].

Numerous treatment methods have been evaluated to improve pain associated with OA. Nowadays therapy options range from pharmacological and non-pharmacological treatments [2]. Among pharmacological therapies, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are most used treatment options for OA because of their well-established effectiveness. However, they work as symptomatic treatments without offering disease modification of OA. Unfortunately, they increase the risk of the side-effects that affect the gastrointestinal and, in some cases, cardiovascular system. Therefore, recently much attention has been paid to other treatment options, which can enhance the clinical symptoms of OA with better safety profile and tolerability, such as symptomatic slow-acting drugs (SYSADOAs)—chondroprotectors [4] that have been shown to reduce the symptoms of pain and functional impairment, with some additional evidence of a disease-modifying effect in the long-term [5]. SYSADOA like glucosamine and chondroitin sulfate are included in The European Society for Clinical and Economic Aspects of Osteoporosis, OA and Musculoskeletal Diseases (ESCEO) Guidelines as the first-line treatment for non-surgical treatment for knee OA [6]. A randomized, double-blind, double-masked, parallel group clinical study examined supplementation, containing glucosamine, chondroitin, hyaluronic acid (HA), type II collagen, and omega-3 fatty acids, for knee and/or hip OA patients over one month. During the study period, statistically significant WOMAC scores and VAS pain score improvements ($p < 0.001$) were observed. Equally important, not only statistical significance was highlighted but also in a clinically relevant context symptom relief was discovered. In other words, a positive synergic effect could be achieved due to a combination of a variety of bioactive agents (e.g. glucosamine, HA, omega-3 fatty acids). Evidently, no complications were detected,

and a promised safety level was observed [7]. A recently conducted overview of guidelines, meta-analyses and clinical trials suggested that glucosamine sulfate and chondroitin sulfate seem to interact simultaneously improving statistically and clinically significant results in pain, stiffness, and physical function. Both of the components are medically safe, moreover compared with NSAIDs, pointing out the ability for long-term use in mild-to-moderate OA disease. Still, a detailed standardization in component formulations and revised patient selection by subgroups might be crucial for outcome evaluation. This formulated approach has the potential to be considered for patients with knee OA, focusing on those, who are seeking an alternative to NSAIDs or are at risk of experiencing adverse drug reactions [8].

Glucosamine is a derivative of cellular glucose metabolism. It is also a component of glycosaminoglycans and proteoglycans in the cartilage matrix that covers the ends of bones, and HA, which is part of the synovial fluid of the joint. Since glucosamine is part of the cartilage matrix of joint tissue, it has been believed for many years that its use can lead to symptomatic relief in OA patients thereby reducing pain and disability [9].

Chondroitin plays a key role in joint and bone metabolism, controlling cartilage matrix integrity, bone mineralization and together with glucosamine result in the activation of a much larger number of matrix proteins than either preparation alone. A clinically significant fact is that both chondroitin and glucosamine are natural, endogenous components of bone tissue and articular cartilage, so the use of both active ingredients is biocompatible and produces many elements of cartilage protection [10]-[12].

Another well-known chondroprotector is hyaluronic acid (HA) which is a glycosaminoglycan that has effects on chondrocytes/synoviocytes and the production of transforming growth factor (TGF)-β, fibroblast-derived growth factor (FGF) and insulin-like growth factor (IGF)-1. Histological evidence suggests that HA prevents cartilage degradation and can promote its regeneration [10] [13].

Collagen is the most abundant protein in the extracellular matrix and is effective in improving the functional state of the joints and reducing pain, it also has a chondroprotective effect. Given its symptomatic and structural effects on cartilage, collagen is believed to be a potential alternative for the treatment of OA [14].

Omega-3 polyunsaturated fatty acids are recognized for their anti-inflammatory properties. The omega-3 fatty acids docosahexaenoic acid (DHA) is an agonist of G-protein coupled receptor 120 (GPR120), which has a leading role in regulating free fatty acid and inhibiting inflammation. GPR120 may be an important mediator of inflammation during the development of OA with DHA. Evidence suggests that Omega-3 may protect against cartilage loss in OA and can reduce inflammatory markers within the joint synovial fluid [15].

While chondroprotectors have been studied individually for their role in OA management, this paper focuses on a one-month intervention with chondroprotective agents in OA patients. This paper aims to examine whether a combination

of glucosamine, chondroitin, HA, omega-3, and type II collagen could be used daily as life quality improving supplementation. In a major advance, a study demonstrated the benefits of glucosamine combined with chondroitin sulfate in knee OA management. The work has led to the conclusion that the combination gains an advantage in the field of OA treatment [16].

2. Materials and Methods

The study was conducted according to the PICOS criteria:

- Population (P): 100 glucosamine complex (GC) and 100 control group (CG) adults aged > 33 years within the practice of a family doctor diagnosed with knee and/or hip OA.
- Intervention (I): one capsule per os of glucosamine complex 2 - 3 times per day after a meal for four weeks daily.
- Comparison (C): CG.
- Outcome (O): Western Ontario and McMaster Universities OA Index (WOMAC scores) and Visual Analogue Scale (VAS) pain score questionnaire before and after the study.
- Study design (S): interventional clinical trial with two groups (glucosamine complex and control group).
- Experiments were conducted according to the Research Ethics Policy, University of Latvia.

Inclusion criteria:

- Inclusion criteria are patients with prolonged joint pain who have been diagnosed with knee and/or hip OA.
- Patients diagnosed with knee and/or hip OA are not using any glucosamine containing complex supplements or OTCs.

Exclusion criteria:

- Patient does not have OA and in the period of using Artroveron® 5in1 COMPLEX WITH OMEGA-3 is using any other glucosamine or chondroprotector-containing supplement or OTCs.
- Patients might be excluded if they did not use the particular glucosamine-containing complex or had any allergies to specific components: glucosamine, chondroitin, HA, collagen or omega-3 or will discontinue the usage of the glucosamine-containing supplement.

Even though participants were not continuously monitored for lifestyle factors and adherence, they were instructed to maintain their usual routines throughout the study period. This represents a limitation, as variations in physical activity, diet, or concurrent therapies may have influenced the outcomes.

Statistical Analysis

The initial results were clustered and coded in the MS Excel spreadsheet. Each research group—Glucosamine complex (GC) and control group (CG)—included

100 patients for WOMAC and VAS assessments. No data was excluded. The resulting outcomes of statistical data processing in IBM Statistical Package of Social Sciences 29.0.0.0. (SPSS) were in the form of descriptive statistics for baseline information (gender, age, body mass index (BMI) distribution; pain in years and medication intake; affected joints—type and number of affected joints), to evaluate WOMAC scores and VAS pain scores. Nonparametric Correlations (Spearman's correlation) (number of affected joints and BMI; pain in years and patient age). Correlation is significant at 0.01 level (2-tailed).

Independent Samples T Test was used to compare the mean results of GC and CG differences between patient age, how long the pain persists and medication intake; differences in WOMAC scores and VAS pain scores; and differences between VAS and medication intake. Statistical significance was defined as a two-sided p-values of less than < 0.050. Moreover, a Paired-Samples T Test was performed to detect the data significance for GC and CG after one month of the study period.

To investigate the differences between GC and CG Nonparametric Test: Related Samples Wilcoxon matched-pair signed-rank (2 samples) was applied. Statistically significant Two-Sided p difference refers to the level of <0.050. Frequencies of descriptive statistics were adopted to determine the mean differences.

3. Results

This comparative study evaluated the response of OA patients' reaction to a complex containing glucosamine, chondroitin sulphate, HA, type II collagen, omega-3 intake, and control.

Table 1 refers to the descriptive statistics. In the study were enrolled 200 patients: 100 WOMAC/VAS GC and 100 WOMAC/VAS CG. During the four weeks of the study period, no patients were lost to follow-up over the course. The GC population consisted of 63 (63%) females and 37 (37%) males compared with CG – 64 (64%) females and 36 (36%) males. The mean GC patients age was 63.9 (11.6) in the range of 33 - 88. CG represented the patients age parameters with a mean of 62.3 (10.1) in the range of 40 - 91. The medians of the groups are equal to 62.

Body mass index (BMI) in GC was defined by a mean of 29.7 (4.8), with a median of 29.2 in the range of 20.3 - 41.4. In Comparison CG reported BMI by a mean of 26.8 (4.7), with a median of 26.3 in the range of 17.4 - 41. Furthermore, the BMI distribution for GC indicates 14% of patients with normal weight, 44% with overweight, and 42% obesity compared with CG at the levels of 39%, 35%, and 26%.

The mean duration for GC OA pain in years indicates 8.8 (5.9), with a median of 8 in the range of 1 - 25. On the contrary, CG pain duration was defined by a mean of 5.8 (5.2) years, with a median of 5.2 in the range of 0-22.

Medication intake (incl. NSAID's regularly/irregularly, opioids, collagen, muscle relaxants, topical ointments, gels, a structured analog of gamma amino butyric acid) reported 63% of the GC and 76% of the CG.

WOMAC and VAS baseline scores were summarized, using descriptive statistics (Table 2).

Table 1. Baseline characteristics of the patients.

	WOMAC/VAS glucosamine complex (N = 100)	WOMAC/VAS control group (N = 100)
Gender (%)		
Female	63	64
Male	37	36
Mean (SD*) age (years)	63.9 (11.6)	62.3 (10.1)
Median	62	62
Range	33 - 88	40-91
Mean (SD) BMI (kg/m^2)	29.7 (4.8)	26.8 (4.7)
Median	29.2	26.3
Range	20.3-41.4	17.4 - 41
BMI distribution** (%)		
Normal weight	14	39
Overweight	44	35
Obesity	42	26
How long the pain persists (years)		
Mean (SD)	8.8 (5.9)	5.8 (5.2)
Median	8	5.2
Range	1-25	0-22
Medication intake (incl. NSAID's) (%)	63	76
No medication intake	37	24

Table 2. Baseline WOMAC scores (0 = none; 4 = extreme) and VAS pain score (0 = no pain; 10 = hurts worst) (N = 200).

	Glucosamine complex (N = 100)	Control group (N = 100)
WOMAC		
Pain score		
Mean (SD)	7.3 (3.8)	6 (4)
Median	7	5
Range	1 - 15	1 - 20
Stiffness score		
Mean (SD)	3.4 (1.7)	2.4 (2)
Median	3	2
Range	0 - 6	0 - 7

Continued

Difficulties score		
Mean (SD)	26.6 (11.3)	22.2 (14)
Median	27	19
Range	6 - 60	3 - 67
VAS		
Mean (SD)	5.8 (1.6)	4.8 (1.8)
Median	6	4.5
Range	3-9	2-8

Glucosamine supplementation-related locations of the OA were noted. In GC enrolled patients reported (Figure 1): right hip 54%, left hip 54%, right knee 72%, and left knee 67%. Compared with CG proportions of affected joints were (Figure 2): right hip 51%, left hip 47%, right knee 47%, and left knee 47%.

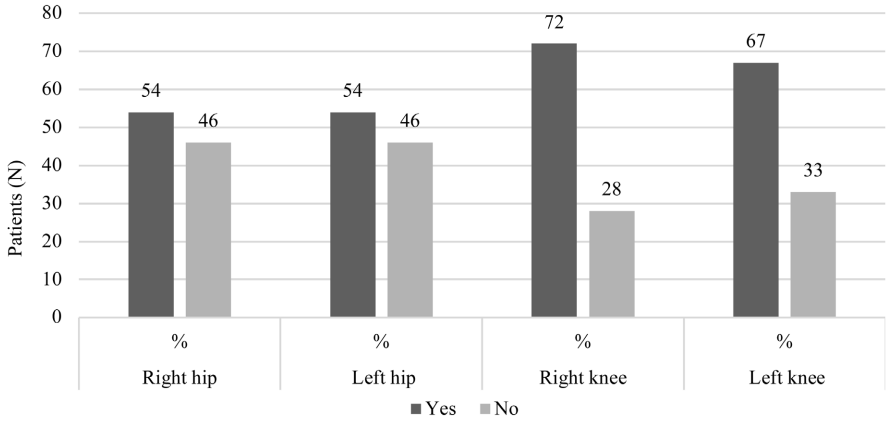

Figure 1. Affected joints—glucosamine complex (N = 100)

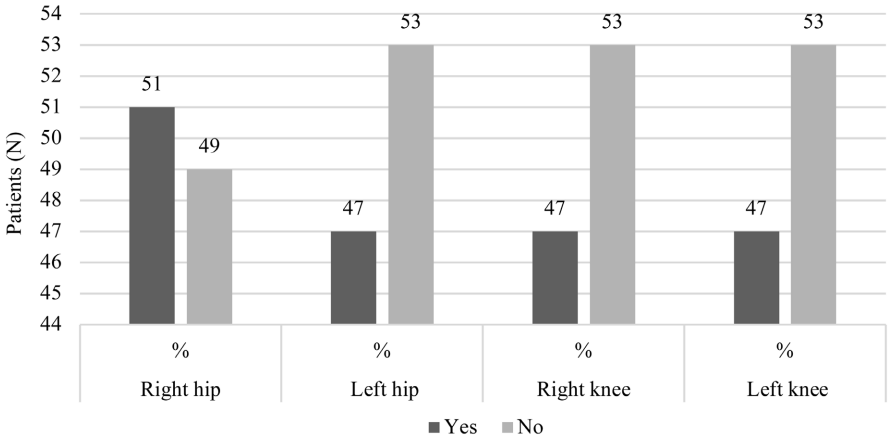

Figure 2. Affected joints—control group (N = 100).

Results of the relationship between number of affected joints and BMI at baseline (Figure 3) presented a weakly statistically significant correlation coefficient

(r = 0.163). An exponential relationship was indicated between how long the pain persists and age at baseline (Figure 4), with a moderately statistically significant correlation coefficient (r = 0.562).

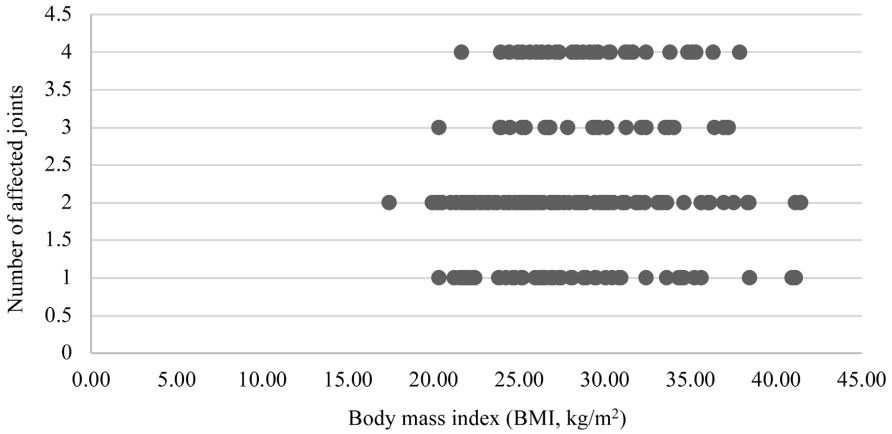

Figure 3. Correlation between the number of affected joints and BMI at baseline (N = 200).

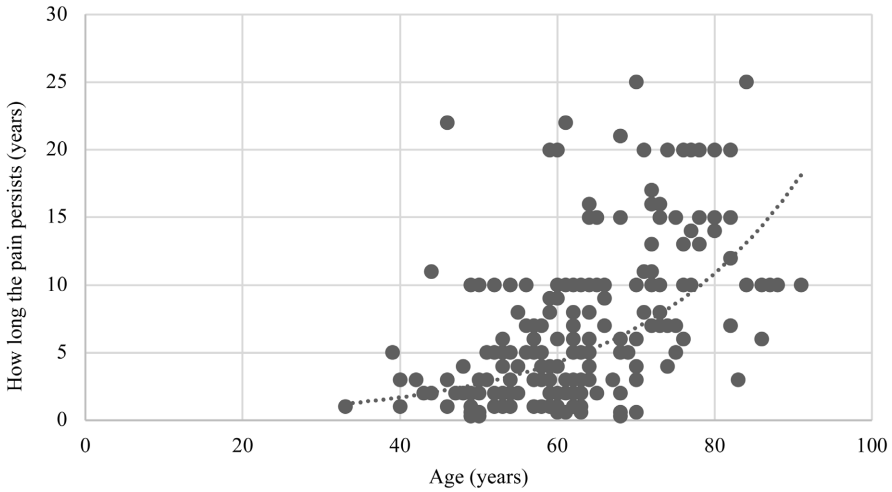

Figure 4. Correlation between how long the pain persists and the age at baseline (N = 200).

The GC showed a statistically significant difference ($p < 0.001$) between age, how long the pain persists, and medication intake compared with CG no statistically significant differences were revealed between age and medication intake ($p = 0.229$), how long the pain persists and medication intake ($p = 0.288$) (Table 3).

WOMAC

Assessment of efficacy included the WOMAC OA Index. This is a validated, self-administered, 24-item questionnaire for patients with OA of the hip and/or knee. WOMAC subscales included administration of pain, stiffness, and difficulty: pain when walking, stair climbing, nocturnal, rest, weight-bearing; stiffness in the morning and the evening; difficulty when descending stairs, ascending stairs, rising from sitting, sitting, standing, bending to the floor, walking on flat, getting

in/out of car, going shopping, putting socks, rising from bed, taking off socks, lying in bed, getting in/out of bath, getting on/off toilet, performing light and heavy domestic duties.

200 patients (100%) completed the full WOMAC scores and VAS pain score. No withdrawal rate appeared. The reduction was calculated based on the mean difference before and after exposure. Results illustrate the mean value with standard deviation.

Table 3. Group differences between age, how long the pain persists and medication intake at baseline.

WOMAC/VAS glucosamine complex (N = 100)			
	Medication intake (incl. NSAID's) (%)	Average	p
Age (years)			
Yes (n-value)	63	68 (10.2)	<0.001
No (n-value)	37	56.8 (10.5)	
How long the pain persists (years)			
Yes (n-value)	63	11.2 (5.9)	<0.001
No (n-value)	37	4.7 (2.8)	
	WOMAC/VAS control group (N = 100)		
	Medication intake (incl. NSAID's) (%)	Average	Significance (two-sided p)
Age (years)			
Yes (n-value)	76	63 (10.5)	0.229
No (n-value)	24	60.1 (8.6)	
How long the pain persists (years)			
Yes (n-value)	76	6.1 (4.8)	0.288
No (n-value)	24	4.8 (6.4)	

Figure 5 illustrates the changes in WOMAC scores during the study period. The change from baseline to week four resulted of the GC WOMAC scores in the reductions of pain −1.3 (1.6), stiffness −0.8 (0.8), and difficulties −5.6 (4.6) compared with CG the reductions in the three sectors were −0.7 (1.3), −0.3 (0.8), and −2.7 (4.4) respectively. Among one joint affected patients of the GC analysis reported differences of pain −0.7 (0.9), stiffness −0.8 (0.6), and difficulties −4.3 (3.8) in contrast CG were −0.7 (1.1), −0.3 (0.6), and −3.3 (4.1); in two joints affected patients of the GC analysis reported differences of pain −1.8 (2.2), stiffness −0.9 (0.8), and difficulties −6.2 (5.3) compared with CG: −0.8 (1.5), −0.2 (0.7), and −2.4 (4.2); in three joints affected patients of the GC were the results of pain −0.9 (0.9), stiffness −0.7 (0.7), and difficulties −4.2 (3.6) compared with CG the reduction in

the three sectors were −0.7 (1.5), −1.3 (1.2), and −6.7 (7.0); in four joints affected patients of the GC analysis reported reductions of pain −1.3 (1.2), stiffness −0.7 (1.0), and difficulties −6.7 (4.4). The CG presented an increase in the three sectors 0.1 (1.3), 0.2 (0.4), and 0.1 (2.6), respectively.

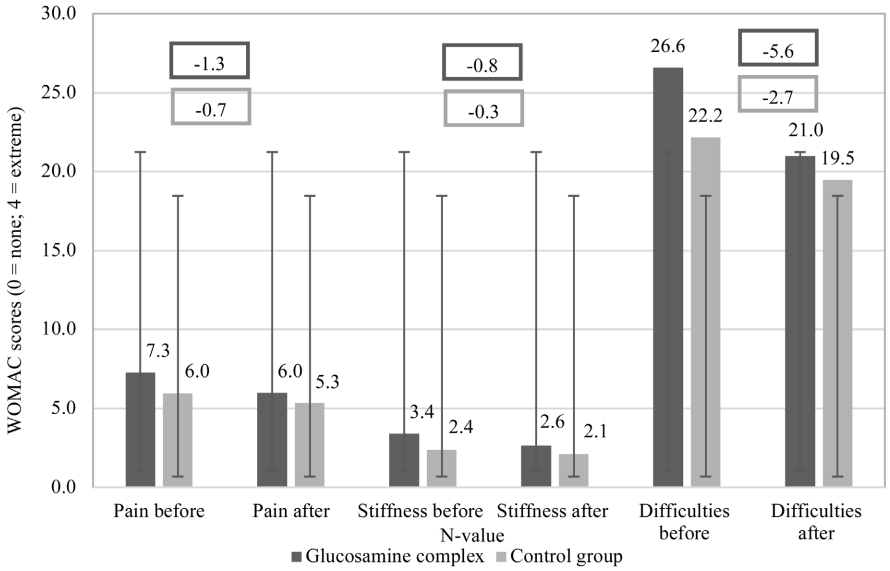

Figure 5. Comparison of WOMAC scores at baseline and after one month for glucosamine complex and control group (N = 200).

Table 4. Group differences in WOMAC scores (0 = none; 4 = extreme).

Glucosamine complex (N = 100)						
Gender (%)	Average pain	p	Average stiff.	p	Average diff.	p
F-63	−1.1 (1.1)	0.115	−0.7 (0.9)	0.694	−4.8 (3.8)	0.019
M-37	−1.6 (2.3)		−0.8 (0.7)		−7 (5.4)	
Control group (N = 100)						
F-64	−0.6 (1.3)	0.726	−0.2 (0.7)	0.655	−2.7 (4.1)	0.885
M-36	−0.7 (1.3)		−0.3 (0.9)		−2.8 (5)	

Furthermore, improvements from baseline through one month were statistically evaluated (Table 4). Results for WOMAC pain scores in Glucosamine complex group in female (63%) and male (37%) populations on average were −1.1 (1.1) and −1.6 (2.3) ($p = 0.115$), for WOMAC stiffness score average of −0.7 (0.9) and −0.8 (0.7) ($p = 0.694$), and for WOMAC difficulties score average of −4.8 (3.8) and −7 (5.4) ($p = 0.019$). These results thus need to be interpreted with care. Potential confounding factors are considered: degenerative age-related musculoskeletal and hormonal changes, involvement in physical activities, and other comorbidities could influence pain perception and respond to GC. Furthermore, due to the smaller male group (37%) a higher variability in terms of standard deviations is seen. Compared with CG improvements were from baseline in the female (64%)

and male (36%) populations an average of −0.6 (1.3) and −0.7 (1.3) for WOMAC pain score (p = 0.726), an average of −0.2 (0.7) and −0.3 (0.9) for WOMAC stiffness score (p = 0.655), and an average of −2.7 (4.1) and −2.8 (5.0) for WOMAC difficulties score (p = 0.885). There were no statistically significant differences between gender populations and groups.

Tables 5-9 strengthen the position that statistically significant differences were observed among patients in the GC group.

VAS

The Visual Analogue Scale was introduced in the 1920s for the evaluation of pain, quality of life, and anxiety. It is presented in the form of a 0.1-m length line divided into ten equal sections, with pain level in words such as "no pain" and "worst pain imaginable", Wong-Baker emotional pictograms that characterize pain level, and activity tolerance scale from "no pain" till "bed regime needed" [17].

Assessment of efficacy (0.1-m VAS) shows the patient's objective pain scores at the baseline and after treatment (Figure 6).

General regression for both groups was noted: −1.0 (0.9) for GC and −0.6 (1.0) for CG. The results indicate no statistically significant difference in gender populations of GC (F-63%, M-37%) and CG (F-64%, M-36%). The current study reports a regression of pain in female and male populations −1.1 (0.9) and −0.8 (0.8) (p = 0.067), −0.6 (0.9) and −0.6 (1.2) (p = 0.961) respectively. Table 10 summarizes the data on VAS pain score at baseline and after one month.

The study group differences between VAS and medication intake were evaluated (Table 10). 63% of patients in the GC used medications including NSAIDs during the study and reported a mean pain reduction of −1.1 (0.9). In contrast, 37% of GC patients did not use medications and reached a positive benefit of −0.8 (0.8). There was no statistically significant group difference (p = 0.173). On the other hand, CG indicated equally decreased rates in subgroups depending on medication intake −0.6 (1.0) (p = 0.971).

Table 5. WOMAC scores at baseline and after one month in glucosamine complex and control groups (N = 200).

	Glucosamine complex (N = 100)			
	WOMAC before (mean (SD))	WOMAC after (mean (SD))	Mean difference (mean (SD))	p
Pain	7.3 (3.8)	6.0 (3.6)	1.3 (1.6)	
Stiffness	3.4 (1.7)	2.6 (1.8)	0.8 (0.8)	<0.001
Difficulty	26.6 (11.3)	21.0 (11.5)	5.6 (4.6)	
	Control group (N = 100)			
Pain	6.0 (4.0)	5.3 (4.1)	0.7 (1.3)	
Stiffness	2.4 (2.0)	2.1 (1.9)	0.3 (0.8)	<0.001
Difficulty	22.2 (14.0)	19.5 (14.4)	2.7 (4.4)	

Table 6. WOMAC Scores at baseline and after one month in glucosamine complex and control groups in patients with one affected joint (N = 52).

Glucosamine complex (N = 18)				
	WOMAC before (mean (SD))	WOMAC after (mean (SD))	Mean difference (mean (SD))	p
Pain	4.4 (2.1)	3.7 (2)	0.7 (0.9)	0.003
Stiffness	2.2 (1.6)	1.4 (1.5)	0.8 (0.6)	<0.001
Difficulty	19.6 (7.7)	15.2 (7.4)	4.3 (3.8)	
Control group (N = 34)				
Pain	5.2 (3.9)	4.4 (4.1)	0.7 (1.1)	<0.001
Stiffness	2.0 (1.8)	1.7 (1.7)	0.3 (0.6)	0.006
Difficulty	20.0 (13.8)	16.8 (14.8)	3.3 (4.1)	<0.001

Table 7. WOMAC Scores at baseline and after one month in glucosamine complex and control groups in patients with two affected joints (N = 90).

Glucosamine complex (N = 40)				
	WOMAC before (mean (SD))	WOMAC after (mean (SD))	Mean difference (mean (SD))	p
Pain	6.8 (4)	5.0 (3.6)	1.8 (2.2)	<0.001
Stiffness	3.0 (1.6)	2.1 (1.7)	0.9 (0.8)	
Difficulty	24.2 (11)	18.0 (11.2)	6.2 (5.3)	
Control group (N = 50)				
Pain	5.6 (3.6)	4.8 (3.5)	0.8 (1.5)	<0.001
Stiffness	2.1 (1.9)	1.9 (1.9)	0.2 (0.7)	0.083
Difficulty	20.6 (13.5)	18.2 (13.2)	2.4 (4.2)	<0.001

Table 8. WOMAC scores at baseline and after one month in glucosamine complex and control groups in patients with three affected joints (N = 25).

Glucosamine complex (N = 19)				
	WOMAC before (mean (SD))	WOMAC after (mean (SD))	Mean difference (mean (SD))	p
Pain	7.1 (2.9)	6.2 (2.8)	0.9 (0.9)	<0.001
Stiffness	3.9 (1.3)	3.3 (1.4)	0.7 (0.7)	
Difficulty	25.7 (9.7)	21.5 (10.1)	4.2 (3.6)	
Control group (N = 6)				
Pain	8.2 (3.5)	7.5 (3.7)	0.7 (1.5)	0.328
Stiffness	4.2 (1.5)	2.8 (2.2)	1.3 (1.2)	0.043
Difficulty	31.5 (12.8)	24.8 (13.7)	6.7 (7.0)	0.068

Table 9. WOMAC scores at baseline and after one month in glucosamine complex and control groups in patients with four affected joints (N = 33)

	WOMAC before (mean (SD))	WOMAC after (mean (SD))	Mean difference (mean (SD))	p
Glucosamine complex (N = 23)				
Pain	10.5 (2.9)	9.2 (2.8)	1.3 (1.2)	<0.001
Stiffness	4.6 (1.1)	3.9 (1.5)	0.7 (1)	0.002
Difficulty	37 (8.4)	30.2 (10.8)	6.7 (4.4)	<0.001
Control group (N = 10)				
Pain	9.6 (4.1)	9.7 (4.5)	0.1 (1.3)	0.811
Stiffness	4.1 (1.4)	4.3 (1.5)	0.2 (0.4)	0.168
Difficulty	31.9 (13.2)	32 (13.8)	0.1 (2.6)	0.904

Table 10. VAS pain score at baseline and after one month (N = 200).

	VAS before (mean (SD))	VAS after (mean (SD))	Mean difference (mean (SD))	p
Glucosamine complex (N = 100)				
VAS (N = 100)	5.8 (1.6)	4.9 (1.5)	1.0 (0.9)	
Female (N = 63)	6.0 (1.6)	5.0 (1.6)	1.0 (0.8)	<0.001
Male (N = 37)	5.6 (1.5)	4.7 (1.5)	0.9 (1.0)	
Control group (N = 100)				
VAS (N = 100)	4.8 (1.8)	4.2 (2.0)	0.6 (1.0)	<0.001
Female (N = 64)	4.6 (1.8)	4 (1.9)	0.6 (1.0)	
Male (N = 36)	5.1 (1.6)	4.5 (2.0)	0.6 (1.1)	0.004

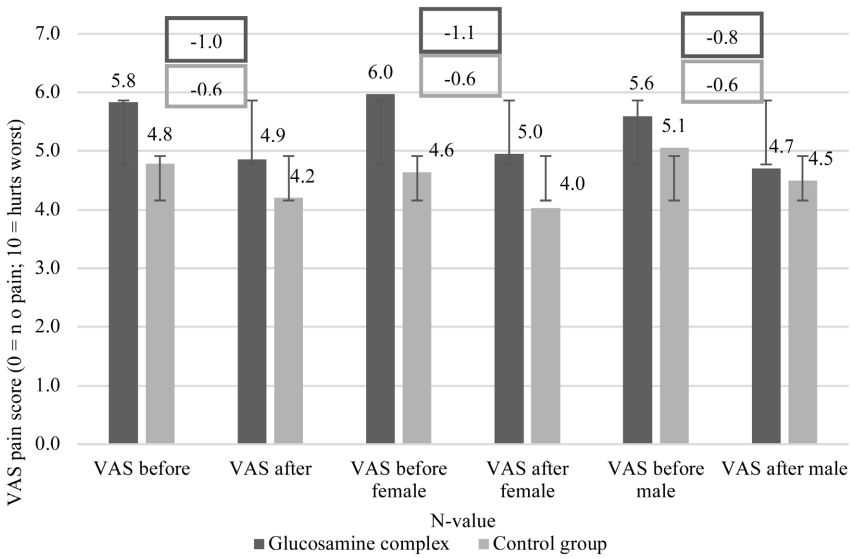

Figure 6. Average VAS pain score at baseline and after one month for glucosamine complex and control group (N = 200).

4. Discussion

The most remarkable results between the groups to emerge from the data is that the WOMAC difficulties subscale confirms statistically significant differences (**Table 4**). In addition, significant differences between age, pain in years, and medication intake in the GC in contrast to the CG were identified (**Table 3**).

Further analyses showed these results are significant at GC's WOMAC pain, stiffness, and difficulty levels. The mean negative differences for WOMAC pain, stiffness, and difficulty have been obtained at the levels of 1.3 (1.6), 0.8 (0.8), and 5.6 (4.6), respectively (**Table 5**). A decline of the WOMAC pain score from 7.3 to 6.0 highlights the mean improvement of 1.3 values. It has been suggested that a minimum clinically important difference (MCID) regarding pain is 1 - 2 values, considering the baseline severity. Moreover, a fall of the WOMAC stiffness score from 3.4 to 2.6 also indicates symptom relief. Taking together, these changes illustrate a reduction in daily discomfort, which may lead to increased involvement in activities [18]. The WOMAC difficulties score resulted from 26.6 to 21.0 (−5.6). More recent evidence proposes that the MCID for the WOMAC difficulties subscale seems to be 9 points. Nevertheless, improvements indicate notable changes in patients' functional gains-improved mobility and reduced need for assistance [19]. Visual analogue scale reduction has been indicated as being clinically relevant at the level of 10-cm (1 point). The changes were observed as follows 0.9 and 0.6 for the GC and CG, respectively. These results proposed a reduction in pain intensity, enhancing sleep, mood, and activity [20]. Another systematic review and meta-analysis stated that *per os* chondroitin suggests a higher effectiveness than placebo in pain reduction and improving physical ability in OA patients. Moreover, only glucosamine indicated a statistical difference compared with placebo [4]. Various combinations of glucosamine and chondroitin with additional components were investigated. Glucosamine with omega-3 fatty acids and glucosamine with *ibuprofenum* were associated with significant reduction in pain compared with placebo. Nevertheless, further research must be considered. Finally, a personal approach to OA management is recommended [21].

A group of researchers conducted experiments on glucosamine and HA recently. They concluded that co-administration enhances pain relief, improves joint function, and decreases OA progression. Monotherapy might be less effective in contrast to combination [22]. Recent findings regarding chondroprotective components have led to a deeper understanding of the action mechanisms. Glucosamine and chondroitin sulfate are key components of cartilage and synovial fluid. These components are involved in structure- and symptom-modifying mechanisms. For example, the synthesis of collagen and proteoglycans is stimulated, and inflammatory and catabolic processes are inhibited. Vital to mention is that oxidative stress might induce chondrocyte apoptosis and protection is provided by the chondroprotectors. A decline of pain and inflammation substances seems to be influenced by the reduction of nitric oxide (NO) and prostaglandin

E_2 (PGE_2). Omega-3 polyunsaturated fatty acids, such as linolenic acid and eicosapentaenoic acid (EPA), found in e.g. walnut, flaxseed, and fish oil, have also beneficial characteristics: reduction of pro-inflammatory cytokines and cartilage-degrading enzymes. In summary, a combination of glucosamine sulfate and omega-3 fatty acids resulted in WOMAC scores therapy success—52.9% *versus* 37.9% without omega-3 fatty acids. Additionally, OA symptoms such as joint stiffness or joint pain decreased at week 13 and continued to decline from 48.5% to 55.5% as compared with 41.7% to 55.3% in the CG [23].

Notwithstanding the fact that pharmacologic therapy seems to be not disease-modifying, it is recommended to use during symptomatic periods. In the ESCEO guidelines, first-line treatments of OA uncover patient education, exercises, pharmaceutical-grade glucosamine sulfate and/or chondroitin sulfate, symptomatic paracetamol (≤3 g/d), and topical NSAIDs in case of lasting disease. It is proposed to examine the effects of symptomatic slow-acting drugs for OA (SYSADOAs), referring to glucosamine and chondroitin sulfate. Moreover, the consensus points up that glucosamine and chondroitin sulfate are investigated as background therapy to NSAIDs. Neither avocado soybean unsaponifiable nor diacerein appears to corroborate the recommendations [6].

In their cutting-edge paper on the landmark GAIT trial (Glucosamine/Chondroitin Arthritis Intervention) of 2006, Clegg *et al.* observed a response to glucosamine, chondroitin sulfate, the combination of them, celecoxib, and oral control. These tests revealed a sevenfold positive effect of the treatment group regarding WOMAC in contrast to the placebo group where the effect was up to 60 percent [24]. Moreover, the Glucosamine/chondroitin Arthritis Intervention Trial deduced WOMAC score reduction ($p = 0.002$) in the moderate-to-severe OA group with the treatment of glucosamine HCl plus chondroitin sulfate from baseline to week 24 [9].

Another point of view was observed in the study by Čeh and Šarabon where chondroprotective complex in combination with exercise in adults with knee OA was assessed. The performed meta-analysis indicated no statistically significant pain decrease through WOMAC scores (no heterogeneity) and VAS pain score (moderate heterogeneity) by the treatment of glucosamine in combination with exercise and exercise-only group. Physical function was assessed in three included studies through WOMAC with no statistically significant improvements (considerable heterogeneity). Also, there was no statistically significant reduction of stiffness (very high heterogeneity). Effects of adding glucosamine or glucosamine combined with chondroitin to exercise on pain and physical function in adults with knee OA: a systematic review and meta-analysis [25]. To sum up, there appears to be an untransparent border between exercise, chondroprotective supplementation, and pain relief therapy evidence. This interaction might be investigated by differing each variable as a disease-modifying factor. Furthermore, patients undergo symptomatic medication in acute conditions whereas exercise therapy's primary goal is continuous. It is worthwhile noting that glucosamine

and chondroitin sulfate background supplementation might be beneficial in a long-term assessment.

The mean negative differences for VAS pain score in GC were obtained at the level of 1.0 (0.9). The performed analysis demonstrated also the impact of the glucosamine complex on the female and male populations (**Table 10**).

Other researchers have sounded a note of caution regarding VAS pain score. Scientists have seen the VAS pain score as a pre-evaluation of the study population to make the methodology more standardized. Moreover, confirmation of unsatisfactory pain relief therapy, including exercises and NSAID's, is a remarkable factor that influences further steps in the participants eligibility [26]. VAS as an ordinal score does not undergo the benefits of an interval or ratio scale. Furthermore, nonparametric statistics are appropriate for analyzing results gained through the VAS pain score. Challenges regarding longer time for patients, choosing the answer (compared to a Likert scale), lower compliance rates, errors made by the clinicians, and data clarification must be considered [27].

In the literature, there are several examples of factors, investigating response to therapy. It is well-known that pain has a multifactorial etiology. More details can be found in different stages of OA, involving multiple anatomical structures (periarticular muscles, ligaments, synovium, and bone). Moreover, environmental and psychosocial aspects seem to be essential [28].

Another aspect relates to the correlation between radiographic findings and the severity of symptoms. Kim and co-workers presented that a small minority of X-rays findings confirmed hip pain, and symptomatic disease was seen due to radiographic imaging [29].

Specifically, to evaluate possible anatomical worsening of cartilage damage induced by OA, characteristic findings might be crucial: hypoechoic lesions viewed on diagnostic ultrasonography (US) in the form of noncontinuous fibers, lack of continuity of the plantar fascia, and disruption or edema in the surrounding tissue [30].

An additional longitudinal analysis concentrated on OA-associated knee manifestation and the benefits of micronutrient supplementation. A knee structures assessments were performed. The assessment was based on a 1.5 T whole-body magnetic resonance imaging (MRI) at baseline and after two years. Radiological imaging showed two sequences: sagittal T1-weighted fat-saturated spoiled gradient echo and sagittal T2-weighted fat-saturated fast spin echo. Morphological structures such as cartilage volume, cartilage defect, bone marrow lesions (BML), and effusion-synovitis volume were evaluated [31]. To demonstrate a specified disease severity characterizing view, radiological methods such as US, X-rays, and MRT could be applied together with VAS pain score.

Additionally in terms of objectivity clinical tests are recommended. Patient performance has been widely investigated due to physical tests such as timed up-and-go, the 40-meter walk tests, the 30-second chair test, the stair-climb test, and the six-minute walk test [32].

A recent systematic review of the literature on this topic found that resistance

training, strengthening, and aquatic are the most beneficial interventions for AO patients. However, the affected joint does not influence intervention results. The essential of this meta-analysis highlights resistant-based exercise-therapy advantages [33].

5. Limitations and Future Research

It is plausible that a few limitations might have influenced the results obtained. The first addresses the period since the patient is being diagnosed. This aspect refers to the level of severity followed by diverse radiological findings. Further data collection is required to improve generalizability with a more adapted methodology and larger dataset. In the same way, due to cell adaptive capabilities to substances, different results may be gained. The second points out the history of chondroprotective supplementation and other treatment procedures.

Given that the findings are based on a different number of scores of the subscores (pain-4, stiffness-2, and difficulty-17), the results from such analyses should therefore be treated with considerable caution. It is noteworthy that a specific localization (knee or hip OA) requires a different biomechanical adaptation. Prior research has thoroughly investigated discrepancies regarding the WOMAC subscale. One of the possible reasons for excluding has been explained is the individually assumed definition under some of the activities (eg. "performing heavy domestic duties" or "performing light domestic duties") [34].

Investigation of a placebo group might be a positive factor of data standardization. The main disadvantage of a control group is an undefined or unknown treatment. During the study period possible changes in used substances might come to light and influence the results observed. Nonetheless, factors such as daily activities, medication intake, and dietary routine might be considered as influenced factors on the treatment efficacy. These results offer vital evidence for a long-term assessment (≥six months) of the chondroprotective complex in terms of evidence. We propose that further research should be improved in the following areas: pre-evaluation of the eligibility criteria to improve data generalizability, objective assessment methods (eg. radiological findings) are combined with WOMAC scores and VAS pain scores, placebo group instead of control group, and longer period of the intervention could improve the management of OA.

6. Conclusion

This study aimed to evaluate the potential benefits of short-term nutrient supplementation (one month) in patients with hip and/or knee OA. The findings suggest that a glucosamine complex named Artroveron® 5in1 COMPLEX WITH OMEGA-3 may help alleviate the key symptoms of OA, pain, stiffness, difficulty in daily activities (descending stairs, ascending stairs, rising from sitting, etc.). Notably, the observed reduction in pain scores indicates that Artroveron® may serve as a complementary approach to OA management, potentially reducing the need for NSAID use and minimizing associated side effects. While the intervention period

was limited to one-month, further research is needed to explore the long-term efficacy and safety of prolonged supplementation in OA therapy.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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