Efficacy of a food supplement with hydrolyzed collagen in improving clinical indices of knee osteoarthritis

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Summary

Knee osteoarthritis (OA) is one of the leading causes of pain and disability worldwide with a significant socio-economic impact, affecting the quality of life of patients and negatively impacting the National Health System. The aim of the study was to evaluate the effect of a food supplement with collagen peptides (molecular weight 1-3 kDa) on OA symptoms (pain and functional limitation). A randomized, double-blind, placebo-controlled, parallel, two-arm clinical trial with a 6-month follow-up period was conducted. The study included 120 patients with a diagnosis of grade 2 or 3 gonarthrosis and arthralgia, with a minimum score of 50 mm (range 0 to 100 mm) on the visual analog scale (VAS) of pain. Sixty patients were assigned to the experimental group (GrA), which received one sachet per day of the food supplement containing 10 g hydrolyzed collagen; the other group (n=60) received one sachet per day with placebo (GrP). Subjects were evaluated at an initial visit before treatment (T0) and at the final visit (T1) at the end of the 6-month follow-up period.

Both treatment groups were comparable at the initial visit (T0). At the final visit (T1), GrA (compared to GrP) experienced a statistically significant decrease in pain intensity (visual analog scale, VAS) and the Lequesne algo-functional index score. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in GrA also decreased at T1. No adverse effects were observed during the study. CH improved osteoarticular pain symptoms and functional capacity in patients with gonarthrosis, with a good tolerability and safety profile. Hydrolyzed collagen (CH) can complement the diet in patients with gonarthrosis and be administered concomitantly with the usual pharmacological treatments. The present study provides relevant information on the efficacy and safety collagen peptides (molecular weight 1-3 kDa) in patients with knee OA that may be useful for healthcare professionals in clinical practice. Corroboration of these results implies further clinical trials in large patient populations.

Abstract

Knee osteoarthritis is a leading cause of pain and disability worldwide, having a considerable socioeconomic impact on both the healthcare system and the patient quality of life. The aim of the study was to assess the effect of a food supplement containing collagen peptides (MW 1-3 kDA) on the symptoms of osteoarthritis (OA) (pain and functional limitation). A 6-month, randomized, double-blind, placebo-controlled and parallel two-arm study was conducted in 120 patients diagnosed with grade 2 or 3 OA and pain, with a minimum score of 50 mm (range 0 to 10 mm) in the visual analogic scale (VAS) for pain. 10 g of the investigational product (n=60) or placebo (n=60) were taken once daily, and subjects were assessed at baseline (T0, pre-treatment) and after a follow-up period of six months (T1). Both groups were comparable at baseline. Compared to placebo, changes in VAS, Lequesne algofunctional index (LAI), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) after six months of treatment, were significantly lower in the group of patients taking the active product. No adverse effects were reported during the study. The CH improved the osteoarticular pain and physical function in patients with knee OA. Furthermore, it was well tolerated

and satisfactory and showed adequate results in terms of safety and acceptability of CH. The food supplement may be complementary of drug therapy in knee osteoarthritis. The present study provides relevant information about the efficacy and safety of collagen peptides that may be useful to doctors and nurses in routine clinical practice. In order to corroborate these results, further clinical trials are needed with a higher number of patients.

Introduction

Osteoarthritis (OA) is a chronic and progressive degenerative disorder that damages the hyaline cartilage (mainly composed of collagen type II) and causes scleroses of the subchondral bone (in which type I collagen predominates) and also affects the white tissues so that, in its natural evolution, it ends up affecting the entire arthroculation. Due to the increase in life expectancy, especially in developed countries, the worldwide prevalence of OA in people over 60 years of age is currently 10% in men and 13% in women[1], with a progressive increase due to the aging of the population and other associated risk factors such as obesity and sedentary lifestyles. The socioeconomic impact of knee OA is very high with devastating repercussions on the quality of life of patients[2]. At present, the main objective of pharmacological treatment is to reduce pain and inflammation, since there are no available therapies to reduce pain and inflammation[3]. Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are used and, due to the chronic nature of the disease, it is common for these drugs to be administered on a daily basis, which poses an added risk of iatrogenic, and adverse drug reactions[4]. Another therapeutic group widely used in this pathology is the group of drugs that act slowly on the symptoms of osteoarthritis (SYSADOA, *Symptomatic Slow Acting Drug for OsteoArthritis*), which includes glucosamine sulfate (GS) and chondroitin sulfate (CS), considered safe and well tolerated by patients[5].

All scientific information available on the different types of treatment and therapeutic adjuncts in OA can contribute to the enrichment and updating of knowledge on this pathology among medical and nursing professionals. In recent years, interventions have been conducted with different supplements to evaluate efficacy and safety in OA, including the use of collagen as an alternative treatment in OA to improve the anabolic response in damaged articular cartilage[6]. CH is a mixture of collagen peptides with a molecular weight between 1-3 kDa. It is obtained from the gelatinization and subsequent enzymatic hydrolysis of native collagen from tissues rich in this protein[7]**.** CH supplements are rich in the amino acids hydroxyproline, proline and glycine. Hydroxyproline is only available in collagen-derived products[8]. Some studies have shown that CH is easily absorbed, has great bioavailability, is well distributed to joint tissues and has analgesic and anti-inflammatory properties, showing efficacy in relieving symptoms and preventing progressive deterioration of joint function, which translates into a reduction in arthralgia and an improvement in the patient's quality of life[9].

In addition, several studies have corroborated its usefulness, not only in the long-term treatment of degenerative joint diseases such as osteoarthritis, but also in the production of beneficial effects on the skin, with a very high safety profile even with prolonged use of the dietary supplement[7-10]. In these circumstances, the daily intake of CH maintained overtime can change the rate of composition of hydroxyproline containing peptides in human blood[10] as well as the activity of exo- or endo-type proteases in the digestive tract, which may promote beneficial effects at the level of articular cartilage[11]. On the other hand Vitamin C seems to exert a chondroprotective effect on articular cartilage, through the stimulation of collagen synthesis, chondrocyte apoptosis, antioxidant effect and the ability to decrease the activity of Nrf2, Nf-κB and metalloprotease (MMP-3)[12] levels.

The Lequesne index (LFI)[13] is used to assess the painful and functional impact of gonarthrosis. It is obtained after the implementation of a questionnaire (in interview format) containing 10 items to assess pain (or joint discomfort), the

maximum walking distance and the activities that the person can carry out in daily life. The IAL questionnaire is well recognized for its adequate validity, reliability and responsiveness. The score range is between 0 and 24 points. Higher scores indicate greater severity of the disease.
According to the score obtained: >14 = extremely severe; 11-13 = very severe; 8-10 = severe; 5-7 = moderate; 1-4 = mild (a patient with a score of more than 11-12 points after appropriate treatment would require surgery).

The main objective of the study was to evaluate the efficacy of a 6-month intake of a supplement containing collagen peptides with an average molecular weight between 1-3 kDa (COLLinstant® from Viscofan DE GmbH) associated with vitamin C, on the evolution of clinical signs and symptoms, mainly on painful symptomatology, as well as on functional capacity in patients with gonarthrosis. In addition, the degree of safety and satisfaction with the product during the treatment follow-up period was analyzed.

Methodology

Study Design
The study was designed as a randomized, double-blind, placebo-controlled, parallel, two-arm, six-month, double-blind clinical trial conducted in the Badajoz Health Area. The study included patients with grade 2 and 3 osteoarthritis (according to clinical and radiological criteria of the American College of Rheumatology[14]), with moderate or severe pain, seen in the nursing and specialist physicians' offices between June 2020 and February 2021, in the Don Benito-Villanueva health area, in the province of Badajoz. Inclusion criteria were: patients aged ≥30 years; diagnosed with osteoarthritis grade 2 and 3, and arthralgia with a minimum score of 50 mm (range 0 to 100 mm) on the visual analogue scale (VAS) for the subjective assessment of pain. Exclusion criteria were: presence of a previous cardiovascular event in the last six months; history of liver or kidney disease; presence of a medical condition requiring chronic treatment with drugs or other substances; excessive alcohol consumption (>20g/day) or abuse of other substances; presence of intolerance or hypersensitivity to the food supplement or to any of its components in isolation; use of any intraarticular injection in the anatomical area under study in the last six months; treatment with SYSADOA in the last 3 months; criteria included in the Clinical Research Guide for medications used in the treatment of osteoarthritis published by the European Medicines Agency of the European Union in 2010[15] and grade 4 radiographic osteoarthritis according to the Kellgren-Lawrence classification[16].

The objectives and procedures of the study were explained and written informed consent was obtained from each patient. All patients included in the study underwent a fasting blood sample for the determination of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). All patients received the same dietary recommendations (from the Spanish Society of Endocrinology and Nutrition), verbally and in writing. The mean nutritional value of energy per day was estimated at 2000 kcal. Patients were randomly assigned to one of the two treatment groups (1:1 ratio) by means of a computer-generated randomization list, either to the placebo-controlled group (GrP) or to the active product treatment group (GrA). **Figure 1** illustrates the process of recruiting and randomizing participants.

The preparation with collagen peptides that was administered to patients was formulated in sachets containing 10 g CH powder for oral suspension. Both types of sachets, containing placebo or food supplement, were externally indistinguishable from each other. For this purpose, the product was delivered in anonymous, coded, identical-looking boxes, so that both the patient and the investigators were unaware of the treatment assignment (double-blind). The identifying coding of the contents was performed by means of a bar code on the outer packaging. All the product administered to the patients (food supplement and placebo) was manufactured by Nutra-Research© SL (Barcelona,

Spain) under a strict protocol of Good Manufacturing Practices. GrA (n= 60) took one sachet per day of the active product containing collagen peptides, lemon flavor, anhydrous citric acid (sweetener), calcium ascorbate (vitamin C), sucralose (sweetener) and stevia (sweetener). A dose of 10.728 g provides 10 g of CH and 80 mg of vitamin C. GrP (n= 60) took one sachet per day with placebo containing only sucralose (sweetener) and stevia (sweetener), in proportions identical to those of the preparation under investigation. All patients received the same instructions to take the contents of one sachet per day, preferably in the morning, for six months, after dilution of the preparation in 250 ml of water, juice or other liquid. Patients were informed of the need to immediately report any changes in their treatment, clinical or laboratory status during the course of the study. At the initial or baseline visit (T0), before ingestion of the product, the patients' sociodemographic and anthropometric data were collected. The clinical symptoms of osteoarthritis, pain and functional capacity were evaluated with the visual analog scale (VAS) of pain and the LAI, respectively[13]. CRP and ESR (from a fasting blood sample) were also analyzed. At visit 2 (T1), after a 6-month treatment period, the VAS pain scale and LAI scores were collected, as follows such as CRP and ESR data.

Sample Size

The calculations of the minimally detectable effect size as well as the sample size for the present study were performed with the G*Power software. We calculated the statistical power to detect a minimally detectable effect (d=60) with a significance level of α=0.05. A result of 0.94 was obtained with 2 groups and 2 time points at the beginning and at the end of the study, with a sample size selection of 120 patients (60 controls and 60 cases) for the pilot study.

Safety assessment

Adverse effects throughout the study and the possible causal relationship with the food supplement were analyzed. In addition to safety, we assessed the degree of satisfaction and acceptance of the product.

Statistical analysis

The IBM® SPSS® Statistics® program (version 25.0) was used. The normality of the data was tested with the Kolmogov-Smirnov test. The normality hypothesis could not be assumed for any of the study variables. For the comparison of intragroup changes between the initial (T0) and final (T1) visits of the study, a paired data analysis was performed using the Wilcoxon test. Comparative analysis of the data between the mean values in the study groups (GrP vs GrA) was performed using the Mann-Whitney U test for independent samples. Data are represented as mean±standard error together with the confidence interval (95% CI). Comparisons between categorical variables with independent or paired data were performed using Pearson's Chisquare test or McNemar's test, respectively. The value of $p< 0.05$ was established as statistically significant for all analyses.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Practice Clinical Guidelines (CPMP/ ICH/135/95). The protocol was approved by the Area's Clinical Research Ethics Committee (CEIC-20/11/19). All the participants gave their informed, written consent. Participant data were identified with a numerical code and were kept unlinked to personal identification to ensure anonymity. The correspondence between the codes and the data was only accessible to the principal investigator. All patient information collected in the study was treated in accordance with the requirements of the current data protection legislation (LO 3/2018, de Protección de Datos, del Reglamento de Protection de Datos).

Results

Study Sample

A total of 120 subjects with gonarthrosis were included in the study and randomly assigned to groups: 60 patients in the group receiving the active product (GrA) and 60 patients in the group administered placebo (GrP). The age range of the population sample varied between 30 and 77 years (median= 55.9 years). In accordance with the objectives of the study, clinical data were collected from all patients at the two scheduled visits: at the initial visit (T0), prior to the administration of the dietary supplement and at the final visit (T1), after six months of treatment. None of the participants dropped out of the study (**Figure 1).**

The treatment groups were comparable in relation to the variables analyzed at baseline (T0). The ratio between men and women was identical (50%) in GrP and GrA. No subject was a smoker at the start of the study. There were also no significant differences between the groups in the proportion of patients who consumed alcohol (p=0.226). The proportion of patients who performed some type of physical exercise (walking) was similar between both treatment groups (p=0.379) (**Table 1**).

There was no difference between the two treatment groups (placebo and and complement) in the number of analgesic drugs taken by patients in the baseline period (T0). Eighty-five percent of the women included in the study were premenopausal, with a similar proportion in both study groups (82.73% in GrP vs. 87.1% in GrA; p=0.638).

Effectiveness of the intervention

VAS scale were compared at the final visit (T1) of the study, between the treatment group receiving placebo (GrP), and the group receiving the food supplement (GrA), a lower pain intensity score was observed in GrA (51.7±11.3 mm in GrP vs. 37.5±8.7 mm in GrA; p=0.0001) (**Figure 2**). The difference observed in the score obtained on the VAS scale, between the means of both groups, was 14.2 points, a difference that was statistically significant. There was a significant intragroup variation in the VAS score in GrA, with a statistically significant decrease in pain intensity at T1 compared to T0 in patients with OA (-43%; P<0.001). No differences were detected between the two periods in GrP. In relation to the functional Lequesne index, the scores obtained at the final visit (T1) were lower in GrA, but no statistically significant differences were observed between both treatment groups (4.5±2.5 points in GrP vs 4±0.9 points in GrA; p=0.390) (Figure 2). However, when intra-group changes in LAI between the initial (T0) and final (T1) visits were analyzed, there was a statistically significant decrease in the score of 2.9 points (-41%; p<0.0001) in the group of patients that received the active treatment (GrA) (**Figure 2**).

In GrP, no intra-group differences in LAI were observed between T0 and T1. Compared to GrP, the C-reactive protein (CRP) values obtained at the final visit (T1) of the study were lower in the group of patients who received the food supplement (2.7±1.6 mg/L in GrP vs. 1.5±1.2 mg/L in GrA, p= 0.001) (**Figure 3**). When the intragroup changes in CRP values were analyzed between the initial visit (T0) and the final visit (T1), a statistically significant decrease was observed in the group of patients with OA who had taken the food supplement (52%, p<0.001) (**Figure 3**). In the placebo-controlled GrP group, no significant changes in CRP values were observed between the two visits (initial and final) of the study (**Figure 3**). The erythrocyte sedimentation rate (ESR) values obtained at visit 2 (T1), after six months of treatment, were lower in GrA compared to GrP (13.3±5.3 mm/h in GrP vs. 6.6±7.0 mm/h in GrA, p=0.0001) (**Figure 3**). At the same time, when the intragroup changes in ESR values between the initial visit (T0) and the final visit (T1) were analyzed, a statistically significant decrease was observed in the GrA group of OA patients who had taken the food supplement (57%, p<0.001) (**Figure 3**). In the placebo-controlled group (GrP), no significant changes in ESR were observed between the two study visits. A significant reduction in analgesic intake was detected in the

experimental group (GrA) during the six month follow-up period. At baseline (T0), 24.6% of patients took some analgesic, a figure that was significantly reduced to 4.9% at the final visit (T1) ($p = 0.002$). Treatment with CH was well tolerated during the study and no adverse events were reported.

Discussion

Gonarthrosis is a chronic disease in which the clinical picture worsens slowly and progressively. Therapeutic measures provide symptomatic relief and are theoretically aimed at delaying the progression of joint damage[17]. The central symptom of patients with OA is pain, which also has a negative impact on the patient's performance of daily activities. The present placebo-controlled clinical trial was designed to analyze the efficacy of a food supplement containing standard molecular weight collagen peptides (1-3 kDa) on clinical signs and symptoms in patients with gonarthrosis. In addition, it has analyzed safety and the degree of acceptability of the treatment by patients. Compared to the placebo group (GrP), a decrease in pain intensity (VAS) was observed at the final visit (T1), in the treatment group that received the food supplement (GrA). The difference observed in the mean scores obtained with the VAS scale at T1, between both treatment groups, was 14.2 points. Based on the data collected in different meta-analyses, the range of the minimum clinically important difference (MCID) for the variable pain, measured with the VAS scale, in patients with knee osteoarthritis, has been estimated at between 8.4 and 19.9 mm[19].

In addition, the GrA recorded a significant reduction in pain intensity between initial and final visits (-43%). This allows us to affirm a priori that the decrease in pain intensity observed at the final visit of the study (T1) in the group receiving the supplement (GrA) is not only statistically significant, but also clinically relevant.

Although different formulations exist, collagen peptides have demonstrated a positive effect on articular cartilage, tendons and ligaments, and significant therapeutic benefits for the treatment of OA[18]. The chondroprotective action seems to be related to biological processes that stimulate the synthesis of elastin, type I and type II collagen and the formation of proteoglycans in the extracellular matrix of the chondrocytes[19]. Increased synthesis of extracellular macromolecules could reduce cartilage degradation, inhibiting proinflammatory processes and significantly reducing pain[9]. There are no conclusive studies for the estimation of the DMCI in the clinical course of ALI. When using this index to assess the long-term impact of active pharmacological treatment for osteoarthritis of the hip, some studies have considered a minimal difference in the effect on the final score between 1.3 and 1.8 points[5,20]. In our study, the GrA who had taken collagen peptides for six months reported a significant improvement of 2.9 points (-41%; $p<0.0001$) in LAI between the initial visit (T0) and the final visit (T1). In contrast, no differences were observed, over the same time period, in the control group of patients who had received placebo (GrP). Several clinical studies have evaluated the efficacy of CH in the treatment of osteoarthritis, showing reductions in joint pain due to wear and tear and improved function[21], indicating that CH has a positive therapeutic role in patients with OA. On the contrary, other authors point out that the effect of collagen in the control of osteoarticular pain is not significant and there is insufficient evidence to make a recommendation for its widespread use in these patients[9,22]. In other studies, the supplement was widely accepted and demonstrated a high safety profile[23,24].

The efficacy and safety results obtained in the present study provide important information for the medical and nursing professional on the properties of collagen peptides as a dietary supplement and complementary to the common pharmacological treatments in knee osteoarthritis. This may contribute to the reduction of NSAID dosage in some patients and the prevention of adverse reactions with the usual medication. Recently, the efficacy of formulations based on oral administration of CH have been compared to intraarticular administration for the control of OA symptoms[25].

The treatment of this pathology requires frequent and controlled administration of the medication; therefore, we consider the use of oral preparations to be more appropriate[26]. Some studies have identified the ingested dose of CH as a determinant of the efficacy of health benefits[27]. In the study by Shigemura et al., effective doses to promote joint health benefit are based on an intake of CH greater than 153.8 mg/kg body weight, as a result of a significant increase in plasma hydroxyproline levels,[10,11] equivalent to the dose of CH contained in the food supplement used in our study.

Other authors have obtained beneficial effects on the symptoms of gonarthrosis with lower doses of CH than those used in our study, but after intra-articular administration or by combining CH with different biactive compounds such as chondroitin sulfate, glucosamine, L-carnitine, vitamins, and minerals[25,26]. The product administered contains, in addition to CH, vitamin C (80 mg). Supplementation with antioxidant agents has become one of the most studied treatments in OA in the last decade. This is related to its ability to attenuate the formation of reactive oxygen species in chondrocytes[6]. Vitamin C has shown encouraging results in terms of the prevention of OA, but not so much in the treatment. Although there are multiple prospective, cross-sectional studies investigating the possible effect of vitamin C on OA, there do not appear to be any double-blind, placebo-controlled human clinical trial concluding such an association[28]. In our study, the duration of treatment with collagen was similar to that of other studies, as was the methodology used to measure the effect of the food supplement on the variable pain and functional limitation in patients with gonarthrosis[23,27]. The relationship between osteoarticular alterations and various serological biomarkers such as ESR and CRP protein, which objectively measure different aspects of the pathological process and can be useful in the management and follow-up of the disease, being the most commonly used in spondyloarthropathies, is well known. A meta-analysis showed higher hematological CRP levels in OA patients than in healthy volunteers[29].

In the present study and in line with other authors, changes were observed after collagen administration in the hematological biomarkers analyzed (CRP & ESR). At the final visit (T1), OA patients had lower CRP concentrations and lower ESR values in the group that received the supplementation compared to the placebo-controlled group. Similarly, in a recent study, CRP concentrations were significantly lower in the group receiving CH compared to patients taking placebo[30]. Similar data have been obtained by Smith et al.[31], highlighting the importance of C-reactive protein in the clinical evaluation of osteoarthritis. In addition, these authors highlight the usefulness of CRP as a possible biomarker of OA severity, demonstrating that patients with elevated CRP levels had simultaneously elevated levels of cytokines and inflammatory changes indicative of synovitis compared to patients in whom lower CRP levels were detected[31].

Limitations of the study

Cytokine levels have not been determined in the present study. Some authors suggest that there may be changes in cytokines related to inflammation (IL-6 and IL-10) and their concentrations at the synovial fluid level in patients with knee OA[27]. Not strictly controlled were diet or daily exercise or other indirect parameters (anxiety, stress, cortisol) that may be related to the pain perceived by the patients. In summary, the daily dietary supplement containing 10 g collagen peptides improved osteoarticular pain and the results obtained in the Lequesne index for assessing functional capacity in patients with gonarthrosis after six months of treatment. A decrease in CRP and ESR was also observed. Patients showed a marked improvement in the performance of daily activities, as well as a reduction in the intake of analgesic and anti-inflammatory medication, which may have a significant impact on the improvement of quality of life. However, further clinical trials in large populations of OA patients are needed to corroborate these results.

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Figures

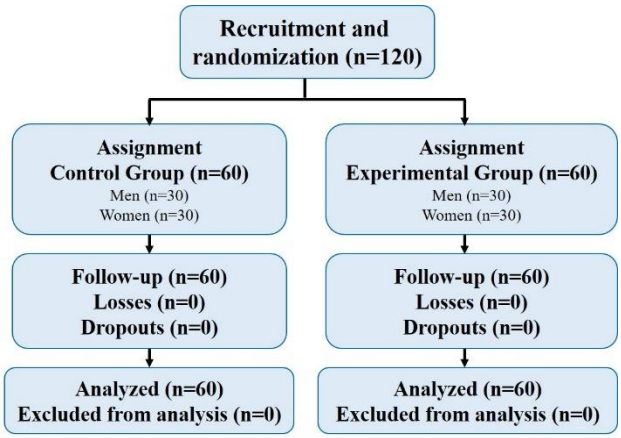

Figure 1. CONSORT flow chart of the study population.

	Total sample (n = 120)		Placebo (n = 60)		Active (n = 60)	
Age (years)	56.6	(±10.5)	56.8	(±9.9)	56.4	(±11.1)
Sex: male/female (%)	60/60	(50%)	30/30	(50%)	30/30	(50%)
BMI	27.8	(±3.8)	27.9	(±3.7)	27.7	(±3.9)
EVA	63.3	(±10.6)	60.3	(±12.2)	66.1	(±8)
IAL	6	(±2)	5.2	(±2.3)	6.9	(±1.2)
CRP (mg/l)	3.3	(±2.3)	3.4	(±2.9)	3.1	(±1.4)
ESR (mm/h)	13.3	(±7.1)	12	(±6.1)	14.6	(±7.7)
Smoking habits (n, %)	0	(0%)	0	(0%)	0	(0%)
Alcohol consumption[1] (n, %)	2	(1.7%)	0	(0%)	2	(3.3%)
Physical activity (walking) (n, %)	108	(90%)	52	(88.1%)	56	91.8%)

Table 1. Baseline characteristics (T0) of the study objects

Data expressed as mean (SD) and frequencies (percentages). Abbreviations: SD: standard deviation; BMI: body mass index; VAS, visual analog scale; LAI, Lequesne algo-functional index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
[1] Expressed in "standard drinking units", equivalent to 10 g of pure alcohol per unit.

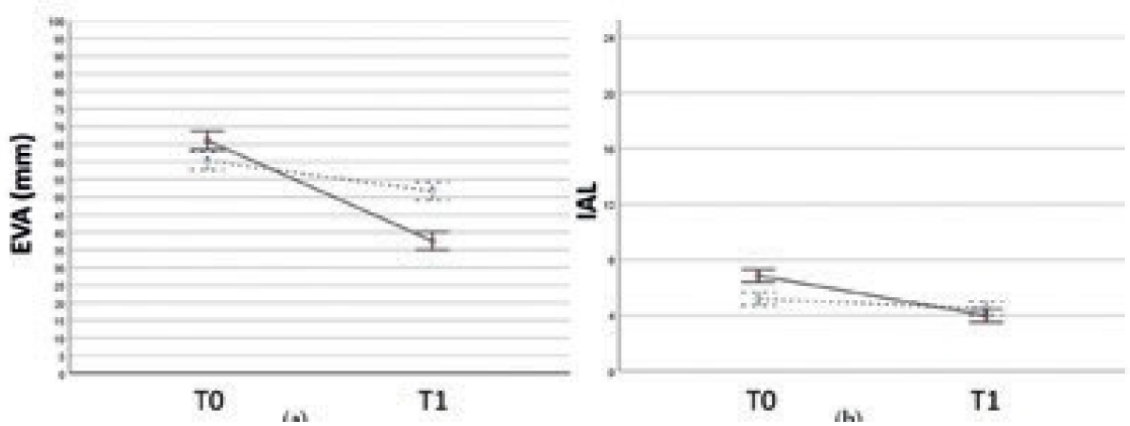

Figure 2. Changes in clinical indices EVA osteoarthritis scale (left) measured and IAL (right), between the initial visit (T0) and the end of the study (T1) after six months of treatment. Comparison of the placebo-controlled group (GrP, dashed line) with the group receiving active treatment (GrA, solid line). Data expressed in mean (SE). Pain intensity in mm as measured by the VAS visual analog scale; the algofunctional Lequesne's index score obtained from completed questionnaires.

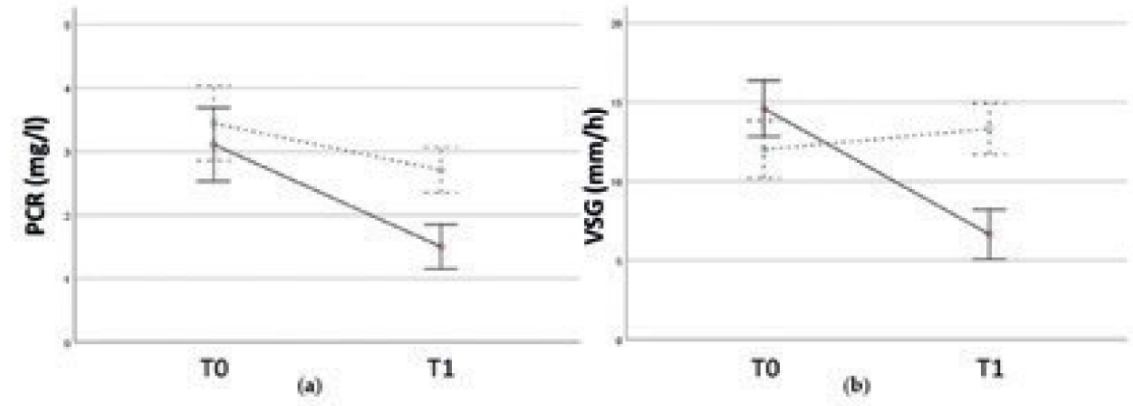

Figure 3. Changes in C-reactive protein (CRP) levels (left) and globular sedimentation rate (ESR, right) between the initial visit (T0) and the end of the study (T1), after six months of treatment of patients with knee osteoarthritis. Comparison of the placebo group (GrP, dashed line) with the group that received active treatment (GrA, solid line). Data shown as mean (SE); CRP in mg/L; ESR in mm/h.