The effects of marine chondroitin sulfate on joint pain and mobility in middle-aged adults

From *in vitro* evidence to real-life study monitored with smartwatch

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ABSTRACT

Osteoarthritis is a common joint disorder and one of the leading causes of disability with ageing. For many years, chondroitin sulfate (CS) has been used as a slow-acting drug to reduce joint pain and improve joint function. More recently, CS has also been used as a dietary supplement to support joint comfort. The existing literature on the clinical effects of CS in osteoarthritis has primarily focused on therapeutic dosages above 800 mg per day, while studies assessing lower doses relevant to nutraceutical applications remain limited. In this context, a real-life study on marine chondroitin sulfate (MCS) investigated the effects of a three-month supplementation in 180 middle-aged subjects with self-reported joint discomfort. Outcomes were assessed using the Visual Analog Scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), as well as mobility and sleep data collected with a smartwatch. The results showed that daily supplementation with 450 mg of MCS led to a 10% improvement in both the total WOMAC score and the WOMAC pain subscale compared with placebo. Joint function and mobility, assessed by the WOMAC function subscale, daily step count, and daily active minutes, were also improved after 12 weeks. Finally, sleep duration measured by smartwatch was significantly increased in the MCS group compared with the placebo. These findings suggest that MCS at a daily dose of 450 mg may improve joint pain, mobility, and sleep, and could represent a natural solution within a nutraceutical approach to joint comfort.

Introduction

According to the latest estimates, the world population aged over 60 is expected to double by 2050[1]. With the ageing of the population, among other conditions like increasing rates of obesity and injury, the prevalence of osteoarthritis, the main joint disease worldwide, will increase globally. Osteoarthritis is an age-related disease but is not an evitable consequence of ageing. The typical onset of the disease is the late 40s to mid-50s, with only 3% of people living with osteoarthritis being under 45[2]. This chronic and degenerative joint disease involves the entire joint structure, including cartilage destruction, inflammation of the synovial membrane and subchondral bone remodeling; and affects mainly hands, spine, knees and hips[3]. Management of osteoarthritis involves several therapeutical and preventive approaches such as weight loss, dietetic measures and physical exercise. Joint pain can be relieved by symptomatic pharmacological treatments among which paracetamol, nonsteroidal anti-inflammatory drugs or slow-acting drugs like glucosamine or chondroitin sulfate[3,4].

Chondroitin sulfate (CS), a sulfated glycosaminoglycan belonging to the proteoglycan family, is a major component of the joint cartilage. The possible activity of CS on joint may result from the protection of cartilage matrix through the activation of proteoglycan synthesis and the reduction of catabolic activity of chondrocytes[5]. The anti-inflammatory activities of chondroitin sulfate have also been described and involve the downregulation of Nf-kB, and the up-regulation of Nrf2 pathway[6].

The therapeutic effects of CS on osteoarthritis management have been investigated in various clinical studies. The authors of a Cochrane review report several benefits of chondroitin sulfate including the improvement of joint pain on knee in studies less than 6 months compared to placebo and measured by Western Ontario and McMaster Universities Osteoarthritis or Lequesne's index[7]. They also report an improvement in the quality of life of people with osteoarthritis who were supplemented with chondroitin sulfate. At a histological level, the clinical studies review highlighted that chondroitin sulfate slightly slows down the narrowing of joint space on X-rays of the affected joint, and has no difference in adverse events versus other treatments[7]. Nevertheless, the inconsistency of the published clinical trials has been reported several times. The results may be influenced by the source, the quality or the purity of the chondroitin sulfate, whose efficacy is often assessed along with glucosamine[4].

The daily doses of chondroitin sulfate in drugs and food supplements depend on regulatory rules of each country. In Italy, the daily dose of chondroitin sulfate authorized in food supplements must not exceed 500mg[8]. In France, this limit is set at 950mg per day[9].

The present study aims to assess the efficacy of a supplementation with chondroitin sulfate from marine origin in the improvement of joint comfort and mobility in middle-aged people, at two dosages: 450mg/d and 900mg/d. Objective measurements such as VAS on joint pain and WOMAC index along with the use of smartwatches were combined with self-assessment questionnaire to validate the effects of the supplementation on osteoarthritis. Preliminary *in vivo* assays on bioavailability of marine chondroitin sulfate and its role on knee cartilage protection are also reported in this work.

Materials and Methods

Test products

The studies were performed using specific hydrolyzed fish cartilage standardized to 90% of chondroitin sulfate according to the European Pharmacopoeia method (Chondro'Sea®, PHARMANAGER INGREDIENTS, France).

Preclinical studies

The bioavailability of the ingredient has been studied *in vivo* in comparison with other sources of chondroitin sulfate of bovine origin at the dosage of 100 mg/kg. Blood samples were collected before administration of the tested products in rats and during 24h after ingestion. The concentrations of deltaUA-GalNac,4S and deltaUA-GalNac,6S in rat plasma were used to determine the pharmacokinetics profiles of the different sources of chondroitin sulfate.

Another preclinical assay has been conducted in an artificially-induced model of knee-osteoarthritis in rats by intra-articular injection of monoiodoacetate (MIA). To assess the effects of an oral administration of the ingredient on cartilage, it was compared to a negative control, not submitted to MIA injection, and Tramadol + MIA as a positive control. At the end of the study, knee joints were collected and stained with Toluidine blue. The area of the tibia and the femur cartilages were measured on both left (without injury) and right (with MIA injection) sides. The difference between the two sides was expressed as a percentage of cartilage degradation.

Treatment	Marine chondroitin sulfate (Mean ± SD)	Bovine chondroitin sulfate (Mean ± SD)	P-value intergroup
C_{max} - DeltaUA-GalNac,4S (µg/kg)	12,77 ± 3,58	14,36 ± 1,56	0.52
t_{max} - DeltaUA-GalNac,4S (h)	0,25 ± 0,00	5,42 ± 4,48	0.12
C_{max} - DeltaUA-GalNac,6S (µg/kg)	12,42 ± 2,69	12,17 ± 1,72	0.90
t_{max} - DeltaUA-GalNac,6S (h)	0,33 ± 0,14	5,42 ± 4,47	0.12

Table 1: Bioavailability assessment after oral administration of MCS and bovine chondroitin sulfate in rats. The data represent the mean ± SD of plasmatic parameters C_{max} and T_{max} of deltaUA-GalNac,4S and deltaUA-GalNac,6S; for n=3.

Design and participants of the real-life study

This randomized double-blind placebo-controlled monocentric study has been conducted in France, in real-life conditions, between January and April 2024.

180 healthy volunteers aged 50 to 75 and suffering from joint discomfort assessed by Lequesne's index 5-11, and VAS 1-5, were involved in the study. All participants received information about the real-life study and gave their written consent to participate. They were randomized into three groups according to quota sampling: Group MCS450, active ingredient at the dosage of 450 mg/d [two capsules containing 225 mg of marine chondroitin sulfate (MCS)], Group MCS900, active ingredient at the dosage of 900 mg/d (four capsules containing 225 mg of MCS), or placebo (two capsules containing acacia fiber).

Participants were asked to take orally the product and to wear a smartwatch over the study period of 12 weeks. They were instructed to follow their normal diet and exercise routine and not consume any medications that may impact the outcome of the trial.

At each of the baseline (Q0), 4 weeks (Q1) and 12 weeks (Q2), assessment of joint function and comfort (VAS, WOMAC questionnaire and its subdomains: pain, function and stiffness), self-assessment questionnaire and compliance to the protocol were recorded. The mobility and sleep data recorded with the smartwatch (number of daily steps, number of steps after waking up, number of active minutes, time to fall asleep, sleep duration) were

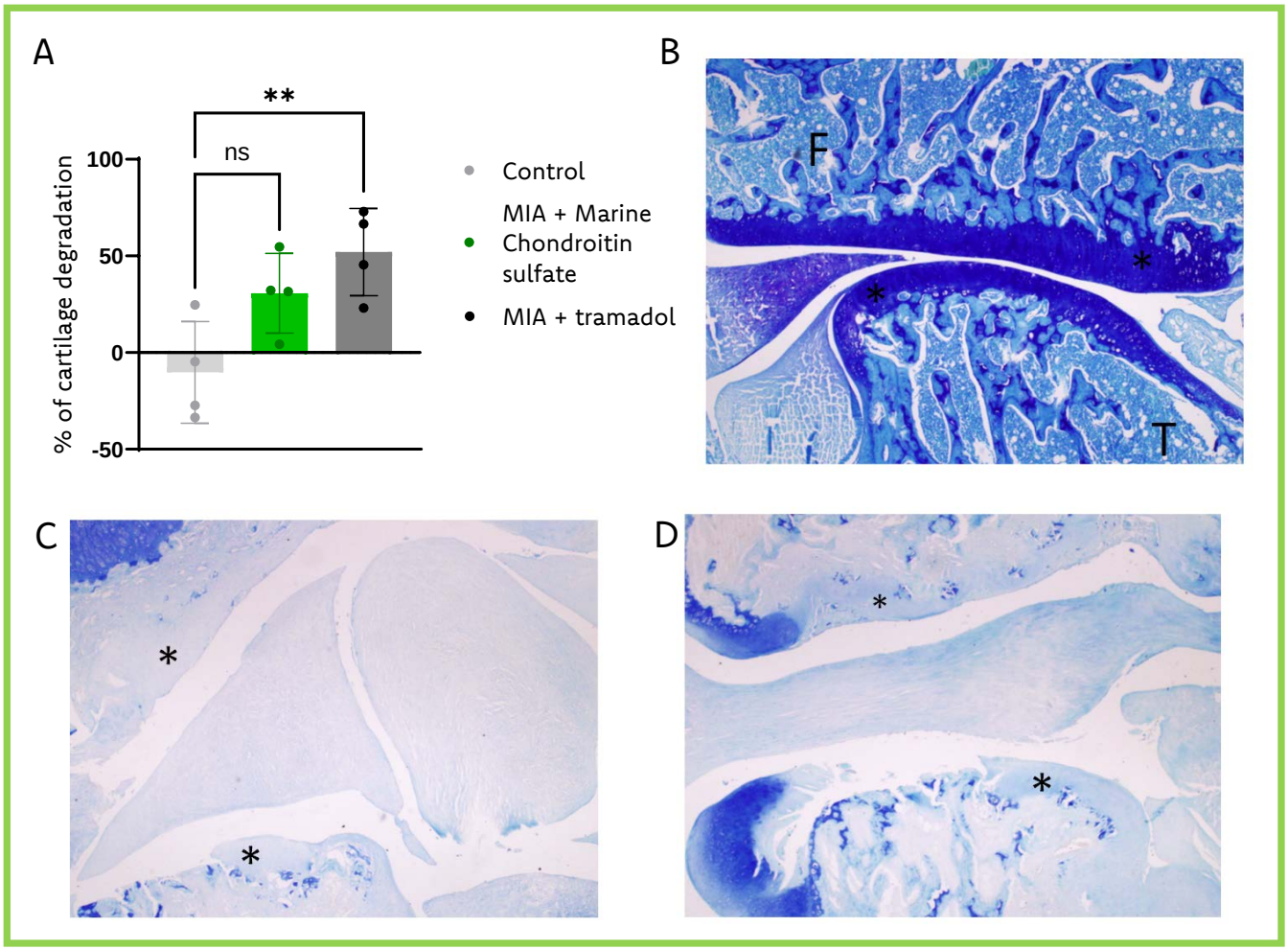

Figure 1: Cartilage degradation of the knee joint. The area of knee cartilage was measured histologically on the femur and the tibia after coloration with blue Toluidine. A. The percentage of cartilage degradation has been calculated as the difference between the left knee (untreated) and the right knee (injected with MIA) for each animal. A representative picture with blue Toluidine of each group has been selected. B. Control group (healthy animal without MIA injection). C. MIA + Marine Chondroitin Sulfate. D. MIA + tramadol. Cartilage was identified with an asterisk. Results are represented as Mean ± SD. Statistical differences have been calculated with a one-way ANOVA with a *post hoc* analysis using the Dunnett's test. ** p-value <0,01; NS: Not significant. F: Femur; T: Tibia

calculated after 4 weeks and 12 weeks, as a mean of the daily records within the last four weeks.

Statistical analysis

Statistical analysis was performed with GraphPad Prism 10.6.0 (GraphPad Software, La Jolla, CA, USA). Normality was tested with the d'Agostino & Pearson test. Homogeneity between groups at baseline was tested by ANOVA. Differences intragroup over time and between treatment groups per time point were calculated by ANOVA or ANOVA with a *post hoc* analysis using the Dunnett's test or the Fisher LSD test. Differences between two groups (Active vs placebo) were tested by unpaired t-test one-tailed or Mann-Whitney two-tailed test. Statistical significance was considered when p-value < 0.05.

Results

Preclinical result on bioavailability

The results of the bioavailability of MCS compared to bovine chondroitin sulfate on two parameters in blood – the maximal concentration (C_{max}, µg/kg) and the time to reach the maximal concentration (t_{max}, h) of chondroitin

sulfate – after oral administration in rats are presented in Table 1. The mean of maximal concentrations of deltaUA-GalNac,4S and deltaUA-GalNac,6S are not significantly different between marine and bovine chondroitin sulfate (p=0.52 and p=0.90). T_{max} of deltaUA-GalNac,4S and deltaUA-GalNac,6S are respectively 0,25h and 0,33h for MCS and 5,42h and 5,42h for bovine chondroitin sulfate. The differences between the two groups are not statistically significant.

Preclinical effect on cartilage protection

The area of joint cartilage after MIA injection in the right knee of rats have been compared to the area of the left knee, which was not submitted to MIA injection. The percentages of cartilage degradation, calculated as the difference between cartilage area in the two knees, are shown in Figure 1 for the 3 groups of animals: control group (without MIA injection), MCS + MIA group, and tramadol + MIA group. Representative pictures of the right knee were presented in Figure 1. The percentage of degradation of the knee cartilage of the MCS group injured with MIA did not significantly differ from the percentage of degradation in the control group without MIA. At the contrary, the percentage of degradation of the knee cartilage of the tramadol group injured with MIA is significantly different from the control group (p<0,01). The results show that the rats supplemented with MCS have less degradation of the knee cartilage than animals treated with tramadol, suggesting a protecting effect of MCS on cartilage.

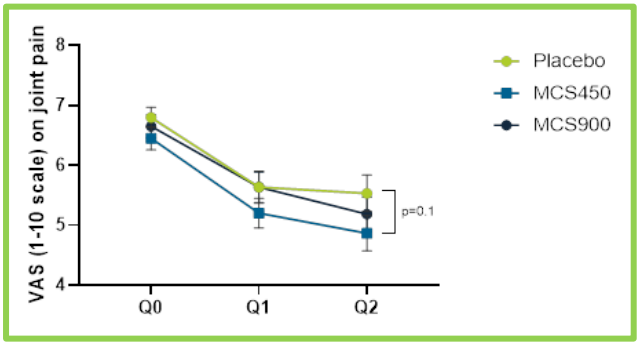

Figure 2: Evolution of the VAS score on joint pain at Q0 (baseline), Q1 (4 weeks) and Q2 (12 weeks), in Placebo group and Supplemented group with marine chondroitin sulfate at 450mg/d (MCS450) and 900mg/d (MCS900). The statistical difference was calculated with a one-way ANOVA with a *post hoc* analysis using the Dunnett's test.

Compliance and tolerance of the real-life study

The 180 volunteers included at baseline completed the 3-month real-life study. At the end of the study, participants were asked if they forgot to take the capsules once or more or if they have taken the supplementation without any oversight. 85%, 80% and 82% of participants fully completed the supplementation in MCS450 group, MCS900 group, and placebo group respectively. None of the participants forgot to take the supplementation more than 4 times over the 90-days period.

Tolerability was also assessed at study completion. Fewer than 10% of participants in each group reported any discomfort during the intervention, with no statistically significant differences between groups.

At baseline, men and women were equally represented in each group. The mean age of participants was 57.4 years old.

Effect on joint comfort

The joint pain assessed using the VAS showed a significant improvement of the score at 4 and 12 weeks compared to baseline for all groups. Although the effect appeared greater in the MCS450 group at the end of the study, the difference was not statistically significant (p=0,1) (Figure 2).

The WOMAC questionnaire was used to assess the global joint pain and function. At baseline, no statistically significant difference was observed in WOMAC score between groups. After 12 weeks, the MCS450 group demonstrated a significant improvement of 5.1 points in the WOMAC total score compared to placebo ($p < 0.05$) (Figure 3). No significant difference was observed between the MCS450 and MCS900 groups.

The scores for WOMAC pain subscale were not statistically different across groups at baseline. At the end of the study, the score of the WOMAC pain subscale had decreased by 10% in the MCS450 group compared to placebo (p=0,05) (Figure 3). There was no significant difference between MCS450 and MCS900 groups (data not shown).

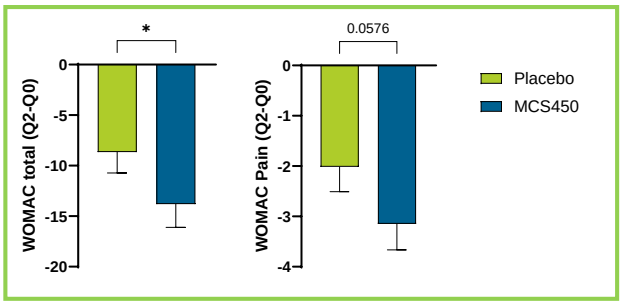

Figure 3: Evolution of WOMAC Total and Pain Subscale Scores after 12 weeks of supplementation versus baseline, in Placebo group and Supplemented group with marine chondroitin sulfate at 450mg/d (MCS450). Mean and SD are presented in the figure. The statistical difference was calculated with the unpaired t-test. * p-value <0,05

Effect on mobility

The results of mobility expressed with the WOMAC function subscale, the WOMAC stiffness subscale and the data recorded with the smartwatch (number of daily steps, number of steps after waking up, number of daily active minutes, time to fall asleep, sleep duration) were presented in Table 2. Results are expressed as the evolution of the parameters after 12 weeks of supplementation versus baseline (ΔQ2-Q0). WOMAC function subscale, number of daily steps, number of steps after waking up and number of daily active minutes are significantly improved in the supplemented group at 450mg/d compared to placebo (p=0,05; p=0,0006; p=0,032; p<0,0001 respectively). These results suggest that the mobility of the volunteers in the supplemented group at 450mg/d is significantly higher compared to placebo. The evolution of the WOMAC stiffness subscale versus baseline, representing the stiffness of the joints after waking up, is not significantly different in the supplemented group compared to placebo (p=0,09). Comparative results have been shown with the supplemented group at the pharmacological dosage of 900mg/d except for the WOMAC function subscale, of which evolution from baseline is not significantly improved compared to placebo (p=0,11; results not shown).

Effect on sleep quality

After 12 weeks, neither time to fall asleep nor sleep duration, calculated as the average of the daily records with the smartwatch on the past four weeks, showed significant changes from baseline in the placebo group. Time to fall asleep was also not significantly improved in both supplemented groups at 450mg/d and 900 mg/d. However, the evolution of sleep duration versus baseline was significantly increased by 8,90min and 11,23min per night respectively after 12 weeks of supplementation (p<0,0001). At the end of the study, the sleep duration had improved by 11% in the MCS450 group compared to that in placebo group (p=0,006).

Treatment	Supplemented group, MCS at 450 mg/d (n=60)			Placebo group (n=60)			p-value intergroup (ΔQ2-Q0)
	Q0	Q2	(ΔQ2-Q0)	Q0	Q2	(ΔQ2-Q0)	
WOMAC function	29,60 ± 13,31	20,18 ± 12,67	-9,42	26,78 ± 11,73	20,98 ± 14,13	-5,8	0,05*
WOMAC stiffness	4,28 ± 1,63	3,05 ± 1,61	-1,23	4,00 ± 1,25	3,15 ± 1,63	-0,85	0,09
Number of daily steps	2825 ± 2160	2967 ± 2251	142	2602 ± 2152	2583 ± 2111	-18,2	0,0006***
Number of steps after waking up	146,0 ± 83,92	151,6 ± 86,29	5,53	141,7 ± 73,01	141,2 ± 70,23	-0,5	0,032*
Number of daily active minutes	81,73 ± 39,71	85,25 ± 41,66	3,52	85,23 ± 36,84	83,42 ± 35,28	1,82	<0,0001****

Table 2: Evaluation of the mobility and joint function in MCS450 group (supplemented group at 450mg/d of MCS) and placebo group. WOMAC function subscale, WOMAC stiffness subscale, Number of daily steps, Number of steps after waking up and Number of daily active minutes were measured at Baseline (Q0) and after 12 weeks (Q2). The evolution versus baseline (ΔQ2-Q0) was calculated for each group. The statistical difference of the evolution versus baseline between placebo group and MCS450 group was tested by unpaired t-test one-tailed or Mann-Whitney two-tailed test. * p-value <0,05; *** p <0,001; **** p <0,0001

Discussion and Conclusion

The effects of CS on osteoarthritis have been widely studied in literature but several biases have been reported. The purity and the source of origin of the CS appear to impact the therapeutic effects of CS in joint health[4]. For instance, in a study on healthy male volunteers comparing the pharmacokinetic profiles between of nonanimal and bovine CS, Volpi et al. concluded that the nonanimal CS resulted in higher and more sustained plasma concentrations than bovine CS, which might be attributed to its lower molecular weight[10]. In fact, CS absorption mainly depends on its molecular weight, its structure (degree of sulfation), its origin and its formulation[11–13]. In the present study, the pharmacokinetics profiles of MCS and bovine CS were assessed in rodents over a period of 24 hours. If the maximal concentration did not differ between the two groups, the time to reach this maximal concentration was quicker in the MCS compared to the bovine CS (0,3h and 5,4h respectively) suggesting an improved bioavailability of MCS that reach the systemic circulation faster than bovine CS. Nevertheless, this difference was not significant due to the small number of animals per group (n=3) and the high intragroup variability.

Whatever the source of origin, another bias that was reported in the literature regarding the effects of CS on osteoarthritis was the number of clinical trials that have been run in combination with glucosamine sulfate (GS)[4,14]. As concluded by Rabade et al. in a meta-analysis of clinical trials on CS, the combination of CS and GS did not significantly improve the symptoms or modify the disease, while the CS alone reveal to have significant therapeutic benefits, especially on the decrease of pain intensity and improvement in the physical function, compared to placebo[14]. The daily dose of CS used in the clinical trials to assess the effects on joint health are between 800mg and 1200mg, considered as a therapeutic dose, and the duration of treatment varies from three months to two years. These doses of CS correspond to pharmacological treatments of osteoarthritis and are not compatible with food supplementation for joint comfort. Therefore, this real-life study involved an active group treated with a daily dose of 450mg, appropriate to food supplements, an active group at the dosage of 900 mg per

day, corresponding to a dose close to the therapeutic dose in France, as a positive control, and a placebo group serving as a negative control. The difference of the knee pain, measured by VAS, between MCS450 group and placebo group after three months of supplementation was not significant, but in the MCS450 group, the pain significantly decreases between one month and three months while the VAS score in the placebo group did not change within the same period (data not shown). Joint comfort was also assessed with the WOMAC questionnaire. At the end of the study, the difference versus baseline in both WOMAC total and WOMAC pain subscale was improved by 10% in the supplemented group MCS450 compared to placebo. This is consistent with the conclusion reported by Singh et al. in a Cochrane review, even if the daily dose used in our study is lower than those used in the clinical trials included in the review[7].

The score versus baseline of the WOMAC function subscale was significantly decreased in the MCS450 group compared to the placebo group suggesting an improvement of the physical function. This finding is in accordance with the results presented in the literature[7,14].

In our study, we included new parameters to assess the physical function and the mobility thanks to daily records obtained with the smartwatch. The number of daily steps in the MCS450 group was increased by 142 steps per day between the beginning and the end of the study, compared to a reduction of 18 steps per day in the placebo group. The number of active minutes per day recorded by the smartwatch was also significantly higher in the MCS450 group compared to placebo. The observed increases in daily step count and active minutes suggest that MCS supplementation may have a beneficial effect on mobility in individuals affected by osteoarthritis. These findings bring a new objective measurement in the joint health assessment in line with the joint function evaluated by WOMAC questionnaire.

Beyond impairing mobility, osteoarthritis also negatively impacts the overall quality of life of patients. The correlation between sleep disorders and joint pain has been highlighted in several cohort studies[15,16]. This present study proposes a novel input in joint pain management by evaluating the sleep duration. In the supplemented group, the sleep duration was enhanced by 9 minutes per night compared to the beginning of the study, corresponding to 4,5 hours more sleep per month.

In light of the above, Chondro'Sea®, hydrolyzed marine chondroitin sulfate, at the daily dose of 450mg, constitutes an effective natural nutraceutical option for the management of joint pain and mobility in middle-aged adults. The pharmacokinetic profile observed in an in vivo study needs to be confirmed in a clinical study in healthy volunteers. To confirm the positive results reported on joint pain and mobility in this real-life study, a placebo-controlled clinical trial assessing the long-term effects of MCS over a period exceeding three months would be valuable.

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