

ORIGINAL ARTICLE

IMPROVED PHYSICAL FUNCTION WITH COMPLEMENTARY USE OF A DIETARY SUPPLEMENT FOR MILD KNEE OSTEOARTHRITIS: A SUBGROUP ANALYSIS

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ABSTRACT

The aim: In this study, we present a sub-analysis of physical functionality in sufferers of mild knee osteoarthritis (OA) following a clinical assessment of a novel nutraceutical supplement Tregocel[®] complementary to standard treatment.

Materials and methods: We evaluated the results of a multicenter, open-label, single-arm efficacy and safety evaluation of a polyherbal nutraceutical, performed in subjects with symptomatic, mild knee OA (n = 107, 59.7 ± 10.8 yrs, 68.2% female) over 36 weeks. Physical function was assessed using a standardized walking challenge (6-min walk test), combined with WOMAC indices and leg flexion measurements. Sub-analysis was performed using a linear mixed model that tracked changes in the walking challenge outcomes over time, adjusted for age, gender, and OA duration.

Results: Walking distance was significantly improved with the duration of nutraceutical use, increasing by 0.72 m (95% CI: 0.56, 0.88) per week of product administration. Similarly, there were significant decreases in WOMAC indices per week for stiffness (-1.6, 95% CI: -1.8, 1.4), daily functioning (-13.5, 95% CI: 14.9, 11.9) and global outcome (-19.2, 95% CI -21.3 – -17.1). Furthermore, supine heel-to-high flexion distance was improved relative to the duration of nutraceutical use.

Conclusions: The use of a polyherbal nutraceutical resulted in clinical improvements in several indices of physical functioning in mild knee OA sufferers.

Trial registration: NCT03636035

KEY WORDS: curcuminoids; osteoarthritis; 6-minute walk test; WOMAC; heel-thigh distance flexion test

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INTRODUCTION

Knee Osteoarthritis (OA) is a disease of global importance that detrimentally affects the day-to-day physical mobility of individuals and has a major impact on community health in general [1]. Data obtained in the 2017 Global Burden of Disease study reported a value of 303.1 million (95% CI 273.3, 338.6) prevalent hip and knee OA cases, with a 9.3% increase between 1990 and 2017 [2].

The incidence of knee OA is related to natural age-related joint degeneration and wear and is more common over the age of 50 [1]. The most common observations are pain and stiffness of the affected joint(s), limiting mobility and flexibility, which may worsen with activity and/or improve with rest. Early morning features lasting more than 30 minutes are also reported [3] along with psychosocial and environmental comorbidities [4]. Since knee OA is caused by physical degeneration of the knee cartilage, it may also be exacerbated by increased wear associated with high-impact physical activity involving the legs and feet, such as ball sports [5]. While knee OA is typically treated with either one or a combination of pharmacological or physical therapies, there has been increasing interest in the efficacy of complementary therapies.

Previously we focused on the overall results of clinical administration of a novel combination of standardized herbal actives (Tregocel[®]) administered in parallel with standard therapies to mild knee OA sufferers [6]. The product contains a patented, clinically trailed curcuminoid preparation (Meriva) and extracts of the herbs *Harpagophytum procumbens*, *Boswellia serrata*, *Apium graveolens*, and *Zingiber officinale*. Curcuminoids [7], boswellic acids [8], ginger, harpagosides, and celery seed flavonoids [9]. All components have been shown to provide clinically relevant pain relief, anti-inflammatory effects, and improved physical performance in knee OA. Meriva[®] has specifically shown improvement in age-related OA, while also supporting delayed muscle soreness [10]. The original trial was performed in 2019, involving recruitment across eight clinical sites in Poland and assessing joint function (WOMAC indices, 6-min walk tests, joint flexibility) and safety parameters.

THE AIM

In this subgroup analysis, we aimed to study the effects of Tregocel[®] on physical performance.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION

The study conformed to the STROBE statement for reporting observational studies [11]. A detailed study description was provided earlier [6]. In short, this was a multicenter, open-label, non-randomized, single-arm study which included a 1-week screening/run-in period, followed by 36 weeks of Tregocel[®] supplementation and a 4-week follow-up period after the last dose of supplementation. The study population consisted of participants with symptomatic mild knee OA requiring pharmacologic treatment for pain.

INVESTIGATIONAL PRODUCT

Subjects received Tregocel[®] supplementation for 36 weeks (two tablets per day). The daily dose was equivalent to 1 g of curcuminoid-phospholipid complex, which is the primary active ingredient. Each Tregocel[®] film-coated tablet contains curcuma phospholipid (500 mg; equiv. curcumin 90 mg), *Boswellia serrata* (Indian frankincense) gum oleoresin extract (500 mg; equiv. boswellic acids – 81.25 g), *Harpagophytum procumbens* (devil's claw) tuber (500 mg), *Apium graveolens* (celery) seed (500 mg), and *Zingiber officinale* (ginger) rhizome (165 mg).

STUDY ASSESSMENTS AND PROCEDURES

Subjects with OA involving other joints were allowed; providing pain in the target knee was the most predominant OA symptom and with no expected impact of pain in other OA locations on the primary outcome measure. Data from the subject medical history, including ongoing treatment and/or therapies and medications, was gathered. Osteoarthritis severity was assessed based on Kellgren-Lawrence classification (grades 0 – 4) [12]. For physical performance, a 6-minute walk test (6MWT) and heel-thigh distance flexion test were performed during clinic visits, based on a recording of the distance covered (in meters) during 6 minutes of walking in a straight line. In heel-thigh distance flexion tests, the investigator evaluated the angle and distance between heel and thigh at maximum knee flexion in both supine and prone positions. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire was also used to assess physical and general performance. WOMAC is a widely used, proprietary health status questionnaire used to evaluate the condition of patients with OA of the knee and hip, including pain (5 items), stiffness (2 items), and physical functioning (17 items). The translated and validated Polish version of the WOMAC (VAS-based) was used in this study, with permission from Prof Nicholas Bellamy, University of Queensland, Herston, Australia (copyright holder <http://www.womac.org>) [13].

STATISTICS

A sample size of 150 was calculated as sufficient to determine a statistically significant mean difference of approximately 30% of standard deviation, assuming the use of

paired Student's t-test, at a significance level $\alpha = 0.05$ and power of 90%. Continuous data are presented as mean and standard deviation (SD), median with 1st and 3rd quartiles (Q1 and Q3), minimum and maximum. Categorical data are presented as numbers and percentages. The distribution of categorical variables was compared between time points using Mc Nemar's test. The distribution of continuous variables was first evaluated with the Shapiro-Wilk test. Then the normally distributed variables were compared between time points using the paired Student's t-test; otherwise, the Wilcoxon test for paired data was used.

As a part of exploratory analysis effect of duration of Tregocel[®] supplementation on efficacy endpoints (physical mobility) was assessed using mixed models adjusted for covariates that potentially influencing therapy results. Linear mixed effect models (random intercept repeated measures models) for primary, secondary efficacy, and exploratory outcome measures were built, with explanatory variables duration of Tregocel[®] supplementation, quartile of baseline 6MWT result, quartile of OA duration, age, and sex of the participant. Analysis of changes of endpoints in time in selected subgroups of the analyzed population was done using the Skillings-Mack test.

The significance level was set at $\alpha = 0.05$. Two-sided tests were used. Statistical analyses were performed using statistical package R, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

STUDY POPULATION

Between January and April 2019, a total number of 107 participants completed the full 36-week Tregocel[®] supplementation period. The mean observation time was 291.1 ± 7.7 days. The mean age was 59.7 ± 10.8 years, and women stand for 68.2% ($n = 73$) of the study population. The right knee was recognized as the target knee in 62.6% ($n = 67$). The distribution of knee OA severity as per Kellgren-Lawrence classification was found to be as follows: class 0 – 4.7%, class 1 – 50.5%, and class 2 – 44.9%. The median duration of OA was 1.8 [Q1-Q3 1.2 – 4.6] years (min 0.4, max 17.7 years), and the mean 6MWT distance was 382.8 ± 88.1 m (min. 162, max. 605 m).

6-MINUTE WALKING TEST

At baseline, the mean 6MWT result was 382.8 ± 88.1 m, and at the end of the study, it was 408.8 ± 96.3 m. The mean difference of 26.0 ± 30.4 m was statistically significant ($p < 0.001$). A statistically significant improvement was observed in all subgroups (quartiles of baseline 6MWT and quartiles of OA duration) (Fig. 1). Additionally, in the analysis of 6MWT results performed using mixed-effect linear model, a significant effect of product administration duration on 6MWT result was identified (6MWT increases by 0.72 m, 95% CI 0.56 to 0.88 m, with an increase in product administration duration by one week) as well as baseline 6MWT result and age affects 6MWT results

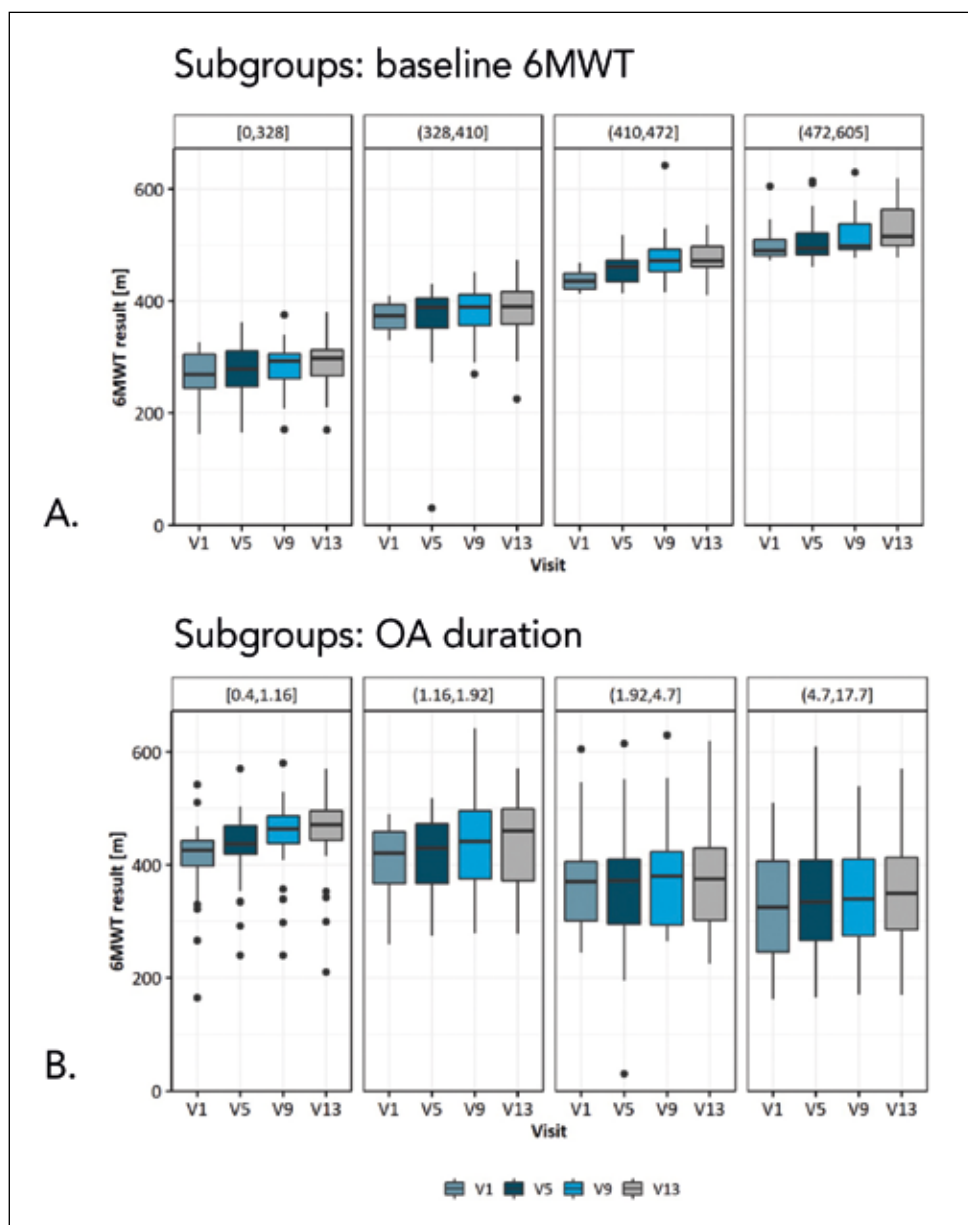


Fig. 1. 6-minute walking test results. (A) By quartiles of baseline results of 6MWT in meters, (B) by quartiles of osteoarthritis duration (OA) in years.

significantly. Gender and OA duration did not affect the 6MWT results (Table I).

WOMAC SCORES

WOMAC scores assessed before the 6MWT in all domains (pain, stiffness, physical function, and total) had improved progressively throughout the study. The scores on the subsequent visits were statistically significantly lower than initial values ($p < 0.001$ for all comparisons). The decrease level was the greatest on the first efficacy assessment after 12 weeks of Tregocel[®] supplementation (about 50% in all domains) and continued to improve in subsequent visits. This was also true for all subgroups (quartiles of baseline 6MWT and quartiles of OA duration) (Fig. 2). In the linear mixed model duration of Tregocel[®] administration was the only factor significantly affecting WOMAC pain (-4.1, 95% CI -4.7 to -3.7 per 1 week of Tregocel[®] supplementation),

stiffness (-1.6, 95% CI -1.8 to -1.4), function (-13.5, 95% CI -14.9 to -11.9) and total result (-19.2, 95% CI -21.3 to -17.1) (Table II).

HEEL-THIGH DISTANCE FLEXION TESTS

Changes in time of supine distance in subgroups of patients defined by quartiles of baseline 6MWT and OA duration are presented in Figure 3. Analysis of changes in time of HTF supine distance and angle as well as prone distance and angle when controlling for age, gender, baseline 6MWT, and OA duration are presented in Table III. HTF supine distance decreased, and HTF prone result increased significantly. It was also observed that age significantly increased the result of HTF supine and prone distance. There were no effects of gender and OA duration on any of the analyzed endpoints. The effect of baseline 6MWT was not consistent.

Table I. Linear mixed model results for 6-minute walking test.

Explained variable	Explanatory variable	Category	Regression coefficient (95% CI)	p-value	
6MWT result	Duration of Tregocel [®] supplementation [week]		0.72 (0.56 – 0.88)	<0.001	
		Age [years]	-1.07 (-1.87 – -0.26)		0.013
		Gender (ref. Male)	Female	-3.21 (-18.92 – 12.48)	0.699
			(328,410)	92.81 (74.20 – 111.43)	
		Quartile of baseline 6MWT result [m] (ref. [0,328])	(410,472)	155.33 (129.47 – 181.18)	<0.001
	(472,605)		219.77 (193.10 – 246.43)		
	(1.16,1.92)		-10.58 (-29.04 – 7.87)		
		Quartile of OA duration [years] (ref. [0.4,1.16])	(1.92,4.7)	-2.67 (-21.98 – 16.63)	0.423
			(4.7,17.7)	-15.76 (-36.72 – 5.18)	

6MWT – 6-minute walking test, OA – osteoarthritis

Additional analyses of changes in time in subgroups defined by quartiles of 6MWT and OA duration showed consistent, statistically significant improvement in time of supine distance in all subgroups. Effect of changes in time mainly was visible in 2nd and 4th quartiles of 6MWT and in 1st and 4th quartiles of OA duration; however, those results should be treated with caution because of smaller sample sizes.

DISCUSSION

In this subgroup analysis, we found that the polyherbal product, Tregocel[®], given as a dietary supplement in parallel with standard medications for mild knee osteoarthritis, improved joint functional capacity, walking efficiency, WOMAC domains, and joint flexibility. These differences appeared as early as 12 weeks of supplementation and continued linearly to completion at 36 weeks.

As mentioned earlier, knee OA is a chronic medical condition of public health importance. Ogunbode et al. performed a cross-sectional study that described adult patients' physical functionality and self-rated health status with clinical knee OA [14]. Respondents with knee OA significantly rated their health worse than those without knee OA ($p < 0.0001$). Experience of pain, stiffness, and performance of daily activities were significantly worse among respondents with knee OA. Those who had knee OA had significantly higher waist ($p < 0.0001$), hip ($p < 0.0001$) and knee circumferences ($p < 0.0001$) respectively. Logistic regression analysis showed increasing age (OR = 1.103; 95% CI = 1.022 – 1.191), self-rated health worse than six months ago (OR = 12.562; 95% CI = 1.178 – 125.243), experience of stiffness after waking up in the morning

(OR = 12.758; 95% CI = 3.572 – 45.569), stiffness after sitting/lying down/resting (OR = 21.517; 95% CI = 2.213 – 209.220) and waist circumference (OR = 1.225; 95% CI = 1.017 – 1.477) to be the most significantly associated with knee osteoarthritis. In our previous manuscript, we also observed similar problems in functional capacity, pain, and morning stiffness [6]. Therefore, in the present subgroup analysis, we verified whether Tregocel[®] supplementation is effective regardless of the baseline functional capacity (distance in 6MWT) as well as the duration of knee OA.

The functional capacity is vital since it is associated with improved quality of life and daily activities. Knee OA is often in older patients, and one of the most frequent comorbidities is obesity. Obesity and knee osteoarthritis are independently disabling conditions and, in combination, pose complex therapeutic challenges [15]. Currently, the standard of care remains initial conservative management with lifestyle changes, including weight loss with concurrent anti-inflammatory regimens. Injections are frequently used to escalate care, but a significant number of patients ultimately resort to total knee arthroplasty [16]. In our study, we proved that Tregocel[®] supplementation led to improved functional capacity supported by the increased distance in 6MWT as well as in the WOMAC physical function scores. Moreover, the supine distance was also improved in the heel-thigh distance flexion test in all subgroups. This might be a new option in conservative management in knee OA.

The ability to perform physical activity is an important factor in measuring knee OA advancement and a method to decrease the progression of knee OA itself and decrease signs and symptoms. Fernandopopulle et al. performed a meta-analysis evaluating the effects of land-based generic physical activity interventions on pain, physical function,

Table II. Linear mixed model results for WOMAC scores.

Explained variable	Explanatory variable	Category	Regression coefficient (95% CI)	p-value LRT
WOMAC PAIN	Duration of Tregocel® supplementation [week]		-4.11 (-4.56 – -3.66)	<0.001
		Age [years]	-0.44 (-1.89 – 1.00)	0.561
	Gender (ref. Male)	Female	-6.07 (-34.37 – 22.23)	0.686
		(328,410)	-21.66 (-55.20 – 11.87)	
	Quartile of baseline 6WMT result [m] (ref. [0,328])	(410,472)	-51.81 (-98.41 – -5.21)	0.188
		(472,605)	-47.61 (-95.67 – 0.43)	
		(1.16,1.92)	27.08 (-6.18 – 60.35)	
		Quartile of OA duration [years] (ref. [0.4,1.16])	(1.92,4.7)	
	(4.7,17.7)		10.69 (-27.06 – 48.45)	
	WOMAC STIFFNESS	Duration of Tregocel® supplementation [week]		-1.60 (-1.81 – -1.39)
Age [years]			-0.15 (-0.83 – 0.53)	0.681
Gender		Female vs Male	4.16 (-9.30 – 17.62)	0.560
		(328,410)	-6.86 (-22.82 – 9.08)	
Quartile of baseline 6WMT result [m] (ref. [0,328])		(410,472)	-19.50 (-41.67 – 2.65)	0.102
		(472,605)	-29.36 (-52.21 – -6.50)	
		(1.16,1.92)	10.46 (-5.35 – 26.28)	
		Quartile of OA duration [years] (ref. [0.4,1.16])	(1.92,4.7)	
(4.7,17.7)			1.10 (-16.85 – 19.06)	
WOMAC PHYSICAL FUNCTION		Duration of Tregocel® supplementation [week]		-13.44 (-14.97 – -11.92)
	Age [years]		-1.51 (-6.46 – 3.43)	0.563
	Gender (ref. Male)	Female	3.87 (-92.86 – 100.60)	0.940
		(328,410)	-76.55 (-191.18 – 38.07)	
	Quartile of baseline 6WMT result [m] (ref. [0,328])	(410,472)	-190.48 (-349.74 – 31.23)	0.145
		(472,605)	-167.49 (-331.72 – 3.26)	
		(1.16,1.92)	89.98 (-23.71 – 203.68)	
		Quartile of OA duration [years] (ref. [0.4,1.16])	(1.92,4.7)	
	(4.7,17.7)		47.39 (-81.64 – 176.42)	
	WOMAC TOTAL	Duration of Tregocel® supplementation [week]		-19.16 (-21.26 – 17.07)

Table II. Cont.

Explained variable	Explanatory variable	Category	Regression coefficient (95% CI)	p-value LRT
	Age [years]		-2.11 (-8.97 – 4.75)	0.562
	Gender (ref. Male)	Female	1.99 (-132.14 – 136.13)	0.978
		(328,410)	-105.06 (-264.02 – 53.88)	
	Quartile of baseline 6MWT result [m] (ref. [0,328])	(410,472)	-261.78 (-482.62 – 40.94)	0.137
		(472,605)	-244.42 (-472.15 – 16.68)	
		(1.16,1.92)	127.56 (-30.10 – 285.22)	
	Quartile of OA duration [years] (ref. [0.4,1.16])	(1.92,4.7)	167.02 (2.12 – 331.92)	0.195
		(4.7,17.7)	59.20 (-119.72 – 238.13)	

6MWT – 6-minute walking test, OA – osteoarthritis

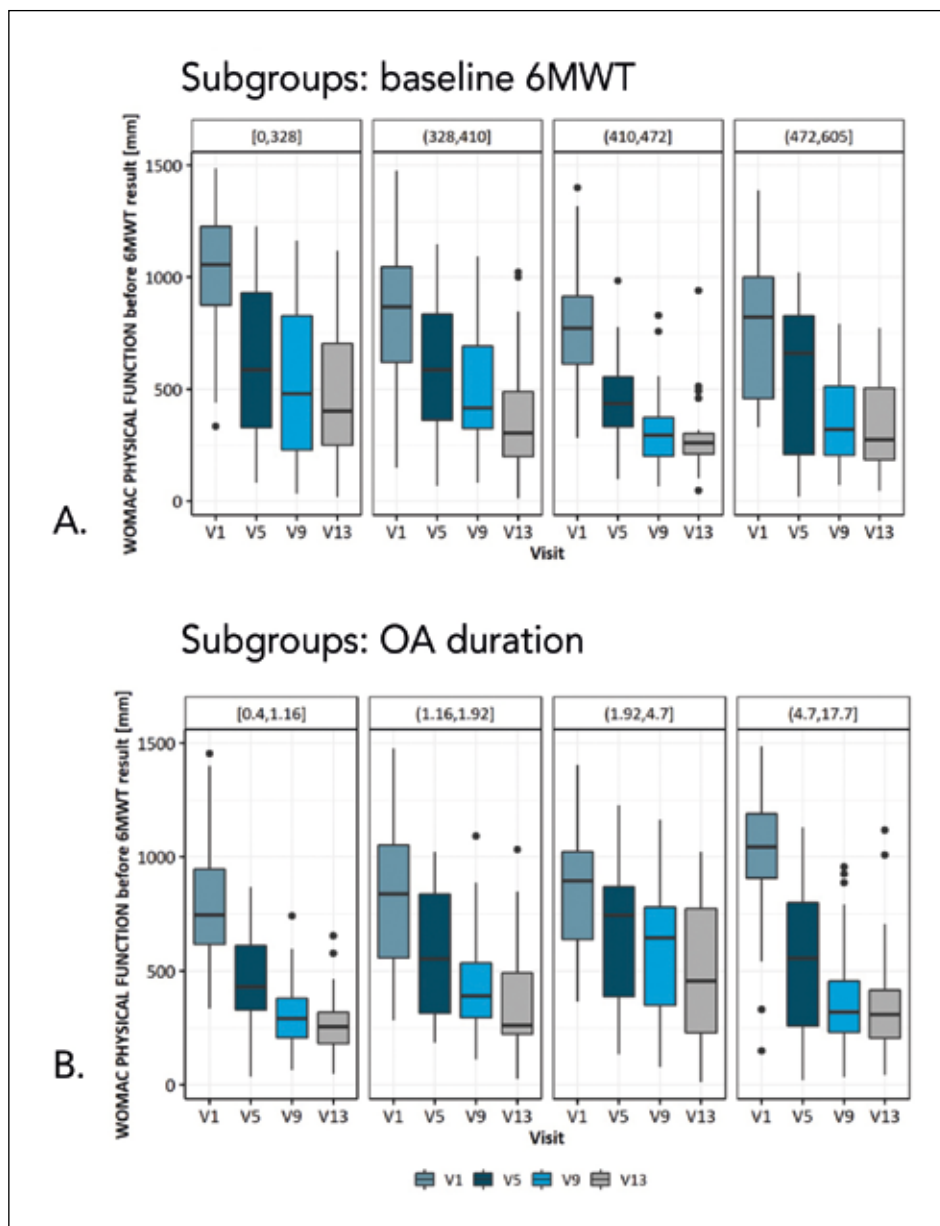


Fig. 2. WOMAC Physical Function results. (A) By quartiles of baseline results of 6MWT in meters, (B) by quartiles of osteoarthritis duration (OA) in years.

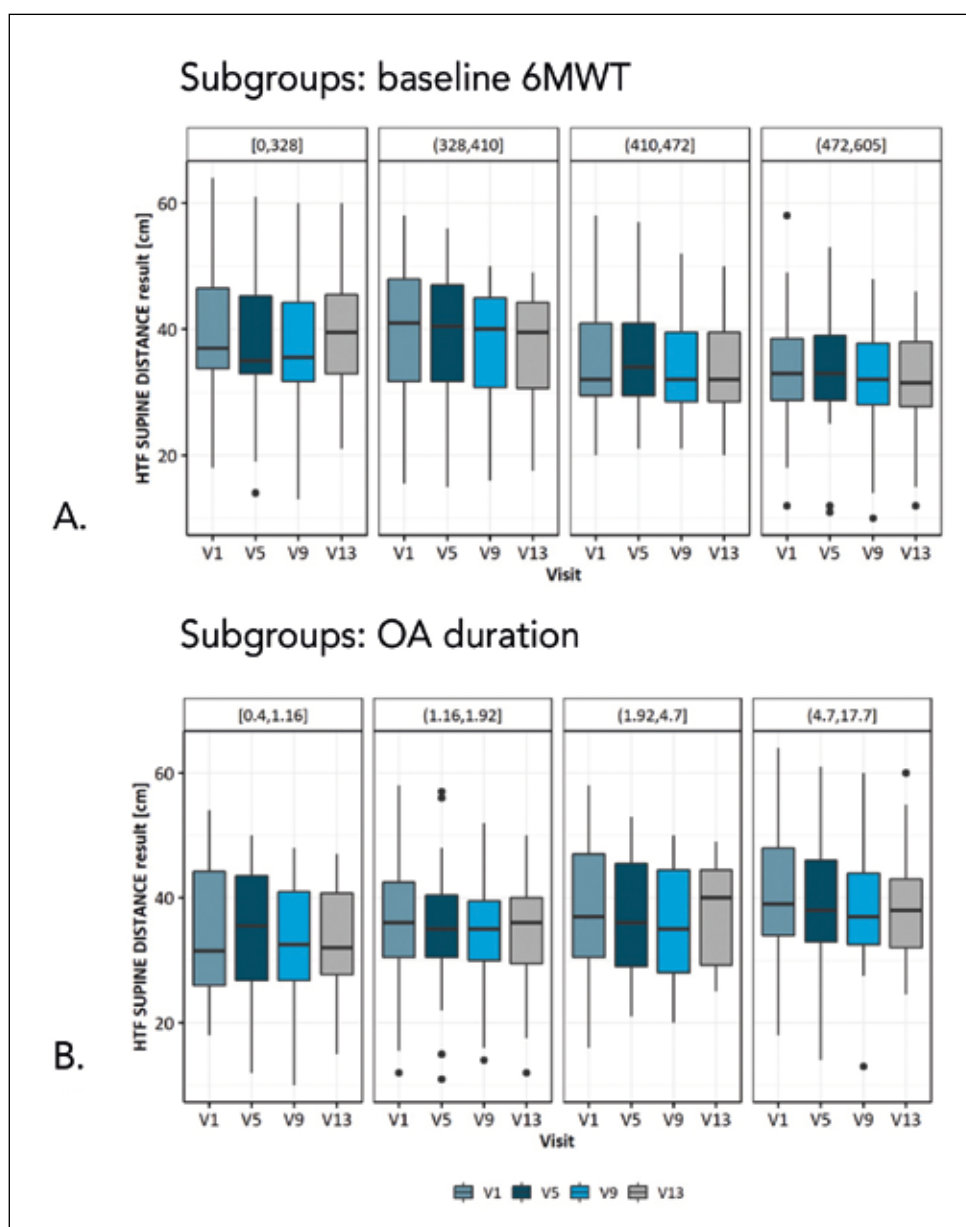


Fig. 3. Heel-thigh distance flexion test – supine distance results. (A) By quartiles of baseline results of 6MWT in meters, (B) by quartiles of osteoarthritis duration (OA) in years.

and physical performance in individuals with hip/knee OA when compared with a control group that received no intervention, minimal intervention, or usual care [17]. Meta-analysis for recreational activity ($n = 3$) demonstrated significant mean difference of -9.56 (95% CI -13.95 to -5.17) for physical function (WOMAC) at 3 months from randomization. The pooled estimate for walking intervention was not significant for pain intensity and physical performance but was significant for physical function ($n = 2$) with a mean difference of -10.38 (95% CI -12.27 to -8.48) at six months. Meta-analysis for conditioning exercise was significant for physical function ($n = 3$) with a mean difference of -3.74 (95% CI -5.70 to -1.78) and physical performance (6-minute walk test) with a mean difference of 42.72 m (95% CI 27.78 to 57.66) at six months. The timed stair-climbing test ($n = 2$) demonstrated a significant effect at 18 months with a mean difference of -0.49 seconds (95% CI, -0.75 to -0.23).

The results of our study with Tregocel[®] (improvement in functional capacity) were consistent with the observations of previous clinical studies involving the curcuminoids-phytosome complex used in the formulation [18, 19] since curcumin has the potential to restrain inflammation and tissue damage in OA [20, 21].

In a systematic review, Onakpoya et al. investigated the efficacy of curcuminoids administered orally in OA [22]. The authors included seven studies with a total number of 797 patients with primary knee OA. Compared with placebo, the use of curcuminoids significantly decreased knee pain ($p = 0.001$) and improved quality of life ($p < 0.001$). Curcuminoid use was also associated with significant improvements in WOMAC total scores as well as with significant reductions in the use of rescue medication. Haroyan et al. proved that curcuminoid complex extract from turmeric rhizome with volatile turmeric oil, combined with an extract of boswellic acids performed better than placebo in physical performance

Table III. Linear mixed model results for heel-thigh distance flexion test results.

Explained variable	Explanatory variable	Category	Regression coefficient (95% CI)	p-value LRT	
HTF supine distance result	Duration of Tregocel [®] supplementation [week]		-0.039 (-0.058 – 0.020)	<0.001	
		Age [years]	0.289 (0.074 – 0.505)	0.012	
	Gender (ref. Male)	Female	0.540 (-3.663 – 4.743)	0.808	
		(328,410)	2.671 (-2.309 – 7.651)		
	Quartile of baseline 6WMT result [m] (ref. [0,328])	(410,472)	3.095 (-3.825 – 10.014)	0.553	
		(472,605)	-0.207 (-7.343 – 6.928)		
	Quartile of OA duration [years] (ref. [0.4,1.16])	(1.16,1.92)	0.025 (-4.915 – 4.965)		
		(1.92,4.7)	2.235 (-2.932 – 7.401)	0.665	
		(4.7,17.7)	2.974 (-2.632 – 8.580)		
		Duration of Tregocel [®] supplementation [week]		-0.015 (-0.048 – 0.018)	0.369
	HTF supine angle result	Age [years]		-0.104 (-0.685 – 0.476)	0.735
			Gender (ref. Male)	Female	-3.393 (-14.736 – 7.949)
Quartile of baseline 6WMT result [m] (ref. [0,328])		(328,410)	7.143 (-6.299 – 20.584)		
		(410,472)	27.174 (8.500 – 45.848)	0.024	
Quartile of OA duration [years] (ref. [0.4,1.16])		(472,605)	7.978 (-11.279 – 27.235)		
		(1.16,1.92)	-11.332 (-24.664 – 2.000)		
		(1.92,4.7)	-6.275 (-20.218 – 7.669)	0.441	
		(4.7,17.7)	-8.934 (-24.064 – 6.196)		
HTF prone distance result		Duration of Tregocel [®] supplementation [week]		-0.026 (-0.057 – 0.004)	0.089
			Age [years]	0.277 (0.014 – 0.540)	0.049
		Gender (ref. Male)	Female	1.309 (-3.826 – 6.445)	0.630
			(328,410)	-1.619 (-7.704 – 4.467)	
	Quartile of baseline 6WMT result [m] (ref. [0,328])	(410,472)	-0.627 (-9.082 – 7.828)	0.637	
		(472,605)	-4.808 (-13.527 – 3.911)		
	Quartile of OA duration [years] (ref. [0.4,1.16])	(1.16,1.92)	0.704 (-5.333 – 6.740)		
		(1.92,4.7)	4.140 (-2.174 – 10.453)	0.632	
		(4.7,17.7)	2.286 (-4.564 – 9.137)		
		Duration of Tregocel [®] supplementation [week]		0.076 (0.029 – 0.122)	0.002
	HTF prone angle result				

Table III. Cont.

Explained variable	Explanatory variable	Category	Regression coefficient (95% CI)	p-value LRT
	Age [years]		0.163 (-0.341 – 0.666)	0.542
	Gender (ref. Male)	Female	-1.312 (-11.142 – 8.518)	0.801
	Quartile of baseline 6WMT result [m] (ref. [0,328])	(328,410)	4.427 (-7.222 – 16.076)	0.037
		(410,472)	22.500 (6.316 – 38.685)	
		(472,605)	8.671 (-8.019 – 25.360)	
		(1.16,1.92)	-10.888 (-22.443 – 0.667)	
	Quartile of OA duration [years] (ref. [0.4,1.16])	(1.92,4.7)	-1.059 (-13.144 – 11.026)	0.285
		(4.7,17.7)	-3.135 (-16.247 – 9.978)	

6WMT – 6-minute walking test, HTF – heel-thigh distance flexion test, OA – osteoarthritis

tests and the WOMAC joint pain index, while when only the curcuminoid complex extract was used it was more effective than placebo only in terms of physical performance tests [23]. A further meta-analysis by Bannuru et al. confirmed that curcuminoids and *Boswellia* formulations might pose a valuable additive to the knee OA treatment regimens [24]. They effectively relieve pain symptoms and simultaneously reduce safety risks.

STUDY LIMITATIONS

Limitations of the present study include the lack of a placebo group for comparison of effects, as well as the use of concomitant therapies (e.g., NSAIDs). To this latter point, the overall use of standard medication or physical treatments showed a linear decrease with Tregocel's use duration (results not shown).

CONCLUSIONS

In this subgroup analysis, we demonstrate that a polyherbal product, Tregocel, given as a dietary supplement in parallel with standard medications for mild knee osteoarthritis, improves joint flexibility, physical functioning, and endurance progressively over a 36-week study period. The results suggest that phytomedicines such as these can be safely and successfully implemented as complementary therapies for osteoarthritis and potentially other forms of joint inflammation.

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