

# Movardol<sup>®</sup> (N-acetylglucosamine, *Boswellia serrata*, ginger) supplementation in the management of knee osteoarthritis: preliminary results from a 6-month registry study

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**Abstract. – OBJECTIVE:** Knee Osteoarthritis (OA) is a chronic disease caused by the deterioration of cartilage in joints, which results in activation of the inflammatory response, pain, and impaired movement. Complementary therapies, particularly supplementation, in the management of moderate/severe knee OA have been gaining attention. This registry study aimed at evaluating the synergistic effect of Movardol<sup>®</sup>, a supplementation containing active ingredients with recognized anti-inflammatory activities on symptoms and levels of circulating biomarkers of knee OA.

**PATIENTS AND METHODS:** 54 subjects with symptomatic, moderate knee OA freely decided to follow either a standard management (SM) (n = 26) or SM plus oral supplementation with Movardol<sup>®</sup> (n = 28). Movardol<sup>®</sup> supplementation containing N-acetyl-D-glucosamine, ginger, and *Boswellia Serrata* extract was taken at the following dosage: 3 tablets/day for one week and then 2 tablets/day. Several parameters were assessed at inclusion and after 1, 3 and 6 months: functional impairment by the Karnofsky Performance Scale Index; pain, stiffness, physical, social and emotional functions by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); total and pain-free walking distance; circulating biomarkers of inflammation and oxidative stress.

**RESULTS:** Significant improvements in the functional outcomes and pain-free walking distance were observed after 1, 3 and 6 months in OA patients supplemented with Movardol<sup>®</sup>. Moreover, all the signs/symptoms of disease assessed by the WOMAC tended to regress over a 6-month period in patients following SM+supplementation. Inflammatory markers and plasmatic content of reactive oxygen species decreased over 6 months, in supplemented patients. Movardol<sup>®</sup> supplementation resulted to be safe and well tolerated, also showing the beneficial effect

in term of a decrease in pharmacological and non-pharmacological treatments and, consequently, reduction in management costs.

**CONCLUSIONS:** These preliminary results indicate the efficacy and safety of Movardol<sup>®</sup> supplementation in the management of moderate knee OA.

*Key Words:*

Knee osteoarthritis, Inflammation, Oral supplementation, N-acetyl-D-glucosamine, Ginger extract, *Boswellia serrata* extract.

## Introduction

Osteoarthritis (OA) is a long-term chronic disease characterized by the deterioration of cartilage in joints, which results in bones rubbing together and creating stiffness, pain, and impaired movement. The erosion of the articular cartilage causes a repetitive inflammatory response followed by a reparative bone response known as osteophytosis<sup>1,2</sup>. The disease most commonly affects the joints in the knees, hands, feet, and spine, and is relatively common in shoulder and hip joints.

OA is one of the ten most disabling diseases in developed countries, with an estimated worldwide prevalence in adults aged over 60 years of 10% in men and 18% in women<sup>3</sup>. Furthermore, the prevalence of OA is rising due to population aging and increasing associated factors such as obesity. This means that by 2050, 130 million people will suffer from OA worldwide, of whom 40 million will be severely disabled by the disease<sup>4</sup>. In particular, the onset of knee OA has been mainly associated with overweight, obesity,

female gender and previous knee injury<sup>5</sup>. Clinicians should take into account these risk factors to identify and manage patients at risk of developing or increasing knee pain. To reduce the burden of knee OA, the European League Against Rheumatism (EULAR) proposed<sup>6</sup> as non-pharmacological core management, the lifestyle changes including diet and exercise for musculoskeletal strengthening and weight loss.

Since almost 80% of patients with OA have constant pain on a regular basis, topical and oral drugs such as analgesics, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are the most common approaches to reducing symptoms and improve patient's quality of life (QoL)<sup>7</sup>. Opioids are another option in patients with marked pain, but they may be associated with poor tolerability<sup>8</sup>. Overall, side effects associated with the long-term use of systemic and local pharmaceuticals have frequently been reported; the use of pharmacological agents should, therefore, be considered with caution by assessing the risk/benefit ratio of the drugs prescribed.

Complementary managements, particularly supplementation, have been gaining importance for moderate/severe knee OA, but studies on these approaches are still limited.

The aim of study was to evaluate the synergistic effect of different active ingredients with recognized anti-inflammatory activities, in improving symptoms and levels of circulating biomarkers of knee OA. A new standardized oral supplementation containing N-acetyl-D-glucosamine, *Boswellia serrata* extracts and *Zingiber officinale* (ginger) extract was investigated in subjects with knee OA, over a 6-month follow-up.

## Patients and Methods

This was a registry supplement study conducted in 54 subjects with the presence of symptomatic OA of the knee. Supplement studies define the field of activity of pharma-standard supplements and their possible preventive, preclinical applications and produce supplementary data to be compared with those from the best available management plans. These types of researches are performed with products with high level of safety and pharmaceutical standards<sup>9-11</sup>.

X-rays showed significant arthritis in both knees without signs of previous fractures. A minimal joint effusion has been diagnosed in all subjects at inclusion by ultrasound. A complete eval-

uation of the arteries and veins by Duplex Doppler revealed no vascular problems at baseline. Ultrafast thermography (Flir 440, Taby, Sweden) indicated an increase in the temperature of the knee of at least 2°C in comparison with the surrounding tissues, at inclusion. They were otherwise healthy with a BMI (body mass index kg/m<sup>2</sup>) < 26. No other significant disease or alterations in blood tests were observed at inclusion.

Informed participants (n = 54) freely decided to follow either a standard management (SM) to control joint pain (control group = 26) or SM associated with oral daily supplementation (supplement group = 28). The supplementation product (Movardol®, Leonardo Medica, Vinci, Florence, Italy) includes N-acetyl-D-glucosamine (500 mg/tablet), Ginger extract containing 5% gingerols (250 mg) and *Boswellia serrata* extract containing 65% boswellic acids (180 mg); supplementation dosage consisted of 3 tablets/day for one week and then 2 tablets/day.

All subjects were evaluated at inclusion and at different time point during the observational period (1, 3 and 6 months): (1) the functional impairment due to knee pain by the Karnofsky Performance Scale Index<sup>12</sup>; (2) pain, stiffness and physical, social and emotional functions were assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)<sup>13</sup>; (3) total and pain-free walking distance by the treadmill test; (4) circulating biomarkers of inflammation; (5) oxidative stress measured by the Free Radical Analytical System (FRAS, H&D srl, Parma, Italy)<sup>14,15</sup>.

## Statistical Analysis

Comparison between groups was performed by using nonparametric tests and ANOVA test, with post hoc Dunnett's correction, as appropriate. *p*-value < 0.05 was considered significant.

## Results

Details of the two groups are shown in Table I. The supplemented group and the control group were comparable in term of age and gender distribution. At 1 month, the Karnofsky Performance Scale revealed significant improvements of the total functional outcome in both groups, with inclusion (Table II). However, differently from the SM only, the SM plus oral supplementation exerted a beneficial effect persisting after 3 and 6 months (91 and 93.2 re-

**Table I.** Details of subjects enrolled in the study.

	Standard management	Standard management + Movardol®
Subjects (females)	26 (10)	28 (10)
Age, years (mean ± SD)	53.1 ± 2	52.3 ± 4.2

SD: standard deviation.

**Table II.** Assessment of the functional impairment by Karnofsky Performance Scale Index (%) in the study groups.

	Standard management	Standard management + Movardol®
Inclusion	75.8 (63-87)	76.2 (59-82)
1 month	81.4 (70-83)*	88.3 (84-100)*
3 months	83.1 (73-94)	91 (85-100)*
6 months	85.2 (71-87)	93.2 (87-97)*

Data are expressed as median (range). \* $p < 0.05$  vs. inclusion.

spectively vs. 76.2 at inclusion, both  $p < 0.05$ ). All the signs/symptoms of the knee OA assessed by the WOMAC (pain, stiffness, physical function, social function, emotional function)

tended to continuously regress over a 6-month period in patients following SM+oral supplementation, compared with the control group (Table III). Table IV shows the results of the treadmill test. At the end of the observational period, patients supplemented with Movardol® were able to walk for a longer total distance ( $332.3 \pm 23.2$  m) than patients following the SM only ( $166.2 \pm 22$  m;  $p < 0.05$ ). Moreover, the pain-free walking distance in the supplemented group increased during the observational period, resulting higher than the control group values at every evaluated time-point (Table IV). Table V summarizes the inflammatory markers and the plasmatic content of reactive oxygen species, evaluated in the study groups. Overall, the study population did not present severe inflammation at inclusion; however, the moderate signs of inflammation decreased over 6 months, following the oral supplementation. We observed a significant decrease of the inflammation biomarkers at 1, 3 and 6 months, in Movardol® supplemented subjects compared with SM-only subjects (Table V). The reduction in plasma free radicals was significant in supplemented patients (Table V).

Table VI shows the effects of Movardol® supplementation in controlling the need for pharmacological and non-pharmacological treatments with a reduction in management costs.

**Table III.** Evaluation of the global condition in knee OA patients assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

	Standard management			Standard management + Movardol®		
	Inclusion	1 month	6 months	Inclusion	1 month	6 months
Pain	15.4 ± 1	15 ± 1.2	14.2 ± 1.1	16.2 ± 1.1	7.2 ± 1.4*	6.6 ± 1*
Stiffness	7.5 ± 1.3	7 ± 0.9	6.6 ± 1	7.6 ± 1	3.6 ± 0.9*	2.2 ± 1.1*
Physical function	54.2 ± 0.9	49 ± 1.2	33.2 ± 2.1	54.3 ± 1	23.1 ± 1.1*	16.1 ± 1.2*
Social function	24 ± 1	22 ± 1.5	13.2 ± 1.4	24.4 ± 1.1	18 ± 1.5*	11 ± 1.3*
Emotional function	32.2 ± 2.1	29.2 ± 1.4	12.1 ± 1.5	34 ± 1.5	16 ± 1.2*	7.3 ± 1.1*

Data are expressed as mean ± standard deviation. \* $p < 0.05$  vs. control group.

**Table IV.** Assessment of the pain-free and total walking distance by the treadmill test.

	Standard management				Standard management + Movardol®			
	Inclusion	1 month	3 months	6 months	Inclusion	1 month	3 months	6 months
Pain free walking distance (m)	72.3 ± 16.9 (21-163)	95 ± 11 (33-182)	119 ± 13.2 (48-212)	124.2 ± 22 (58-198)	65.3 ± 4.5 (20-155)	187 ± 7* (19-284)	198.4 ± 13.2* (55-396)	221 ± 17* (90-429)
Total walking distance (m)	78.4 ± 12 (27-188)	–	–	166.2 ± 22 (79-287)	74 ± 23.4 (34-180)	–	–	332.3 ± 23.2* (133-732)

Data are expressed as mean ± standard deviation (range). \* $p < 0.05$  vs. control group.

**Table V.** Assessment of the pain-free and total walking distance by the treadmill test.

	Standard management				Standard management + Movardol®			
	Inclusion	1 month	3 months	6 months	Inclusion	1 month	3 months	6 months
<b>Inflammation</b>								
sVCAM-1 (ng/mL)	651 ± 28	639 ± 19	640 ± 19	565 ± 23	644 ± 33	511 ± 34*	502 ± 22*	499 ± 21*
ERS (mm/hour)	26.2 ± 2	22 ± 1.3	18.2 ± 4.4	18.3 ± 4.2	24.5 ± 1.9	15.4 ± 2*	13.3 ± 3*	8.4 ± 2*
Fibrinogen (mg/mL)	3.6 ± 0.3	3 ± 0.4	3.1 ± 0.7	3.1 ± 0.6	3.4 ± 0.4	1.9 ± 1*	1.8 ± 0.7*	-
CRP (mg/L)	12.4 ± 1.1	8.3 ± 1.4	6.6 ± 1	6.2 ± 0.3	11 ± 1	4.9 ± 0.4*	4.1 ± 0.2*	3.7 ± 0.6*
<b>Oxidative stress</b>								
Plasmatic reactive oxygen metabolites (Carr Units)	388 ± 29	387 ± 28	397 ± 22	388 ± 24	398 ± 33	344 ± 26*	341 ± 16*	332 ± 21*

sVCAM-1 = serum Vascular Cell Adhesion Molecule-1; ERS = Erythrocyte Sedimentation Rate; CRP = C-reactive protein. Data are expressed as mean ± standard deviation. \**p* < 0.05 vs. control group.

Consistently, we also observed a significant reduction in gastrointestinal complications (likely due to the use of anti-inflammatory drugs) in supplemented subjects (-76% and -78%, at 3 and 6 months respectively), compared to the control group (-22% and -23%, at 3 and 6 months respectively). In the SM+Movardol® group, 4 patients out of 28 (on 12 separate occasions) needed for a rescue medication to reduce the knee pain (vs. 11/26 patients of the SM group, on 19 separate occasions). All subjects completed the study and the compliance to the supplementation was optimal, with 97.9% of the doses correctly used.

No safety and tolerability issues were observed during the observational period. The rou-

tine blood tests (including hematocrit, kidney and liver functions, urinary parameters) were all within normal values at inclusion and at 6 months, and no significant variations were observed during the study period (data not shown). The fasting sugar and glycated hemoglobin values were also within the normal range with the supplementation, and comparable to values from the control group (data not shown).

### Discussion

So far, none of the pharmacological treatments available for osteoarthritic conditions has shown

**Table VI.** Decrease in percentage of pharmacological and non-pharmacological treatments, and management costs in the study groups.

	Standard management			Standard management + Movardol®		
	Inclusion	1 month	6 months	Inclusion	1 month	6 months
<b>Need for concomitant drugs and treatment</b>						
Use of NSAIDs/painkillers	-12%	-9%	-12%	-58%	-66%*	-68%*
Use of other drugs	-22%	-23%	-25%	-45%	-48%*	-55%*
Use of non-pharmacological treatments	-23%	-16%	-32%	-33%	-42%*	-71%*
Hospital admission/specialist consultation	-32%	-30%	-33%	-56%	-61%*	-73%*
<b>Management costs</b>						
Management costs for the health provider	-18%	-22%	-24%	-47%	-51%*	-55%*
Management costs for the patient	-	-	-24%	-	-	-67%*

\**p* < 0.05 vs. control group.

efficacy and complete tolerability/safety in long-term administration; therefore, a combination of different therapeutic options is a preferable approach. Previous researches<sup>16</sup> investigated the efficacy of nutritional supplements in the management of pain and inflammation in OA; however, the mixed results obtained highlight the importance and need for continuing research in this field. To this purpose, the present study tested the synergic effect of an oral supplementation containing N-acetyl-D-glucosamine, ginger, and *Boswellia serrata* in the treatment of knee OA.

N-acetyl-D-glucosamine (NAG) is the acetylated derivative of glucosamine, an amino sugar synthesized from glucose that is essential for the biosynthesis of the major constituent of extracellular matrix macromolecules such as glycosaminoglycans, glycolipids, and glycoproteins<sup>17</sup>. In particular, glucosamine is precursor of NAG in the hexosamine biosynthesis pathway, leading to the synthesis of hyaluronic acid, an essential component of skin, cartilage, synovial fluid and blood vessel. The use of NAG has some advantages compared to glucosamine: it has a stronger anti-inflammatory action, does not induce insulin-resistance and does not inhibit the synthesis of endogenous glucosamine<sup>18</sup>.

In the last decades, extracts of the gum resin of *Boswellia serrata* and other *Boswellia species* have experienced increasing popularity in Western countries for the treatment of a variety of inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, and asthma<sup>19-22</sup>. A recent Cochrane review reported evidence on the efficacy of *Boswellia serrata* in alleviating pain and improving functions in OA patients<sup>23</sup>. Boswellic acids, the pharmacologically active ingredients of these extracts, exert many anti-inflammatory activities such as the inhibition of the 5-lipoxygenase, the key enzyme in leukotriene biosynthesis<sup>22</sup>. Ginger is a widely used condiment and has long been prescribed for a variety of conditions including digestive problems, colds, fevers and arthritis, due to its circulatory stimulant and anti-inflammatory effects<sup>25-28</sup>. Preclinical researches have shown anti-inflammatory and analgesic properties of ginger and ginger constituents, including inhibition of cyclooxygenase (COX)<sup>29</sup>, 5-lipoxygenase<sup>30</sup>, proinflammatory chemokines<sup>31</sup> and inhibition of transient receptor potential (TRP) channel activity<sup>32</sup>. Furthermore, bioactive compounds in the ginger root also resulted to promote the antioxidant defense systems in cells and mice<sup>33</sup>.

The approach to manage knee OA using this new supplement combination, in this registry study produced positive effects on functional and inflammation parameters. In particular, a short supplementation with Movardol<sup>®</sup> promoted significant improvements in signs/symptoms of knee OA over a 6-month follow-up period. Generally, the reduction in knee pain as well as the improvement in walking distance ameliorate the QoL and could lead to an increased physical exercise capacity in OA patients, therefore associated with a better metabolic turnover, a decrease in lipids and glucose levels and a better control of all cardiovascular risk factors. Overall, our study population did not present severe inflammation at inclusion. However, consisting of the well-known anti-inflammatory activity of its components, Movardol<sup>®</sup> oral supplementation significantly reduced the moderate inflammation associated with knee osteoarthritis. We also observed a significant reduction of the use of pharmacological and non-pharmacological treatments in the OA patients undertaking oral supplementation.

The safety and tolerability of Movardol<sup>®</sup> observed in this study represent an essential element in consideration of the possible self-management by the patients. This result had beneficial effects in term of complications associated with long-term use of anti-inflammatory drugs, the economic burden of knee OA for patients and healthcare providers. Further, larger, controlled clinical investigations should be conducted including the evaluation of problems linked to possible interaction with drugs used by patients with OA (i.e. anticoagulants, anti-platelet agents, statins, etc.).

This type of product can be used safely, particularly in chronic conditions.

## Conclusions

Research findings support the concept that oral supplementation with a combination of products of natural origin can be effectively used to target multiple OA signs and symptoms and even markers. The results obtained support the efficacy and safety of Movardol<sup>®</sup> supplementation in the management of knee OA.

## Acknowledgements

We thank Sara Parodi, Ph.D, who provided medical writing services, supported by internal funds.

**Conflict of Interest**

BG is a partner of Leonardo Medica srl., Vinci, Florence, Italy. The other Authors declare no conflicts of interest.

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