Clinical Research Article

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The role of nutraceuticals in the management of temporomandibular disorders

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Abstract

Objectives: Temporomandibular disorders (TMDs) are usually treated with occlusal appliances and supportive treatments such as physical therapy and drugs. Supplements can be included among potential supportive therapies, with the aim of reducing the use of drugs. To evaluate the efficacy of nutraceuticals' short-term treatment in subjects with temporomandibular disorders.
Methods: The study started in January 2021 and ended in January 2022. Subjects with temporomandibular disorders and a verbal numeric scale >40 were recruited and randomly assigned to one of the following groups. If waiting to start a therapy, to the nutraceutical group or to the no treatment group, while if already undergoing splint therapy, to nutraceautical+splint group or to splint therapy group. Nutraceutical used was composed by Boswellia Serrata Casperome, Magnesium, Tryptophan and vitamins B2 and D with a posology of one tablet/day before sleep for 40 days. Presence of temporomandibular pain, headache, neck pain and sleep/emotional disorders were assessed at T0 and at T1, after 40 days. ANOVA was performed to compare treatments with nutraceuticals and their respective controls, as for the variables related to painful symptomatology. Chi- Squared was conducted to assess differences in sleep/emotional disorders between groups. The statistical significance was $p<0.05$.
Results: The groups using nutraceuticals showed statistically significant improvements over controls for most of the variables analyzed.
Conclusions: The use of nutraceutical seems to be a valuable support for TMD therapy in the short term either alone or combined with occlusal splint therapy.

Keywords: nutraceuticals; temporomandibular disorders; splint therapy; sleep disorders

Introduction

Temporomandibular disorders (TMDs) are a subgroup of craniofacial pain disorders, involving pain and dysfunction of the temporomandibular joint (TMJ), masticatory muscles and associated musculoskeletal structures of the head and neck. It is the most common cause of nondental pain in the orofacial region [1]. Several approaches are proposed for TMD treatment and the most common one is the one with occlusal appliances [2, 3]. Among supportive therapies, in addition to physical rehabilitation, clinical studies suggest the use of pharmacological therapy not only to alleviate the painful symptoms of muscles and joints of the temporomandibular region but also to curb associated comorbidities such as headache, neck pain, sleep/emotional disorders [4]. The most important categories of drugs are non-steroidal anti-inflammatory drugs, corticosteroids, muscle relaxants, benzodiazepines, anti-convulsivants, tricyclic antidepressants [5].

In recent years, there has been a strong interest among scientists and researchers in the use of nutraceuticals for the treatment of different disorders and diseases [6]. The term nutraceutical, which derives from the fusion of the words "nutrient" and "pharmaceutical" identifies a product containing one or more substances usually contained in foodstuffs, subsequently concentrated and purified, presented in the form of a pharmaceutical product (tablets, pills, drops), taken for preventive or curative purposes [7]. Currently, the fields of application are wide and varied: supplementing the normal diet, strengthening the immune system, increasing energy, bone health, cardiovascular wellbeing, preventing general health problems, osteoarticular problems, skin problems, strengthening hair and nails, gastrointestinal problems, weight management and loss, eye health, mental health and concentration [8].

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Despite a plethora of evidence supports the health benefits and value of nutraceuticals in the treatment and prevention of different disease and the important role these compounds play in physiological functions [9, 10], regarding TDM management, to our knowledge, only two trials adopt nutraceutical as supportive therapy [11, 12].

Accordingly, since nutraceuticals may be non-only adopted in preventative medicine but as complementary or alternative treatments to chronic disease [13, 14], we investigated the use of a broad-spectrum nutraceutical, indicated especially for muscle relaxation and sleep, which are elements impacting on TMDs, as a supportive short-term therapy.

Materials and methods

Participants

The sample was selected from a population of subjects diagnosed with temporomandibular disorder at the Gnathology Service. The diagnosis was made according to Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) by experienced and calibrated practitioners. Subjects who met the inclusion criteria - and had no grounds for exclusion - were recruited for the study. Inclusion and exclusion criteria were reported in Table 1.

The sample was collected, between January 2021 and January 2022, at the Clinical Gnathology Service of the Integrated Head and Neck Care Department of the Policlinico Umberto I, "Sapienza" University of Rome. The trial protocol was approved by the Institutional Ethics Committee of La Sapienza, University of Rome - Protocol n° 000698. ISRCTN protocol n° 7192478.

The research was conducted in accordance with the World Medical Association's Code of Ethics (Declaration of Helsinki) for experiments on humans. Written informed consent was obtained from each patient.

Trial design

The authors designed a randomized clinical trial. Nutraceutical administration was evaluated as a single treatment (Option 1) or in combination with the splint therapy (Option 2). Consequently, two arms for each treatment option were considered. Computer-generated randomization with random allocation sequence with a block size of two was adopted. Specifically, in case of the absence of ongoing splint therapy, patients were randomly divided in:

Control **Group I** - no treatment vs. **Group II** - treatment with nutraceutical.

The choice of this procedure is to evaluate the action of the supplement without the interference of other therapies.

While in case of ongoing occlusal splint therapy:

Control **Group III** - treatment with occlusal splint only vs. **Group IV** - treatment with nutraceutical and splint therapy.

The appliance used was a repositioning splint, which aimed at restoring temporomandibular joint disc-condyle balance and promoting masticatory muscle relaxation, according to a protocol assessed in a previous study [3]. The splint has been realized using auto-polymerizing acrylic resin with even bilateral occlusal contacts on the flat splint surface and it has been customized for each patient. It is usually worn by the patient 2 h a day and all night.

Intervention

After the recruitment phase, subjects assigned to Group II and IV had to take one tablet of the supplement per day before sleep for 40 days.

Table 1: Inclusion and exclusion criteria for treatment with nutraceuticals.

Inclusion criteria	Exclusion criteria
– Presence of dysfunctions of the cranio-cervical muscles, in the presence or absence of parafunctions – Presence of muscle pain at the level of the masseter of medium-high intensity with a minimum value of 40 and a maximum of 100, according to the VNS (verbal numerical scale), spontaneous and/or investigated by palpatory manoeuvres – Presence of arthralgia at the level of the temporomandibular joint – Presence of the following comorbidities such as: headache attributed to TMD and neck pain – Presence of sleep disturbances (except for OSAS) and emotional factors (stress and anxiety) investigated with a nominal scale (presence or absence) – Patients waiting for or undergoing conservative gnathological therapy	– Subjects affected by psychiatric pathologies – Subjects with systemic pathologies with disease-related muscular impairment – Persons undergoing pain therapy or myorelaxant medication

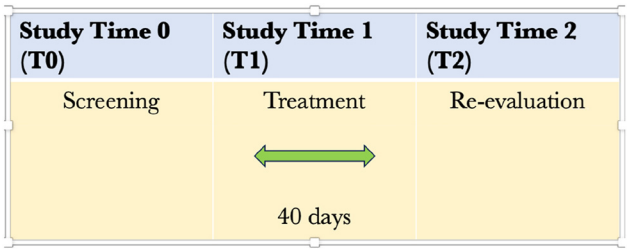

Figure 1: Study phases.

The administered nutraceutical was based on Magnesium, Tryptophane, Boswellia Serrata Casperome®, Vitamins B2, D, PP.

Phases

The study reported the following phases as shown in Figure 1.

Outcomes

The primary outcome was muscle pain (location, intensity according to the verbal numerical scale (VNS)*), joint pain (location, intensity according to the verbal numerical scale (VNS)*); comorbidity such as headache, cervicalgia (location, intensity according to the verbal-numerical scale - VNS), presence/absence of sleep/emotional disturbances. Moreover, also personal data (age, marital status, occupation, etc.), analysis of mandibular function (presence of articular noises, evaluation of functional excursions and maximum mouth opening) and palpatory examination were collected. The VNS allows a quantitative analysis of the intensity of subjective pain, perceived by the patient, according to a scale from 0 to 100. Zero indicated no pain; 20 the presence of discomfort up to 100 which was the strongest pain the patient could imagine. The patient underwent an assessment of spontaneous pain and/or pain caused by palpatory maneuvers.

As secondary outcome, sleep disturbance and emotional factors such as anxiety and stress, the impact of pain on quality of life were assessed by a dichotomous scale (presence or absence). Finally, a series of dichotomous questions and a numerical rating scale from 0 to 10 were adopted to assess the patient's perceived overall improvement.

Sample size

Total sample size was calculated with a confidence level of 95 %, a confidence interval of 5 % and a power of 80 %. The expected size was 175 subjects.

Statistical analysis

A descriptive analysis was carried out to outline the socio-demographic characteristics of the patients (age, gender). Repeated-measures analysis of variance (ANOVA) was then performed to compare the effectiveness of nutraceutical therapy and the difference between pre- and post-treatment assessment. All evaluated outcomes were considered as dependent variable in separate analyses. In addition, ANOVAs were conducted to show the subjective improvement reported by patients following the use of the different nutraceuticals. Finally, chi- squared analyses were conducted to reveal differences in proportions of nominal outcomes (sleep disturbance, psychological disturbance, and side effects). All analyses were conducted with Jasp software and $p<0.05$ was selected as significance level.

Results

As reported in the CONSORT flow diagram (Figure 2), a total of 193 patients (149 females, 44 males; mean age 40.39±16.06) with TMD completed the study.

- Control Group I - no treatment (n=70; 51 females and 19 males; mean age 39.82±15.75);
- Group II - nutraceutical treatment (n=61; 46 females and 15 males; mean age 40.42±16.65);
- Control Group III - splint therapy only (n=47; 41 females and 6 males; mean age 38.40±14.96);
- Group IV - nutraceutical and splint therapy (n=15; 11 females and 4 males; mean age 42.93±15.87).

The reasons why people dropped out of the study in both arms were reported to be attributable to the cost of the supplement and the lack of adherence to the protocol indicated for taking the supplement.

Nutraceutical vs. no-treatment

The first aim of this study was to evaluate the efficacy of the nutraceutical and accordingly repeated-measures ANOVAs were conducted considering therapy (nutraceutical; no therapy) and time (pre; post).

Regarding both left and right TMJ pain

There was a significant difference considering main effects of therapy (right: $F_{1,129}=5.30$; $p=0.02$; mean difference=12.69; left: $F_{1,129}=7.70$; $p=0.006$; mean difference=14.65) and time (right: $F_{1,129}=7.62$; $p=0.007$; mean difference=3.46; left:

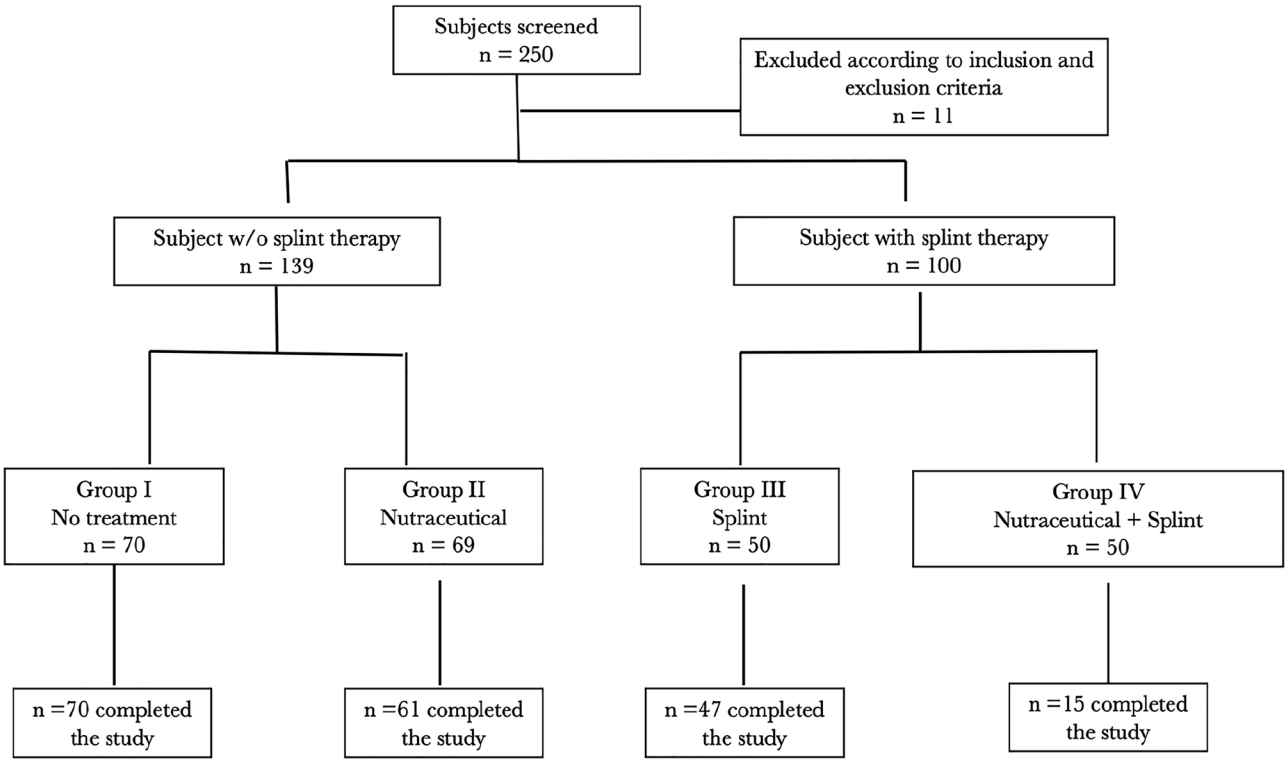

Figure 2: CONSORT flow diagram.

F1,129=8.95; p=0.003; mean difference=3.35), as well as an interaction effects (right: F1,129=15.21; p=0.0001; left: F1,129=15.09; p=0.0001) was evidenced. Specifically, treatment with nutraceutical showed an improvement (right: mean difference=8.36 p=0.0001; left: mean difference=7.70 p=0.0001); while there was no improvement in patients who did not take the nutraceutical.

Regarding both left and right muscle pain

A significant difference of therapy (right: F1,129=16.43; p=0.0001; mean difference=18.19; left: F1,129=3.61; p=0.04; mean difference=8.46) and time (right: F1,129=98.04; p=0.0001; mean difference=15.000; left: F1,129=124.69; p=0.0001; mean difference=16.63) emerged. In addition, there was evidence of a therapy × time interaction effect (right: F1,129=98.04; p=0.0001; left: F1,129=124.69; p=0.0001). Nutraceutical therapy appear to be associated with an improvement in symptoms (right: mean difference=30.00; p=0.0001; left: mean difference=33.27; p=0.0001); while there was no improvement in patients who did not take the nutraceutical.

Considering both left and right headache

A significant difference of therapy (right: F1,129=10.28; p=0.002; mean difference=19.19; left: F1,129=6.67; p=0.01; mean difference=15.44) and time (right: F1,129=36.92; p=0.0001; mean difference=10.49; left: F1,129=44.80; p=0.0001; mean difference=11.72) emerged, as well as therapy × time interaction effect was shown (right: F1,129=36.92; p=0.0001; left: F1,129=44.80; p=0.0001). Nutraceutical therapy was related to an improvement in symptomatology (right: mean difference=20.98; p=0.0001; left: mean difference=23.44; p=0.0001); while there was no improvement in patients who did not take the nutraceutical.

Regarding both left and cervicalgia

A significant difference of therapy (right: F1,129=4.77; p=0.03; mean difference=13.23; left: F1,129=24.67; p=0.001; mean difference=7.45) and time (right: F1,129=21.97; p=0.0001; mean difference=6.63; left: F1,129=1.13; p=0.28; mean difference=6.50) emerged. In addition, there was evidence of a therapy x time interaction effect (right: F1,129=21.97; p=0.0001; left: F1,129=24.67; p=0.0001). In patients on nutraceutical therapy, an improvement in symptoms was shown in the post evaluation (right: mean difference=13.27; p=0.0001; left: mean difference=14.91; p=0.0001); while there was no improvement in patients who did not take the nutraceutical.

Chi squared analysis showed in patients on nutraceutical therapy a significant reduction in sleep disturbance

(p≤0.0001) and related emotional factors (stress and anxiety) (p=0.006) in post evaluation.

Nutraceutical + splint vs. splint only

In order to evaluate the efficacy of the treatment performed with the nutraceutical and the occlusal splint device and to compare it with conventional therapies performed by occlusal splints alone, repeated-measures ANOVAs were conducted considering therapy (nutraceutical and splint; splint therapy) and time (pre; post).

Regarding right and left TMJ pain

There was a significant difference of therapy (right: F1,129=2.57; p=0.05; left: mean difference=14.91; p=0.0001) and time (right: F1,129=14.44; p=0.001; mean difference=5.44; left: F1,129=7.62; p=0.006; mean difference=3.56). In addition, there was evidence of a therapy × time interaction effect (right: F1,129=7.06; p=0.0001; left: F1,129=4.66; p=0.01). In patients on nutraceutical therapy combined with occlusal splint therapy, an improvement in symptomatology was shown at post evaluation (right: mean difference=9.67; p=0.01; left: mean difference=7.13; p=0.05); while, only in right TMJ there was an improvement by resorting to the single use of conservative occlusal therapy with splinting (mean difference=8.08; p=0.01).

Regarding right and left muscle pain

A significant difference of therapy (right: F1,129=5.64; p=0.004; left: F1,129=2.83; p=0.04) and time (right: F1,129=78.46; p=0.0001; mean difference=15.000; left: F1,129=71.85; p=0.0001; mean difference=12.88) emerged. In addition, there was evidence of a therapy × time interaction effect (right: F1,129=78.46; p=0.0001; left: F1,129=37.14; p=0.0001). In patients on nutraceutical therapy combined with splint occlusal therapy, an improvement in symptomatology was shown at post evaluation (right: mean difference=40.96; p=0.0001; left: mean difference=32.25; p=0.0001); while there was no improvement by resorting to the single use of conservative occlusal therapy with splinting.

Regarding right and left headache

A significant difference of therapy (right: F1,129=3.14; p=0.04; left: F1,129=3.14; p=0.04) and time (right: F1,129=53.07; p=0.0001; mean difference=11.54; left: F1,129=54.80; p=0.0001; mean difference=11.54) emerged. In addition, a therapy × time interaction effect was shown (right: F1,129=22.01; p=0.0001; left: F1,129=23.83; p=0.0001). In patients on nutraceutical therapy combined with splint occlusal therapy, an improvement in symptomatology was shown in the post evaluation (right: mean difference=26.12; p=0.0001; left: mean difference=26.77; p=0.0001); while there was an improvement by resorting to the single use of conservative occlusal therapy with splinting (mean difference=8.53; p=0.02), while only in left pain there was an improvement by resorting to the single use of conservative occlusal therapy with splinting (mean difference=7.83; p=0.03).

Regarding right and left cervicalgia

There was a significant difference of therapy (right: F1,129=4.89; p=0.009; left: F1,129=31.62; p=0.0001), while there was no significant difference of time (F1,129<1). In addition, there was evidence of a therapy × time interaction effect (right: F1,129=3.80; p=0.02; left: F1,129=12.74; p=0.001). However, no significant interaction was found between patients on nutraceutical therapy combined with occlusal splint therapy and patients with single use of conservative occlusal splint therapy.

Chi squared analysis showed in patients treated with nutraceutical therapy in both arms a significant reduction in sleep disturbance (p≤0.0001) and related emotional factors (stress, anxiety) (p=0.006) in post evaluation.

Discussion

The aim of this study was to investigate the use of nutraceuticals, single or combined with other conventional therapies, in the management of pain resulting from temporomandibular dysfunction, its comorbidities, and associated anxiety and sleep disorders. Our results underline a significant improvement due to use of nutraceuticals (i.e., magnesium, tryptophan, Boswellia, vitamins B2 and D), both when administered alone and in combination with a splint therapy, in all the parameters examined - osteoarticular and neuromuscular symptoms, headache, neck pain, sleep and mood disorders.

To our knowledge this is the first study that adopt this specific nutraceutical combination in relation to TDM. Indeed, despite a plethora of evidence supports the health benefits and value of nutraceuticals in the treatment and prevention of different disease and the important role these compounds play in physiological functions [9, 10], regarding TDM management few studies adopt nutraceutical supplies. For example, Cornelison et al. [11] focused on dietary supplement with grape seed extract in animal showed that this supply prevents development of trigeminal sensitization

and inhibits pain signaling in a preclinical chronic temporomandibular disorder model.

Another studies, conducted by Marini et al. [12], compared the effects of palmitoylethanolamide (PEA) and ibuprofen in the management of pain from osteoarthritis, located at the temporomandibular joint suggesting that PEA is effective in treating temporomandibular joint inflammatory pain. Our results are surely in line with previous studies. However, compared to previous studies, we choose this specific nutraceutical supplies to cover as many aspects and facets of this dysfunctional picture as possible, acting on several fronts, from the purely anti-inflammatory and muscle-relaxing to the hypnic pattern. We make this choose since unlike other joint and muscle areas, the temporomandibular joint and its associated structures are characterized not only by purely biomechanical dysfunctions, but also by dysfunctions conditioned by disturbances in the psycho-emotional-relational sphere. Accordingly, our results furnished evidence that nutraceutical supplies not only improve pain management but also have a psychophysiological benefit.

Nutraceutical and pain management

A meta-analysis conducted by Aghamohammadi et al. [15] showed that ingredient such as Sierrasil, SKI306X or *Clematis mandshurica*, *Trichosanthes kirilowii* and *Prunella vulgaris*, passion fruit extract, *Curcuma longa*, *Boswellia serrata*, pycnogenol and L-carnitine are effectiveness to reduce pain in short term. Specifically, was revealed the efficacy of Boswellia Serrata [16, 17], in the management of osteo-articular pain. Since it is the active ingredient in both the nutraceuticals used in our study, this could explain our results. Moreover, vitamin D, which is one of the components of the nutraceuticals used in our study, does not have a statistically significant efficacy in the algic component [18, 19]. Another active ingredient used as an anti-inflammatory in joint pain is bromelain with anti-edemigenic action, the activity of which has been proven in subjects with knee osteoarthritis. In our study, patients with single- or bilateral temporomandibular joint pain who were treated with nutraceuticals containing *B. serrata* and bromelain showed an improvement in osteoarticular pain compared with the control group.

Nutraceuticals and headache

Group B vitamins, including B2, have been shown to be effective in headache sufferers in literature studies such as Dragan et al. [20]. In this review, studies by Gaul et al. [21] and Gazerani et al. [22] are also mentioned, in which vitamin D3 is also reported to be effective in improving the intensity or frequency of migraine attacks. This is in line with the findings in our study, in which headache was significantly improved.

Nutraceuticals and neuromuscular relaxation

Magnesium sulphate is one of the components of the nutraceuticals used in our study, with the specific indication of recovery of muscular pain symptoms. In the literature, its effect has been demonstrated at the pre-synaptic termination of the neuromuscular plate, where it inhibits the release of acetylcholine. In addition, the increase in extracellular magnesium concentration seems to reduce both the amplitude of the response evoked by acetylcholine at the moment of induction of depolarization of the muscle membrane and the conductance of the nicotinic channels of acetylcholine itself. It also appears to enhance the effect of non-depolarizing muscle relaxants such as vecuronium [23–25]. There are currently no other substances with such a muscle-relaxing effect reported in the scientific literature that are not pharmacological substances. In our study, patients also experienced an improvement in both masticatory and cervical muscle tension with magnesium sulphate supplements.

Nutraceuticals and sleep disorders

The literature reports the effectiveness of both magnesium and tryptophan, and of melatonin derived from them, in treating insomnia.

In addition, both magnesium and tryptophan, through the production of serotonin, are used in the treatment of depressive states, especially in patients with poor adherence to traditional drug therapy, due to side effects and costs [26–28]. In this case, the non-pharmacological substances most frequently mentioned in studies are melatonin and 5HTP (5-hydroxytryptamine) as its precursor [29]. Other substances such as L-theanine, passionflower and chamomile do not have a direct hypno-inducing effect, but more on the cognitive aspect of mental relaxation. As for valerian, which is supposed to have strong hypno-inducing properties, the literature is still of poor quality to prove its actual effectiveness. Even in the current study, in which supplements containing tryptophan and magnesium were used, patients reported an improvement in sleep quality in all

measurements. It is not possible to give more specific information in this area, as the expected patient response to the questionnaire was dichotomous and did not include indications of the number of hours of sleep per night, latency in falling asleep, etc. Chi squared analysis showed that patients receiving nutraceutical therapy had a significant reduction in sleep disorders and related emotional factors (stress and anxiety) in the post evaluation.

Limitations of the study

Some limitations should be underlined in this study, such as the lack of placebo groups, the small sample with an unbalanced size and the short time of observation. Accordingly, some aspects remain unclarified such as the long-term effects of the treatment. Nevertheless, since the total lack of side effects, our results remain of particular interest. However, the choice to include both patients who started the treatment and patients already treated with a splint therapy could represent a bias of the study. However, the choice was due to better understand, as for patients under gnathological treatment, if the combination of splint plus supplement could be more advantageous than splint alone and as for those awaiting treatment, the action of the supplement without the interference of other therapies. We hope that further study may overcome these limitations. In the future, it might be useful to evaluate when it is most suitable to administer the supplement (whether before, during or after a splint treatment), by developing a study with the following treatment-arms: supplement at t1 and splint at t2; supplement and splint at the same time; splint at t1 and supplement at t2.

Conclusions

In the light of the findings of this study, further investigation is required to create systematic protocols for the management of nutraceuticals in TMD therapy, and to better define their contours in clinical practice. In fact, it will be advisable to give the most specific and targeted indications for use possible, describing the dosage required, the therapeutic indications, the possibility of interaction with other supplements and/or drugs and in what way.

The advantages of a therapy involving the use of nutraceuticals are certainly their minimal invasiveness, low toxicity for the body and ease of use. A major limitation, however, is that the costs are still high, and this is currently limiting the possibility of increasing the number of users.

Research ethics: The local Institutional Review Board deemed the study exempt from review.
Informed consent: Informed consent was obtained from all individuals included in this study.
Author contributions: All the authors have accepted responsibility for the entire content of this manuscript and approved submission.
Competing interests: There is no conflict of interest.
Research funding: None declared.
Data availability: The raw data can be obtained on request from the corresponding author.

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