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# Efficacy of a medical device based on magnesium alginate, calcium carbonate, potassium bicarbonate, sodium hyaluronate and chondroitin sulfate in the adjuvant treatment of non-erosive gastroesophageal reflux disease (NERD)

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## Abstract

Treatment of non-erosive gastroesophageal reflux disease (NERD) is based on the use of proton pump inhibitors (PPIs), but clinical experience shows that patients with NERD often complain of dissatisfaction with PPI monotherapy and with their health-related quality of life. Hence, the need to identify effective alternative therapeutic actions emerges.

This retrospective pilot study was carried out on 66 subjects divided into two groups: 33 patients with NERD took a medical device (MD) containing magnesium alginate, calcium carbonate, potassium bicarbonate, sodium hyaluronate and chondroitin sulfate for 60 consecutive days, while the other 33 patients with NERD concomitantly took a PPI and the aforementioned medical device for 60 consecutive days. The medical device was taken after the main meals and before bedtime. Symptoms were assessed using the Gastroesophageal Reflux Disease Impact Scale (GIS) questionnaire and reflux-related quality of life using the Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) questionnaire before starting treatment, after 30 days of treatment, at the end of 60 days of treatment and 30 days after the discontinuation of the treatment.

Patients in both Groups showed a clinically significant improvement. In particular, after 30 days of therapy, the mean percentage reduction of the total GIS score compared to T0 was 50.1% in the MD Group and 46.7% in the MD+PPI Group. After 60 days of therapy, the mean percentage reduction of the total GIS score compared to T0 was 55.5% in the MD Group and 53.9% in the MD+PPI Group.

The benefits obtained by patients in both Groups resulted in a significant improvement in the reflux-related quality of life, which was confirmed by the significant reduction in the GERD-HRQL questionnaire score.

The results obtained in the two Groups were superimposable, demonstrating that in the analyzed sample of patients with NERD, therapy with the medical device alone yielded the same therapeutic effects as the combination therapy with PPI and medical device.

**Keywords:** Gastroesophageal Reflux Disease; Nonerosive Reflux Disease; Medical Device; Magnesium Alginate; Health-Related Quality of Life; Proton Pump Inhibitors

## Introduction

Gastroesophageal reflux disease (GERD) is a common disorder of

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the upper gastrointestinal tract. The prevalence of reflux symptoms is steadily increasing in developed countries [1]. The prevalence of GERD based on symptom perception in individual cross-sectional surveys varies from 2.5% to over 25%, depending on the criteria used to define the presence and frequency of symptoms and the geographic location of the study [2]. In fact, reflux disease is much less prevalent in Asia than in Western countries [2]. Studies demonstrate that young people are increasingly affected, probably due to changes in dietary patterns and the increase in overweight or morbid obesity in both adolescents and pediatric populations [2].

The different manifestations of GERD include non-erosive reflux disease (NERD) and erosive esophagitis (EE). Complications of GERD, which are generally limited to patients with EE, include ulceration, stricture and Barrett's esophagus with the associated risk of esophageal adenocarcinoma [3]. NERD is the most frequent phenotype of GERD, affecting approximately 70% of patients with reflux disease, and is characterized by the presence of typical GERD symptoms associated with pathological reflux but by the absence of lesions of the esophageal mucosa detectable by endoscopy [4,5]. Despite the absence of mucosal lesions detectable on endoscopy, many patients with NERD present with severe symptoms and impaired quality of life [6,7]. Acid-suppression therapy with proton pump inhibitors (PPIs) has been shown to be the most effective therapeutic strategy for both NERD and EE [8-10]. PPIs have been shown to be superior to histamine H2 receptor antagonists in symptom control, erosion healing, and relapse prevention [8-10].

However, NERD patients more often show sufficient resolution than complete resolution of symptoms within 4 weeks of PPI treatment [11]. The response rate to symptomatic treatment is significantly lower in NERD patients than in EE patients receiving the standard dose of PPI [11]. In the first 4 weeks of treatment, NERD patients show a progressive increase in therapeutic gain towards complete resolution of symptoms, suggesting that the trend towards symptom improvement may continue over time with continued therapy [11]. Furthermore, up to 75% of NERD patients and up to 90% of EE patients may experience a symptomatic relapse within six months of treatment discontinuation [12]. Therefore, many patients undergo long-term treatment to maintain adequate control of symptoms and, in the case of EE patients, erosion healing. This tends to lead to overuse of PPIs, especially among NERD patients, increasing overall costs and risks [13]. Increased PPI use causes a parallel increase in concerns about adverse effects. The safety profile of PPIs is generally considered good, with less than 1%-2% of patients experiencing adverse effects and requiring drug discontinuation [14]. However, the results of several studies, mainly including case-control studies and meta-analyses, have raised concerns about adverse effects associated with long-term use of PPIs. These include possible alterations of the intestinal microbiome, enteric infections (due to the lack of sterilization of food during the formation of the gastric bolus), altered pepsin formation and consequent non-optimal protein digestion, fundic glandular hyperplasia, drug interactions, inhibition of the binding between vitamin B12 and intrinsic factor, a glycoprotein produced by gastric oxyntic cells that binds vitamin B12 and transports it to the last ileal loop where it is physiologically absorbed, causing possible malabsorption of vitamin B12 [15].

Due to the costs and potential risks of PPI treatment, efforts have been made to develop effective alternative strategies for the long-term treatment of GERD and, in particular, NERD [16-18].

Clinical experience clearly shows that patients with NERD often complain of the inefficacy of PPI monotherapy. It can be deduced that the lack of an effective treatment for NERD may drive patients with NERD to complain of an unsatisfactory health-related quality of life.

Given the above-mentioned considerations, the authors of this study believe that it is desirable to identify effective therapeutic strategies to protect the mucosa and to reduce the peculiar symptoms and signs of NERD. To meet this need, for some time now, it has been our practice to treat patients with NERD who come to our attention with medical devices made available by pharmaceutical companies and to systematically collect evidence of their efficacy to identify the formula that best suits the needs of these patients.

This study aims to evaluate the effects of NERD treatment with an oral medical device (MD) that is believed to prevent reflux of gastric contents, neutralize the acid pocket that forms near the gastroesophageal junction during meals and protect the esophageal mucosa, as we hypothesize that the combination of these three actions is very promising in the effective management of the symptoms and signs of NERD along with the use of PPIs or not. Therefore, the main objective of this study is to evaluate the efficacy of the medical device in protecting the esophageal mucosa from the aggression of gastric reflux and in reducing the signs and symptoms of NERD. The comparison between a group of patients treated with MD alone and a group of patients treated with MD concomitantly with PPI treatment intends to verify whether the combination of the two products can yield an additive effect in symptom control, with a greater benefit for patients. It is believed that an actually effective therapy continued for 60 consecutive days should reduce the score of the appropriate questionnaire (Gastroesophageal Reflux Disease Impact Scale) concerning the symptoms by at least 50%. In addition, the secondary endpoint of this study is to verify the efficacy of the medical device in improving the

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quality of life of patients with NERD as well as the patient satisfaction with this therapy. Finally, a further endpoint is to compare the efficacy of the medical device with the efficacy of the combination of the medical device with PPIs by comparing a group of patients treated with the medical device alone and a group of patients treated with the medical device and PPIs simultaneously.

## Materials and Methods

### Medical device tested

The medical device tested (MD; CE certificate No. IT299455-3 issued on 31 July 2020; manufactured by Salix S.r.l. Monte di Malo (VI), Italy) has been on the market in Italy since 1 October 2020. MD contains magnesium alginate, calcium carbonate, potassium bicarbonate, sodium hyaluronate (HA) and sodium chondroitin sulfate (CS). HA has a high molecular weight, between 1800 and 2000 kDa, and is obtained through biotechnological processes. CS is derived from fermentation. Magnesium alginate has been included in the formula as a gelling agent, whereas HA and CS have been included in the formula as mucoadhesive agents. According to the information leaflet, the product is indicated for the treatment of gastroesophageal reflux to reduce the symptoms associated with this latter, such as heartburn, acid regurgitation, reflux esophagitis, dysphagia and odynophagia.

### Study design

This is a retrospective pilot study in which the parameters detected in two groups of patients with NERD are compared before starting therapy, during therapy, at the end of therapy and one month after the discontinuation of the therapy.

Two groups of patients are compared: the PPI Group takes the standard treatment with PPI, according to standard clinical practice; the MD+PPI Group takes the combination of PPI (at doses set out in the standard clinical practice) and MD. The study was carried out according to Good Clinical Practice guidelines [19] and the Declaration of Helsinki [20].

### Anamnesis and physical examination

The subjects underwent a physical examination and a comprehensive medical history including the evaluation of symptoms, allergies, diet, alcohol intake, smoking, work activity, family history of digestive system diseases and other pathologies, operations undergone, comorbidities and ongoing therapies.

### Gastroesophageal Reflux Disease Impact Scale (GIS)

The GIS questionnaire was developed to rapidly determine the severity of symptoms and the impact of GERD during the week preceding the survey [21]. It includes 9 questions that identify the frequency of any symptoms, the frequency of any impact on sleep, diet, usual activities and work and the frequency of the need to resort to additional drugs compared to those already prescribed by the doctor induced by reflux disease. The answers allow you to choose among “every day”, “often”, “sometimes”, “never”. Each answer in the questionnaire is assigned the following score: every day = 4; often = 3; sometimes = 2; never = 1.

The answers are then grouped into the following 3 areas:

1. Upper GI symptoms: Pain in the chest or behind the breastbone? Burning sensation in the chest or behind the breastbone? Pain or burning in the upper stomach?
2. Other acid-related GI symptoms: Regurgitation or acid taste in the mouth? Sore throat or hoarseness that is related to heartburn or acid reflux?
3. Impact of symptoms: How often have you had difficulty getting a good night’s sleep because of your symptoms? How often have your symptoms prevented you from eating or drinking any foods you like? How frequently have your symptoms kept you from being fully productive in your job or daily activities? How often do you take additional medication other than what the physician told you to take?

For each of the above areas, an intermediate score is calculated, and this score is always between 1 and 4. Finally, the total score is calculated by averaging the 3 intermediate scores.

### Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) Questionnaire

The GERD-HRQL questionnaire was developed and validated to measure the change in typical GERD symptoms, such as heartburn and regurgitation, in response to medical or surgical treatment [22]. This questionnaire aims to rapidly determine the symptomatic severity and impact of GERD during the two weeks preceding the survey. It consists of 11 questions. The first 10 questions are answered by entering a cross to the score that best describes the situation: 0 = no symptoms; 1 = symptoms noticeable but not bothersome; 2 = symptoms noticeable and bothersome but not every day; 3 = symptoms bothersome every day; 4 = symptoms that affect daily activities; 5 = symptoms are incapacitating, unable to do daily activities. The sum of the scores obtained from 10 questions gives a total score that ranges from 0 to 50.

### Rating on the efficacy and pleasantness of the therapy

Patients were asked to express their rating on the efficacy and pleasantness of the therapy they underwent, using two scales comprising 5 different ratings: excellent, good, satisfactory, poor, none.

### Subjects evaluated

The two groups analyzed included adult male and female

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patients affected by NERD. The patients enrolled had to be over 18 years of age, with an endoscopic diagnosis of GERD - NERD made with an endoscopy done in the 6 months preceding the enrollment visit at the time of starting the therapies. Patients also had to present symptoms of GERD for at least 6 months and at least 3 times a week in the last month. They had to have at least 2 of the following symptoms: heartburn, acid regurgitation, retrosternal pain, acid taste in the mouth.

Patients who had not yet undertaken continuous therapies for the treatment of NERD or who had discontinued any therapies in the 15 days before starting to take MD or MD+PPI were enrolled. T0, the time when the patients filled out the questionnaires for the first time, was therefore at least 15 days after the discontinuation of any therapy related to GERD.

Patients diagnosed with erosive esophagitis, Barrett's esophagus, gastric or duodenal ulcer, hiatal hernia, or other gastrointestinal pathologies that could interfere with the study were excluded, according to the judgment of the investigators. Patients who had changed their diet during the observation period, who had undergone previous major gastric or gastrointestinal surgery, who had food intolerances or allergies, who were chronically taking steroid drugs and non-steroidal anti-inflammatory drugs, with a BMI > 35 kg/m$^2$, who had metabolic syndrome, who were already being treated with therapies other than PPIs for GERD, and who were pregnant or breastfeeding were also excluded. Finally, patients with psychiatric disease, mental incapacity or language barriers that could compromise the quality of the data collected were excluded.

As per the practice of the doctors who authored this study and in compliance with current regulations, patients signed regular informed consent both for the proposed therapy and for the processing of personal data. According to the practice of the investigators, at the start of therapy, a medical history form was filled out for each patient with all the data collected and a form was attached to be filled out at the next visit. This made it possible to retrospectively have all the necessary data.

### Visit timeline

The patients included in the MD Group and the MD+PPI Group were checked on four occasions: before starting therapy (T0), after 30 days of therapy (T1), after 60 days of therapy (T2) and 30 days after the discontinuation of the therapy (T3). At T0, T1, T2 and T3, the patients filled out the GIS and GERD-HRQL questionnaires. At T1 and T2, information on any adverse effects induced by the therapy was collected. At T2, the patients expressed their opinion on the efficacy and pleasantness of the therapy.

From the time of starting the intake (T0) and in the following 60 days (from T0 to T2), patients took MD in the amount of one stick pack after each of the two main meals of the day and before going to bed for night sleep.

### Statistical analysis

Descriptive statistics were used to summarize the characteristics of the cohorts in terms of median, mean and standard deviation (SD) or frequencies when appropriate.

The therapeutic effect was estimated in terms of the change in outcome in treated patients between the visit at T0 and the visits at T1, T2 and T3. The significance of differences was determined by applying the non-parametric Mann-Whitney test for paired data of treated patients and the non-parametric Wilcoxon test for unpaired data in the case of comparison of changes across patients who underwent different treatments. In all analyses carried out, the results were considered statistically significant at $P < 0.05$.

For statistical processing, GraphPad Prism version 8.0.2 for Windows, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com was used.

## Results

Patients who were treated between February 2023 and March 2024 and who adhered to doctor's prescriptions during the treatment period were included in the study. Sixty-six patients with NERD were included in the study, including 33 patients in the MD Group, and 33 patients in the MD+PPI Groups. Table 1 reports the demographic data and medical history of the patients enrolled in the study. Occasional alcohol intake is defined as alcohol intake at least once in the last 30 days, while moderate alcohol intake is defined as alcohol consumption of up to 2 cans of beer or up to 2 glasses of wine or up to 2 small glasses of liquor per day. Patients who consumed higher quantities of alcoholic beverages were excluded from the study.

The demographic data and medical history of two Groups did not differ significantly from each other, except for two parameters: there is a significantly higher number of patients who consumed a moderate amount of alcohol ($P = 0.0227$) and who consumed up to 4 cups of coffee per day ($P = 0.0226$) among the patients of the MD+PPI Group.

In the MD+PPI Group, 12 patients took esomeprazole 40 mg, 5 patients took esomeprazole 20 mg, 8 patients took pantoprazole 20 mg, 4 patients took lansoprazole 15 mg, 1 patient took omeprazole 40 mg and 3 patients took omeprazole 20 mg.

In the patients of the MD Group and in the patients of the MD+PPI Group at T0, the correlation between the results of the questionnaires to which they were subjected is evident, confirming the correlation between the symptoms presented and the reflux-related quality of life (Table 2).

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**Table 1:** Demographic and medical history data of patients included in the study. Data are expressed as mean ± SD, unless otherwise indicated.

| Variable | | Patients in MD Group (n=33) | Patients in MD + PPI Group (n=33) |
|---|---|---|---|
| Age (years) | | 48.8 ± 17.1 | 47.5 ± 16.4 |
| Gender, % F (n) | | 66.6 (22) | 51.5 (17) |
| Height (m) | | 170.0 ± 8.67 | 170.0 ± 8.23 |
| Weight (kg) | | 72.5 ± 12.3 | 70.6 ± 13.9 |
| BMI | | 25.0 ± 2.74 | 24.4 ± 3.91 |
| Smoking, % Yes (n) | | 27.3 (9) | 33.3 (11) |
| Alcohol consumption, % (n) | No | 24.3 (8) | 12.1 (4) |
| | Occasional | 63.6 (21) | 48.5 (16) |
| | Moderate | 12.1 (4) | 39.4 (13) |
| Coffee consumption, % (n) | No | 30.3 (10) | 15.2 (5) |
| | Up to 2 cups | 63.6 (21) | 54.5 (18) |
| | Up to 4 cups | 6.1 (2) | 30.3 (10) |
| Physical activity, % (n) | No | 45.5 (15) | 42.4 (14) |
| | Moderate | 30.3 (10) | 45.4 (15) |
| | Intense | 21.2 (7) | 9.1 (3) |
| | Competitive | 3.0 (1) | 3.0 (1) |
| Duration of symptoms to date (months) | | 8.24 ± 5.48 | 9.0 ± 5.20 |
| Days with symptoms per week | | 5.18 ± 1.70 | 5.64 ± 1.64 |
| Previous treatment of NERD | | 84.8% (28) | 90.9% (30) |
| Previous treatment with PPIs and/or prokinetics | | 54.5% (18) | 60.6% (20) |
| Previous treatment with antacids | | 33.3% (11) | 30.3% (10) |
| Previous treatment with medical devices or food supplements | | 9.1% (3) | 18.2% (6) |
| Allergies, % (n) | | 21.2 (7) | 21.2 (7) |
| Familial history of gastrointestinal diseases, % (n) | | 24.2 (8) | 24.2 (8) |

**Table 2:** Correlation between the evaluation tools adopted in the study by calculating the Spearman correlation coefficient.

| Spearman correlation | T0 | |
|---|---|---|
| | r-value | P-value |
| GIS vs GERD-HRQL in MD Group | 0.352 | 0.0443 |
| GIS vs GERD-HRQL in MD+PPI Group | 0.514 | 0.0022 |

In the MD Group, the T1 control was carried out on average 30.8 ± 0.95 days after T0; the T2 control was carried out on average 31.1 ± 1.62 days after T1; the T3 control was carried out on average 30.9 ± 1.41 days after T2. In the MD + PPI Group, the T1 control was carried out on average 31.6 ± 1.66 days after T0; the T2 control was carried out on average 31.1 ± 4.32 days after T1; the T3 control was carried out on average 30.3 ± 2.27 days after T2. During the treatment period, no adverse effects attributable to the products taken were reported in either group.

## Gastroesophageal Reflux Disease Impact Scale (GIS)

In the MD Group and MD+PPI Group, the total GIS score significantly decreased at T1 compared to T0 and further decreased statistically significantly at T2 compared to T1, demonstrating the improvement of NERD symptoms.

After 30 days of therapy (T1), the mean percentage reduction of the total GIS score compared to T0 was 50.1% in the MD Group and 46.7% in the MD+PPI Group.

After 60 days of therapy (T2), the mean percentage reduction of the total GIS score compared to T0 was 55.5% in the MD Group and 53.9% in the MD+PPI Group.

The total GIS score in the MD Group increased at T3, 30 days after the discontinuation of the therapy, reaching a statistically significant difference compared to T2 but without reaching a statistically significant difference compared to T1, also remaining significantly lower than T0 (Table 3, Figure 1). The total GIS score in the MD+PPI Group increased at T3, reaching a statistically significant difference compared to T2

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and T1, and remaining significantly lower than at T0 (Table 3, Figure 1). No significant difference is found between the scores of the two Groups at T0, T1, T2 and T3.

Based on the questionnaire scores grouped in the three areas of "Upper GI symptoms", "Other acid-related GI symptoms" and "Impact of symptoms" of the MD Group and the MD+PPI Group, it is noted that all undergo a statistically significant reduction from T0 to T1 and that all remain significantly lower than T0 both at T2 and T3 (Table 3, `Figure 1).

**Table 3:** Medians, 25th and 75th percentiles and means ± SD of the total score and the individual GIS area scores found in the MD Group and in the MD+PPI Group at the time of starting therapy (T0), after 30 days of therapy (T1), after 60 days of therapy (T2) and after 30 days from the discontinuation of the therapy (T3) and statistical significance of the comparisons. NS: not statistically significant.

| GERD Impact Scale | Parameters | MD Group | | | | MD + PPI Group | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T0 | T1 | T2 | T3 | T0 | T1 | T2 | T3 |
| Total | Median | 8.00 [8.00 - 9.04] | 4.00 [3.63 - 4.38] | 3.58 [3.00 - 4.08] | 4.25 [4.00 - 4.67] | 8.00 [7.71 - 8.83] | 4.33 [3.75 - 5.08] | 3.50 [3.00 - 4.29] | 4.58 [4.04 - 5.25] |
| | [25th – 75th] | | | | | | | | |
| | Mean ± SD | 8.60 ± 1.03 | 4.28 ± 1.11 | 3.78 ± 0.76 | 4.45 ± 0.69 | 8.43 ± 1.02 | 4.54 ± 1.37 | 3.91 ± 1.33 | 4.77 ± 1.09 |
| | P-value vs T0 | | < 0.0001 | < 0.0001 | < 0.0001 | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T1 | | | 0.0012 | NS | | | < 0.0001 | 0.0261 |
| | P-value vs T2 | | | | < 0.0001 | | | | < 0.0001 |
| | P-value T0 MD vs T0 MD+PPI | NS | | | | | | | |
| | P-value T1 MD vs T1 MD+PPI | | NS | | | | | | |
| | P-value T2 MD vs T2 MD+PPI | | | NS | | | | | |
| | P-value T3 MD vs T3 MD+PPI | | | | NS | | | | |
| Upper GI symptoms | Median | 3.00 [3.00 - 3.33] | 1.00 [1.00 - 1.67] | 1.00 [1.00 - 1.33] | 1.33 [1.33 - 1.67] | 3.00 [3.00 - 3.00] | 1.33 [1.00 - 1.33] | 1.00 [1.00 - 1.33] | 1.33 [1.00 - 1.33] |
| | [25th – 75th] | | | | | | | | |
| | Mean ± SD | 3.18 ± 0.32 | 1.30 ± 0.42 | 1.20 ± 0.37 | 1.42 ± 0.38 | 3.07 ± 0.30 | 1.41 ± 0.59 | 1.20 ± 0.42 | 1.31 ± 0.42 |
| | P-value vs T0 | | < 0.0001 | < 0.0001 | < 0.0001 | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T1 | | | NS | NS | | | 0.002 | NS |
| | P-value vs T2 | | | | 0.0014 | | | | 0.0329 |
| | P-value T0 MD vs T0 MD+PPI | NS | | | | | | | |
| | P-value T1 MD vs T1 MD+PPI | | NS | | | | | | |
| | P-value T2 MD vs T2 MD+PPI | | | NS | | | | | |
| | P-value T3 MD vs T3 MD+PPI | | | | NS | | | | |
| Other acid-related GI symptoms | Median | 3.00 [3.00 - 3.00] | 1.50 [1.00 - 2.00] | 1.50 [1.00 - 1.50] | 1.50 [1.50 - 2.00] | 3.00 [2.50 - 3.50] | 1.50 [1.50 - 2.00] | 1.00 [1.00 - 2.00] | 2.00 [1.50 - 2.50] |
| | [25th – 75th] | | | | | | | | |
| | Mean ± SD | 3.12 ± 0.28 | 1.59 ± 0.54 | 1.41 ± 0.38 | 1.71 ± 0.45 | 3.08 ± 0.49 | 1.74 ± 0.64 | 1.45 ± 0.60 | 2.05 ± 0.51 |
| | P-value vs T0 | | < 0.0001 | < 0.0001 | < 0.0001 | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T1 | | | NS | NS | | | 0.0464 | 0.0001 |
| | P-value vs T2 | | | | 0.0038 | | | | < 0.0001 |
| | P-value T0 MD vs T0 MD+PPI | NS | | | | | | | |
| | P-value T1 MD vs T1 MD+PPI | | NS | | | | | | |
| | P-value T2 MD vs T2 MD+PPI | | | NS | | | | | |
| | P-value T3 MD vs T3 MD+PPI | | | | 0.008 | | | | |

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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Impact of symptoms | Median [25th – 75th] | 2.00 [2.00 - 2.25] | 1.25 [1.00 - 1.50] | 1.25 [1.00 - 1.25] | 1.25 [1.00 - 1.50] | 2.00 [2.00 - 2.50] | 1.25 [1.00 - 1.88] | 1.00 [1.00 - 1.75] | 1.25 [1.00 - 1.75] |
| | Mean ± SD | 2.30 ± 0.65 | 1.44 ± 0.57 | 1.30 ± 0.50 | 1.42 ± 0.56 | 2.29 ± 0.42 | 1.57 ± 0.71 | 1.47 ± 0.73 | 1.57 ± 0.69 |
| | P-value vs T0 | | < 0.0001 | < 0.0001 | < 0.0001 | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T1 | | | 0.0084 | NS | | | 0.0002 | NS |
| | P-value vs T2 | | | | 0.0089 | | | | 0.0003 |
| | P-value T0 MD vs T0 MD+PPI | NS | | | | | | | |
| | P-value T1 MD vs T1 MD+PPI | | NS | | | | | | |
| | P-value T2 MD vs T2 MD+PPI | | | NS | | | | | |
| | P-value T3 MD vs T3 MD+PPI | | | | NS | | | | |

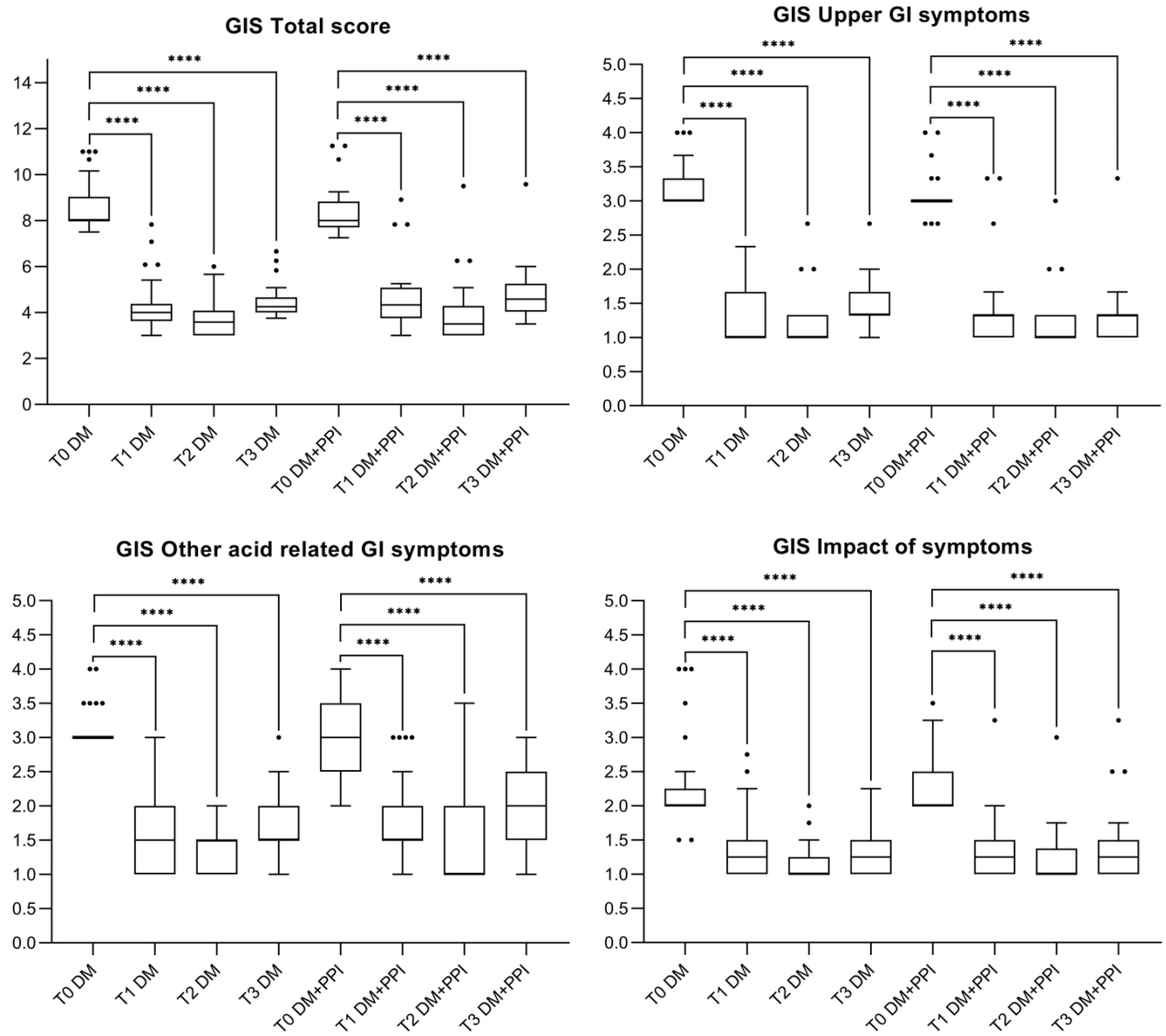


**Figure 1:** MD treatment and combined MD+PPI treatment for 60 days (T2) significantly reduced the total GIS score and the "Upper GI symptoms", "Other acid-related GI symptoms" and "Impact of symptoms" scores. The scores remained significantly lower than the scores at T0 even after 30 days of the discontinuation of the therapy (T3) (****p<0.0001).

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For "Upper GI symptoms" area, a more marked improvement is noted in the MD Group between T0 and T1 compared to the MD+PPI Group, but without reaching a statistically significant difference between the two Groups. The further reduction of the score between T1 and T2 is not statistically significant in the MD Group, while it is statistically significant in the MD+PPI Group. The score increases at T3, reaching a statistically significant difference in both Groups compared to T2 but not compared to T1. No significant difference is found between the scores of the two Groups at T0, T1, T2 and T3 (Table 3, Figure 1).

For "Other acid-related GI symptoms" area, a more marked improvement is noted in the MD Group between T0 and T1 compared to the MD+PPI Group, but without reaching a statistically significant difference between the two Groups. The further reduction of the score between T1 and T2 is not statistically significant in the MD Group, while it is statistically significant in the MD+PPI Group. The score increases at T3 reaching a statistically significant difference in the MD+PPI Group, but not in the MD Group, compared to T1 and reaching a statistically significant difference in both Groups compared to T2. No significant difference is found between the scores of the two Groups at T0, T1, T2 while there is a significant difference between the scores of the two Groups at T3 (Table 3, Figure 1).

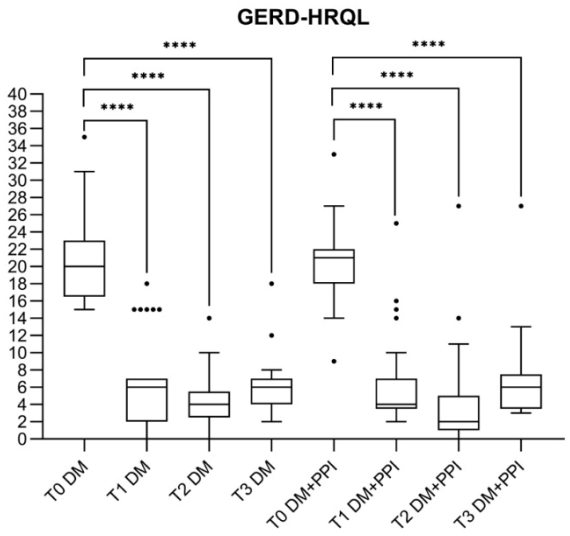


**Figure 2:** MD and MD+PPI treatment for 30 (T1) and 60 days (T2) significantly reduced the total GERD-HRQL score. The total score remained significantly lower than the score at T0 even 30 days after the discontinuation of MD therapy and MD+PPI therapy (T3) even if it significantly worsened compared to T2 but not compared to T1 (****p<0.0001).

For "Impact of symptoms" area, a more marked improvement is noted in the MD Group between T0 and T1 compared to the MD+PPI Group, but without reaching a statistically significant difference between the two Groups. The further reduction in score between T1 and T2 was statistically significant in both Groups. The score increases at T3, reaching a statistically significant difference in both Groups compared to T2 but not compared to T1. No significant difference is found between the scores of the two Groups at T0, T1, T2 and T3 (Table 3, Figure 1).

## Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) Questionnaire

In the MD Group and MD+PPI Group, the total GERD-HRQL score significantly decreased at T1 compared to T0 and further improved at T2 compared to T1, demonstrating the improvement in the quality of life of patients with NERD.

After 30 days of therapy (T1), the reduction of the GERD-HRQL questionnaire score compared to T0 was 71.9% and 70.2% in the MD Group and in the MD+PPI Group, respectively.

**Table 4:** Medians, 25th and 75th percentiles and means ± SD of the total score of GERD-HRQL found in the MD Group and in the MD+PPI Group at the time of starting therapy (T0), after 30 days of therapy (T1), after 60 days of therapy (T2) and after 30 days from the discontinuation of the therapy (T3) and statistical significance of the comparisons. NS: not statistically significant.

| GERD HRQL | Parameters | MD Group (n=33) | | | | MD + PPI Group (n=33) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T0 | T1 | T2 | T3 | T0 | T1 | T2 | T3 |
| Total | Median [25th – 75th] | 20.00 [16.50 - 23.00] | 6.00 [2.00 - 7.00] | 4.00 [2.50 - 5.50] | 6.00 [4.00 - 7.00] | 21.00 [18.00 - 22.00] | 4.00 [3.50 - 7.00] | 2.00 [1.00 - 5.00] | 6.00 [3.50 - 7.50] |
| | Mean ± SD | 20.30 ± 4.55 | 6.24 ± 4.94 | 4.15 ± 2.74 | 6.03 ± 3.11 | 20.15 ± 4.50 | 6.27 ± 4.84 | 4.09 ± 5.25 | 6.70 ± 4.53 |
| | P-value vs T0 | | < 0.0001 | < 0.0001 | < 0.0001 | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T1 | | | 0.0002 | NS | | | < 0.0001 | NS |
| | P-value vs T2 | | | | < 0.0001 | | | | < 0.0001 |
| | P-value T0 MD vs T0 MD+PPI | NS | | | | | | | |
| | P-value T1 MD vs T1 MD+PPI | | NS | | | | | | |
| | P-value T2 MD vs T2 MD+PPI | | | NS | | | | | |
| | P-value T3 MD vs T3 MD+PPI | | | | NS | | | | |

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After 60 days of therapy (T2), the reduction of the GERD-HRQL questionnaire score compared to T0 was 80.6% and 81.5% in the MD Group and in the MD+PPI Group, respectively.

In both Groups, at T3, 30 days after the discontinuation of therapies, the score shows a statistically significant worsening compared to T2 but remains significantly lower than T0 and not significantly different from T1 (Table 4, Figure 2).

At T0, T1, T2 and T3, the total score of GERD-HRQL in patients in the MD Group is not significantly different from that of patients in the MD+PPI Group.

### Rating on the efficacy and pleasantness of the therapy

The patients enrolled in the study answered the following question: after how many days from starting to use the medical device did the most bothersome symptoms disappear? The average number of days was 9.0 ± 3.97 for the patients in the MD Group and 9.52 ± 4.65 for the patients in the MD+PPI Group.

After 60 days of therapy (T2), the patients expressed an opinion on the efficacy of the therapy. The opinions of the patients in the MD Group were as follows: 39.4% (13 patients) excellent, 45.5% (15 patients) good, 12.1% (4 patients) satisfactory, 3.0% (1 patient) poor. The opinions of the patients in the MD + PPI Group were as follows: 39.4% (13 patients) excellent, 33.3% (11 patients) good, 21.2% (7 patients) satisfactory, 6.1% (2 patients) poor.

After 60 days of therapy (T2), the patients expressed an opinion on the pleasantness of MD. The opinions of the patients in the two Groups were as follows: 40.9% (27 patients) excellent, 40.9% (27 patients) good, 13.6% (9 patients) satisfactory, 4.6% (3 patients) poor.

## Discussion

In this study, the symptomatic effect of MD and the combination of MD and PPI was investigated: after 30 days of treatment with MD and MD+PPI, the total GIS score improved significantly compared to T0, decreasing on average by 50.1% and 46.7%, respectively. The first value is equivalent to the 50% threshold that we considered essential to consider the therapy effective, while the second is slightly lower. After 60 days of treatment with MD and MD+PPI, the total GIS score improved further compared to T0, decreasing on average by 55.5% and 53.9% respectively, corresponding to values higher than the 50% threshold that we considered essential to consider the therapy effective.

According to patients' statements, the average number of days of treatment necessary for the disappearance of the most bothersome symptoms was 9.0 ± 3.97 for the patients of the MD Group and 9.52 ± 4.65 for the patients of the MD+PPI Group.

In the sample of patients treated, the combination of MD with PPI drugs yielded no additive effect in symptom control. The benefit obtained with MD alone does not differ from the benefit obtained with MD+PPI.

After 60 days of therapy, the reduction in the score obtained from GERD-HRQL questionnaire aimed at evaluating the quality of life of patients in relation to reflux disease was 80.6% and 81.5% in the MD Group and in the MD+PPI Group, respectively.

This confirms the efficacy of the two therapies in inducing a significant improvement in the quality of life in relation to the reflux disease of the patients.

When the three GIS areas were considered separately, all of them showed a statistically significant reduction from T0 to T2. The trend of the scores of the individual areas is homogeneous and reflects the trend of the total GIS score. This means that the two therapies do not exert a more accentuated action on a single group of NERD symptoms, but rather, a broad action, affecting all the symptoms that characterize NERD.

The combination of these observations confirms that treatment with MD and treatment with MD+PPI result in a significant improvement in NERD symptoms.

The trend of GERD-HRQL scores suggests that the improvement perceived by patients in both Groups is significant in the first 30 days of treatment, from T0 to T1, and that a further significant improvement is also evident in the subsequent 30 days of treatment, from T1 to T2, compared to the results obtained in the first 30 days.

The visit carried out 30 days after the discontinuation of the treatment (T3) shows that in both Groups the total GIS and GERD-HRQL scores worsened compared to T2 but remained significantly better than the total scores at T0.

All these observations suggest that both the use of MD alone and its combined use with PPI resulted in the fact that the perception of the reduction of NERD symptoms increases progressively in the 60 days of treatment and that the therapeutic result obtained in the 60 days of treatment with MD is partially maintained after 30 days from the discontinuation of the treatment. This suggests that it is advisable to continue the treatment for at least 60 days and periodically repeat the treatment to ensure the resolution of NERD signs and symptoms and the maintenance of the result achieved.

The comparison between patients treated with MD and those treated with MD+PPI does not reveal significant differences either during treatment or 30 days after the

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discontinuation of the treatment. Some trends (faster worsening of the total score of the GIS questionnaire and of the score of the "Other acid-related GI symptoms" area of GIS after the discontinuation of the therapy with MD+PPI compared to therapy with MD alone) are noted, suggesting the requirement of a larger sample size to be adequately investigated. It is believed that the small sample treated in this study does not allow to venture a guess on the meaning of these trends.

The evidence collected allows to hypothesize that in a sample of patients affected by NERD similar to the one examined in this study, therapy with MD may be sufficient for adequate symptomatic control, without the need to resort to PPIs. As MD is a medical device, it does not have any pharmacological action. Its action is purely physical. In other words, it cannot induce the adverse effects of PPIs and a tolerance cannot occur even if the treatment is continued for long periods.

Scientific literature states that a medical device containing appropriate doses of magnesium alginate, calcium carbonate and potassium bicarbonate should perform three actions. As a first action, magnesium alginate, calcium carbonate and potassium bicarbonate form the so-called floating raft upon contact with the acidic gastric contents. The floating raft is intended to physically hinder gastroesophageal reflux after meals [23]. As a second action, calcium carbonate and potassium bicarbonate neutralize the hydrochloric acid that accumulates after meals at the gastroesophageal junction in the reservoir called “acid pocket”. The neutralization of the hydrochloric acid in the acid pocket reduces its erosive effect [23]. As a third action, sodium hyaluronate and chondroitin sulfate mixture has a viscous behavior and forms a transitory protective film that adheres to the esophageal mucosa [24]. This film is intended to protect the esophagus from contact with the gastric contents, thus promoting the repair processes [24].

In a recently published study, the efficacy of MD in forming a protective barrier was evaluated in vitro using a reconstructed human oral epithelium cellular model, monitoring the formulation's ability to reduce the passage of substances, as well as the ability to reduce inflammation and toxic effects induced by exposure to an irritant. The study demonstrated that MD is able to create a barrier at the epithelial cell level that significantly reduces caffeine absorption and that it is able to significantly reduce toxicity and inflammation induced by Triton X-100 [25].

In clinical studies, formulas that combine alginate, carbonates and bicarbonates have demonstrated their benefit in controlling the symptoms of GERD [23,26-28]. In a prospective open-label randomized parallel-group clinical trial published in 2011, the combination of alginate, potassium bicarbonate and omeprazole was found to be more effective than omeprazole alone in the treatment of NERD [29]. In a double-blind parallel clinical trial published in 2013, alginate was shown to be as effective as omeprazole in providing relief from NERD symptoms [30].

Some clinical trials have also documented the beneficial effects of the combination of sodium hyaluronate and chondroitin sulfate in the treatment of NERD symptoms [31,32].

Based on this evidence, it was expected that MD intake could have an effective symptomatic action in the treatment of NERD, perhaps even superior to that of alginate, with or without carbonates and bicarbonates, or to that of the combination of hyaluronic acid and chondroitin sulfate, as its composition includes all these ingredients.

An original feature of the present study is the aim of achieving a reduction in the GIS questionnaire score by at least 50%. Generally, the comparison between the patients' status before and after treatment is considered sufficient. If the therapeutic actions adopted in the study have already proven effective in treating the disorder considered, a statistically significant improvement in the parameters chosen for the clinical evaluation is easily achievable. However, the statistical significance of the improvement obtained is not sufficient: in fact, it is not certain that a patient who had a statistically significant reduction in the score of a questionnaire intended to evaluate symptoms is also satisfied with the result obtained. Therefore, the objective of reducing the score of the questionnaire adopted in this study by 50% aims to at least partially overcome this potential bias in verifying the therapeutic efficacy and aims to help establish how long the treatment should be continued to obtain the best results.

pH-impedance studies allow to classify the patients with NERD into three subgroups, namely those with true NERD, those with hypersensitive esophagus and those with functional heartburn (FH) [33]. The FH subgroup represents a mean of 26% of patients with NERD [33]. As the patients included in this study did not undergo a pH-impedance study, the percentage of patients with FH cannot be estimated within the patient Groups. However, pH-impedance study is not routinely performed in clinical practice. This makes the patient Groups and the results of this study more similar to what physicians face in their daily practice, as stated by other researchers [30,34].

A limitation of this study is its retrospective design. This implies the inclusion of patients who have completed the therapeutic cycle and does not allow us to investigate whether there are potential reasons that lead to the discontinuation of the therapy. On the other hand, what has driven us to

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reorganize the collected data and process them was the feeling that the patients liked the therapy and, therefore, were quite adherent to the prescription. However, this is a feeling that we cannot demonstrate.

The lack of a control arm treated with placebo can be considered a further limitation of this study. We would like to point out that we do not consider the comparison with a placebo-treated group necessary, first of all because PPIs, alginates associated with alkalinizing substances and the combination of sodium hyaluronate and chondroitin sulfate have already been tested in clinical studies versus placebo in the treatment of reflux disease. Both alginates associated or not with alkalinizing substances [27,28], and the combination of sodium hyaluronate and chondroitin sulphate [31,32] have been shown to be more effective than the placebo, allowing us to assume that MD combining alginate, alkalinizing substances, sodium hyaluronate and chondroitin sulphate in its formula can easily provide clinical effects superior to those of the placebo. Furthermore, our goal is not to prescribe medical devices that exceed the efficacy of the placebo, a result that is very easily achievable, but rather to try to bring our patients back to a state of health similar to that of healthy subjects. Finally, this study was carried out as part of our usual clinical practice and we do not consider it ethically correct to subject patients who rely on us with the hope of resolving the disorders they suffer from to a placebo treatment.

## Conclusions

NERD is the most common phenotype of gastroesophageal reflux disease. The type and intensity of symptoms are in clear discrepancy with the absence of esophageal lesions. The close correlation between NERD and lifestyle changes is known, but there is an increasing need for a simple, repeatable, effective and safe therapy in the short, medium and long term. The absence of Barrett's esophagus allows for the safe application of a cytoprotective and alkalinizing therapy, based on medical devices with a barrier function, compared to an antisecretory therapy based on PPIs.

The hypothesis we formulated seems to be confirmed by the results of the study performed: an oral medical device that physically hinders the reflux of gastric contents, neutralizes the hydrochloric acid of the acid pocket that forms near the gastroesophageal junction during meals and protects the esophageal mucosa by an adhesive film is able to effectively control the symptoms of NERD, in conjunction or not with the use of PPIs.

This study highlights an improvement of all the parameters evaluated after 30 and 60 consecutive days of MD intake by patients affected by NERD. In fact, the symptoms of NERD are significantly improved thanks to the treatment. Furthermore, patients stated that they perceived the disappearance of the most bothersome symptoms a mean of 9 days after the intake of the therapies.

The same parameters slightly worsen during the 30 days following the discontinuation of the therapy, demonstrating that in the case of NERD, it is preferable to undertake a prolonged therapy over time or to repeat the therapy cyclically to maintain the stability of the results obtained.

In conclusion, the results of this pilot and retrospective clinical study represent a first demonstration of the efficacy of a medical device composed of magnesium alginate, calcium carbonate, potassium bicarbonate, sodium hyaluronate and chondroitin sulfate in reducing the symptoms commonly associated with NERD and in improving the health-related quality of life.

The study also shows that the product under study is considered effective by patients and is appreciated by them, which are essential for ensuring their compliance. It is desirable that the patient undergoing MD therapy is more motivated to take care of his/her health, improving his/her hygienic-dietary habits and thus contributing, further, to the reduction of the typical NERD symptoms.

The authors are aware of the fact that confirmation of the results obtained in this pilot study requires further clinical studies with a prospective design and adequate statistical power.

## Conflict of interest

Daniela Sgarbi and Rinaldo Carmelo Nicita declare that they have no commercial relationships (e.g. consultancy, stock ownership, shareholding, patent/licensing agreement, etc.) that could pose a conflict of interest about the submitted article.

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