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Effect of an extra-virgin olive oil enriched with probiotics or antioxidants on functional dyspepsia: a pilot study

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Abstract. – BACKGROUND: While antioxidants and probiotics have been proposed for the treatment of functional dyspepsia, current data are still heterogeneous and studies are poorly designed. Extra-virgin olive oil, a common ingredient of Mediterranean diet, has shown antioxidant properties.

AIMS: To evaluate the effect of extra-virgin olive oil enriched with antioxidants or probiotics on functional dyspepsia.

PATIENTS AND METHODS: This study has been designed as a "proof of concept". Extra-virgin olive oil enriched with antioxidants or probiotics was blindly added to the common diet of 8 subjects with functional dyspepsia for 7 days. Dyspeptic symptoms were then evaluated in all patients.

RESULTS AND CONCLUSIONS: A significant improvement of dyspeptic symptoms was observed in subjects receiving the antioxidant or probiotic enriched oil diet, with a greater effect observed for the latter. Larger studies are now needed to confirm these data.

Key Words:
Functional dyspepsia, Probiotics, Antioxidants, Extra-virgin olive oil.

Introduction

In a great number of cases, dyspepsia is not caused by an organic disease, but has a functional origin[1]. According to the classification of "Rome III"[2], functional dyspepsia should include one or more of the following symptoms: bothersome postprandial fullness, early satiety, epigastric pain, epigastric heartburn, as well as no evidence of organic disease (including those evaluable at endoscopy) that could explain the symptoms. The onset of those symptoms is supposed to be 6 months before diagnosis with an occurrence in the last 3 months. Symptoms of dyspepsia have an unclear origin, and overlap with others typical of functional syndromes of the digestive tract – such as irritable bowel syndrome –, cardiac chest pain and functional heartburn. The pathophysiological mechanisms of functional dyspepsia involves gastrointestinal motility, visceral sensitivity and psychological factors (personality, psychological state, social support) that modulate the perception, interpretation and the response to environmental stimuli. Since the pathophysiology of functional dyspepsia is still unclear, the therapeutic approach to the disease is quite confusing. Up to now, no drug has shown a significant effect on functional dyspepsia[1]. On this subject, important studies have been published about the relationship between dyspepsia, free radicals and antioxidants. In particular, the activity of reactive oxygen species (ROS) in *Helicobacter (H.) pylori*-related gastritis has been evaluated. Gastric mucosal levels of reduced glutathione and malondialdehyde, measured from gastric biopsies of patients with gastritis and peptic ulcer, were respectively lower and higher compared to controls, possibly meaning that the depletion of reduced glutathione in the gastric mucosa may be caused by the accumulation of free radicals[3]. On the other hand, beta-carotene and alpha-tocopherol are decreased in the gastric juice during the course of different pathological conditions, such as alcoholism and *H. pylori* infection, which in turn may be a cause of atrophic gastritis or intestinal metaplasia[4]. Another study has assessed the activity of free radicals and the plasmatic levels of antioxidant vitamin levels in dyspeptic patients, and their correlation with smoking and *H. pylori* infection. At univariate analysis, plasmatic free radical activity

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was higher in males, smokers and *H. pylori*-positive subjects. However, after multiple regression analysis (adjusted for male sex and smoking), there was no significant association between plasma free radical activity and *H. pylori* infection. The reason for the higher prevalence of *H. pylori* and peptic disease in smokers with dyspepsia is unclear, but may be related to the reduction of antioxidant defenses[5]. The activity of free radicals and the concentration of ascorbic acid in the gastric mucosa, and their correlation with the infection and subsequent *H. pylori* eradication has also been studied; even though ROS possibly play a role in *H. pylori*-gastritis, the mucosal concentration of ascorbic acid is not reduced in this particular condition[6]. Moreover, Nair et al[7] have analyzed the concentrations of antioxidant micronutrients in gastric biopsies of patients with gastritis and gastric ulcer: the degree of depletion of antioxidants was higher in gastric ulcers (no differences based on etiology, NSAIDs or *H. pylori*) than in gastritis and healthy controls. This phenomenon seems to be a nonspecific response, not linked to *H. pylori* infection. Prabba et al[8] conducted a study on the use of a methanol extract of seeds of *Pongamia pinnata* (Linn), containing flavonoids, in the treatment of peptic ulcer of rats, showing a reduction of mucosal levels of lipid peroxidation, nitric oxide, catalase and superoxide dismutase. The effects of the seeds of *P. pinnata* may be mediated by flavonoids. The role of melatonin (with known antioxidant properties) in the oxidative damage of gastric mucosa in patients with functional dyspepsia has also been studied[9] in 2 groups of patients with gastritis, either *H. pylori*-negative and *H. pylori*-positive, as well as in controls. Oxidative stress was evaluated before and after the use of melatonin for a period of 3 months. Melatonin administration reduced significantly the rate of gastric mucosal oxidative damage. Finally, a pre-treatment with antioxidants (thiol-reducing agent dithiothreitol) has also been demonstrated to be effective against the omeprazole-induced toxicity in an experimental model of infectious gastritis, while vitamin C has also a very similar effect[10]. Another therapeutic area of functional dyspepsia is related to the use of probiotics. In a recent randomized, placebo-controlled clinical trial[11], the use of a dietary supplementation with *Bacillus coagulans* in adult patients with functional dyspepsia has been evaluated; a significant reduction of symptoms such as abdominal pain and abdominal distension was observed. Furthermore, there is evidence of the efficacy of *Lactobacillus rhamnosus* GG in different functional gastrointestinal disorders, particularly IBS, in a pediatric population[12]. Although some probiotics have already been proven to exert an effect on diarrhea as well as in other common GI symptoms, such as bloating and constipation[13-19], there is an average number of studies regarding their effect on functional dyspepsia.

Considering the heterogeneity of the studies performed so far on the role of probiotics and antioxidants in the treatment of functional dyspepsia[20], we have designed a study aimed at evaluating the effects of an extra-virgin stoned olive oil (Oo) (silos No. 22 of the "Pietro D'Amico" mill, Cisternino, BR, Italy) enriched with antioxidants (Oo/Ao) or probiotics (Oo/Pr) on the expression of GI symptoms of patients affected by this clinical condition.

Patients and Methods

44 subjects referred to our Outpatients Clinic of General Gastroenterology for the occurrence of dyspeptic symptoms underwent the following investigations to exclude organic causes of dyspepsia and other diseases:

- Oriented medical history to exclude consumption of alcohol, non steroidal anti-inflammatory drugs (NSAIDs) and other drugs, cigarettes;
- Blood tests (blood urea nitrogen, glucose, ALT, AST, GGT, alkaline phosphatase, triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, complete blood count, erythrocyte sedimentation rate, anti-transglutaminase antibodies), to rule out systemic diseases;
- Urea ^{13}C Breath test, glucose and lactose H2 Breath test, respectively to exclude *H. pylori* infection, small intestinal bacterial overgrowth and lactose malabsorption.

Exclusion criteria were ongoing or recently discontinued (less than one month after the breath-tests) antibiotic therapy, *H. pylori* infection, small intestinal bacterial overgrowth, lactose malabsorption (positivity of lactose H2 breath test); known entheropaties (such as celiac disease and Crohn's disease), treatment with steroids, NSAIDS or other drugs harmful for the GI tract; major diseases (ischemic heart disease, diabetes mellitus, kidney diseases, liver diseases, etc.); inability to understand or sign the document of consent, minority, pregnancy.

According to Rome III criteria, 10 patients were diagnosed with functional dyspepsia. Of these, 8 agreed to participate in the study, after signing a written informed consent.

Initially, each patient produced a validated questionnaire[21] designed to evaluate, at baseline, the severity of eight GI symptoms (nausea, vomiting, postprandial fullness, halitosis, belching, early satiety, postprandial gastric distension, pain/upper abdominal discomfort quadrants), based on a visual analogue scale (VAS), consisting of a short line with two verbal descriptions at each end, "no symptoms", on the left, and "the greatest possible symptom", on the right, and patients were asked to mark on the line intensity of each symptom.

Oo/Ao was prepared in a set of two vials, with the following formulations:

- Selenium methionine (41.5 mcg), Q10 coenzyme (25 mg), ascorbyl palmitate (16 mg), resveratrol (7.5 mg), silicon dioxide (about 65 mg);
- 6% lycopene (5 mg), coenzyme Q10 (25 mg), silicon dioxide (110 mg).

Each subject received two vials of 9 ml (equal to the daily food requirement), with a dosing cap (each containing respectively the formulation No. 1 and formulation No. 2) per day, to be added to the meals.

Oo/Pr was developed using the following formulation: *Lactobacillus reuterii* 100 billion/g (0.04 g), *Lactobacillus rhamnosus* GG 350 billion/g (0.1143 g), *Saccharomyces boulardi* 20 billion/g (0.08 g), vitamin B6 hydrochloride (0.00102 g), inositol (0.025 g), silica (0.01255 g); Q10 coenzyme (25 mg).

During the study, all patients maintained a stable and common diet, enriched with olive oil as follows: Oo/Ao for 7 days, No oil for 7-days; Oo/Pr for 7 days, No oil for 7 days; and finally extra virgin olive without any enrichment (Oo) for 7 days. The total duration of treatment was 28 days for each participant.

All patients completed the validated questionnaire for the assessment of dyspeptic symptoms after each treatment cycle.

Statistical Analysis

Data were analized using Fisher's test and Chi square test. p values <0.05 were considered significant. Since the study has been designed as a "proof of concept" the sample size was not calculated.

Results

The effects of the administration of extra-virgin olive oils enriched with probiotics (OO/Pr) and antioxidants (OO/Ao) are summarized in the Figure 1. In particular, concerning halitosis and vomiting no significant differences were observed between baseline and post-treatment among different groups. Conversely, a significant amelioration of nausea was observed in subjects receiving Oo/Pr compared to Oo ($p < 0.05$) or Oo/Ao ($p = 0.04$). Moreover, adding Oo/Pr to the common diet resulted in a significant amelioration of the symptom "pain/discomfort in abdominal upper quadrants" compared to Oo ($p < 0.01$). Oo/Pr was more effective than Oo ($p < 0.05$) and Oo/Ao ($p < 0.05$) in relieving belching and also showed greater efficacy in alleviating "postprandial gastric distension" and "postprandial fullness" as compared to Oo ($p < 0.001$ for both symptoms) and Oo/Ao ($p < 0.001$ for gastric distension and $p < 0.06$ for fullness). For both symptoms no significant differences were observed between Oo/Ao and Oo.

Discussion

Extra-virgin oil has been used for centuries as food and condiment and its nutritional qualities have been evaluated in many scientific studies. Oleocantal (deacetoxy-ligstrosid-aglycol), a compound with activity similar to that of Ibuprofen, was found in extra-virgin oil at concentrations ranging from 22 to 190 μg for gram of oil[22]. Extra-virgin oil is also a goo lipophilic vehicle with effectiveness in producing an increase of vitamin E when compared to other vehicle such as soybean oil and butter[23].

This study compared the effectiveness of Oo/Pr and Oo/Ao in controlling symptoms of functional dyspepsia, defined by using the Rome III criteria, when compared with Oo. Our findings have shown an effect of both enriched formulations of oils in dyspeptic symptoms compared with oil alone, except for halitosis and vomiting. However, a statistical significance was reached only for the probiotic enriched formulation.

In particular, the effectiveness of Oo/Pr was usually greater than the effectiveness of Oo/Ao, with a significant difference for some symptoms, such as pain/epigastric discomfort, early satiety and postprandial fullness. On this subject, we

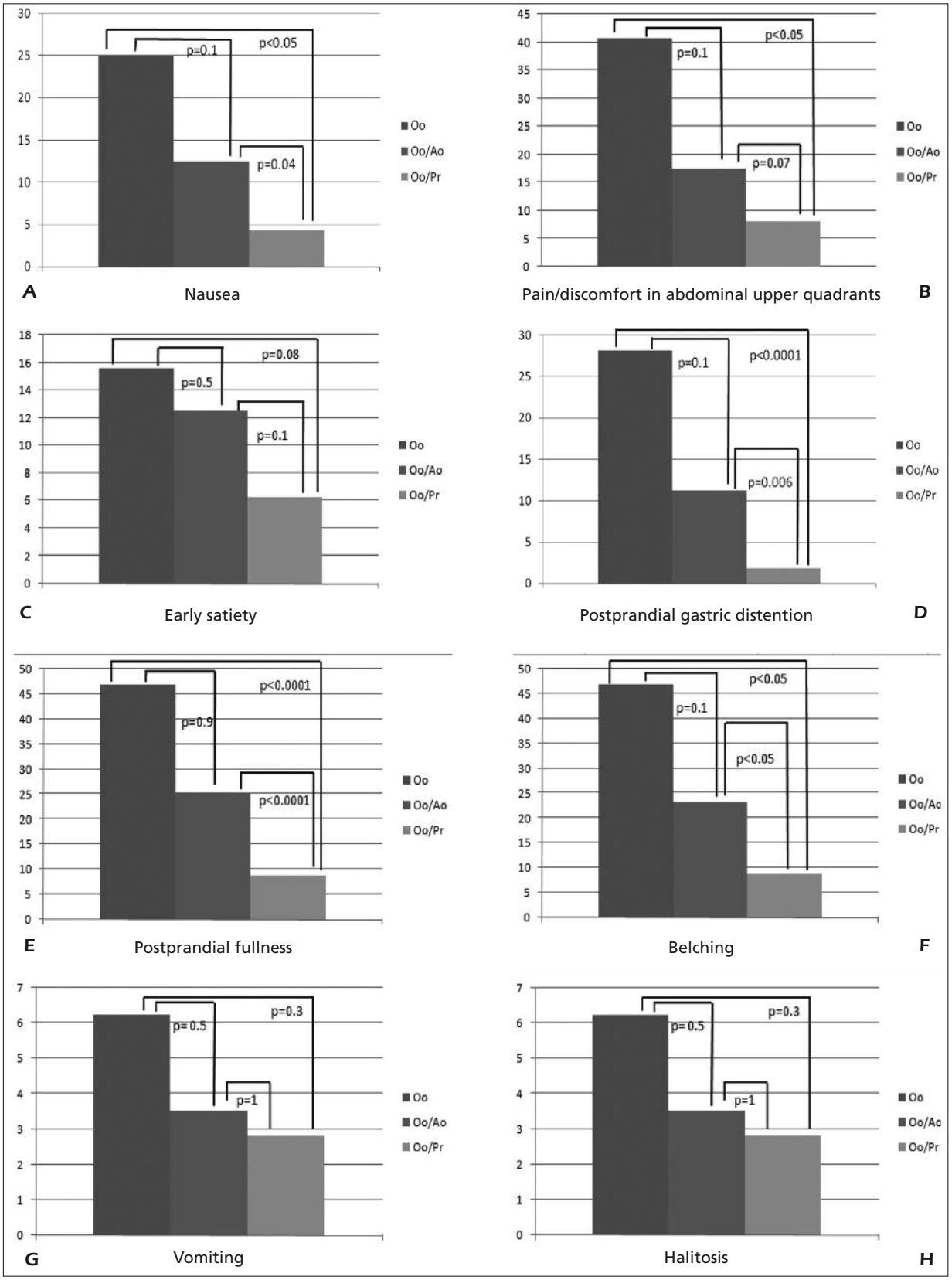

Figure 1. Comparison of each treatment (Oo, Oo/Ao, Oo/Pr) for the different symptoms of the VAS Scale (espressed as mean of VAS score) for functional dyspepsia.

may hypothesize a positive effect of Resveratrol, which may exert a similar action of Pterostilben, as already suggested[24].

The differences observed between probiotics and antioxidants may be explained by the different mechanism of action of those compounds. Probiotics have a short-term action, that is characterized by remodeling of gut microbiota and the complex network pattern between microflora and intestinal control systems (myoenteric complexes and immunity)[25], which in turn may positively affect the expression of GI symptoms. Antioxidants usually have a local effect but with a long-term action[26].

Nevertheless, despite our findings, we are not allowed to draw any definitive conclusions concerning the way of action of probiotics and antioxidants in patients with functional dyspepsia, because of the low sample size and the lack of information concerning the molecular effects of those substances on the GI mucosa of our patients.

Conclusions

This is a pilot study conducted on a small sample of patients. It shows for the first time that an extra-virgin olive oil enriched with probiotics added to the common diet significantly improved the expression of some GI symptoms in patients with functional dyspepsia. Larger studies are now needed in order to further validate these results.

Conflict of Interest

None declared.

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