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CLINICAL RESEARCH

Chios mastic treatment of patients with active Crohn's disease

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Abstract

AIM: To evaluate the effectiveness of mastic administration on the clinical course and plasma inflammatory mediators of patients with active Crohn's disease (CD).

METHODS: This pilot study was conducted in patients with established mild to moderately active CD, attending the outpatient clinics of the hospital, and in healthy controls. Ten patients and 8 controls were recruited for a 4-wk treatment with mastic caps (6 caps/d, 0.37 g/cap). All patients successfully completed the protocol. CD Activity Index (CDAI), Nutritional Risk Index (NRI), C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), monocyte chemotactic protein-1 (MCP-1), and total antioxidant potential (TAP) were evaluated in the plasma at baseline and at the end of the treatment period. Results were expressed as mean values ± SE and $P < 0.05$ was considered to indicate statistical significance.

RESULTS: Patients exhibited significant reduction of CDAI (222.9 ± 18.7 *vs* 136.3 ± 12.3, $P = 0.05$) as compared to pretreament values. Plasma IL-6 was significantly decreased (21.2 ± 9.3 pg/mL *vs* 7.2 ± 2.8 pg/ mL, $P = 0.027$), and so did CRP (40.3 ± 13.1 mg/mL *vs* 19.7 ± 5.5, $P = 0.028$). TAP was significantly increased (0.15 ± 0.09 *vs* 0.57 ± 0.15 mmol/L uric acid, $P = 0.036$). No patient or control exhibited any kind of side effects.

CONCLUSION: The results suggest that mastic significantly decreased the activity index and the plasma levels of IL-6 and CRP in patients with mildly to moderately active CD. Further double-blind, placebo-controlled studies in a larger number of patients are required to clarify the role of this natural product in the treatment of patients with CD.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of unknown etiology that may affect any level of the gastrointestinal tract[1-3]. It is well established that immunological mechanisms are involved in the pathogenesis of the disease. Inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have a pivotal role in induction and amplification of the inflammatory cascade. Particularly, IL-6 stimulates T-cell and B-cell proliferation and differentiation[4], while it mediates the hepatic expression of acute phase proteins[5]. Increased concentration of TNF-α and monocyte chemoattractant protein-1 (MCP-1) have been reported in patients with CD[6]. Additionally, during chronic inflammation, when sustained production of reactive oxygen and nitrogen species occurs, antioxidant defenses may weaken, resulting in a situation termed oxidative stress[7]. Thus, in patients with CD, elevated oxidized low-density lipoprotein levels have been reported compared to healthy controls[6].

Despite the large number of therapeutic agents available today, none can be considered as completely satisfactory either due to resistant cases or because of significant side effects. To our knowledge, there are only scattered reports of natural compounds that potentially reverse relapse in CD. Trebble and co-workers[8] demonstrated an anti-inflammatory activity of fish oil and antioxidant supplementation evaluated in mononuclear cells of CD patients, while Lavy *et al*[9] demonstrated the effectiveness of the antioxidant β-carotene in a rat model as a prophylactic dietary measure in reducing the effects of acid induced enteritis, thus raising the possibility that patients with CD may benefit from the consumption of natural β-carotene. Also the flavonoid rutin, a well-established antioxidant compound, has been suggested as a therapeutic agent in CD. Rutin has been shown to attenuate pro-inflammatory cytokine production in both colonic

mucosa and peritoneal macrophages of experimental animals[10]. Treatment with food phytochemicals has been shown to be safe, sustainable and practical and changes of dietary habits have been advocated in the therapy of CD[11].

Pistacia lentiscus var. Chia (Anacardiaceae), well known as Chios mastic gum, is an evergreen shrub widely distributed in the Mediterranean region. Many ancient Greek authors, including Dioscurides and Theophrastus, mentioned Chios mastic for its healing properties in intestines, stomach and liver. Mastic has also been reported to possess antioxidant[12] and antibacterial[13] activity. With reference to gastrointestinal disorders, the effectiveness of the resin against peptic ulcers is evident[14] in most studies, while only in two reports there is no effect on *H pylori* eradication *in vivo*[15,16]. Furthermore, regarding gastric mucosa, the plant has been shown to be hepatoprotective in tetrachloride-intoxicated rats[17] and to suppress the extent of iron-induced lipid peroxidation in rat liver homogenates[18], without any toxic effect. A major constituent of mastic, namely oleanolic acid, is among the best-known triterpenes with biological properties against chemically induced liver injury in laboratory animals, exerting anti-inflammatory and antitumor-promotion effects[19]. This background information led us to examine the effects of supplementation with mastic in patients with active CD. This study is the first ever reported to evaluate mastic for possible clinical effectiveness in patients with CD.

MATERIALS AND METHODS

Study population

Ten consecutive patients with established CD and eight healthy controls were recruited to participate in the trial. All patients were attending the outpatient clinic of the Department of Gastroenterology, Saint Panteleimon General State Hospital in Nicea, Athens. Clinical evidence of mild to moderate Crohn's disease exacerbation was defined by a score of CD Activity Index (CDAI) higher than 150. Patients with clinical evidence of recurrence and CDAI higher than 400 were excluded from the study. Patients receiving mesalazine or antibiotics during the time of relapse were asked to continue treatment. None was receiving elemental diet or parenteral nutrition or antioxidant/mineral supplements and none was under treatment with immunosuppressives, immunomodulators and/or corticosteroids. Eight healthy volunteers with normal serum concentrations of C-reactive protein (CRP) (< 5 mg/L) and albumin (> 40 g/L) served as controls. Assessed by Medical History questionnaires, controls included in the study were healthy persons without chronic inflammatory disorder. Exclusion criteria for control recruitment were a body mass index (BMI) higher than 30 and anti-inflammatory drug treatment or antioxidant vitamin/mineral supplementation prior to trial. All volunteers gave a written consent after having received thourough information about the aims and procedure of the study. The Ethical Committees of both Harokopio University and Saint Panteleimon General State Hospital approved the protocol. Table 1 shows some demographic characteristics of patients and controls.

Table 1 Demographic characteristics and medications of patients with CD and controls

Characteristic	Patients	Controls
Age (yr)		
Mean	36.9	31.5
Range	18-73	25-45
Sex		
Female	5	4
Male	5	4
Duration of disease (yr)	6.4 (± 3.9)	-
Concomitant medication		-
None	3	
Mesalazine	3	-
Metronidazole	2	
Azathioprine	2	
Location of Crohn's disease		-
Small bowel	4	-
Small and large bowel	6	-
Fistulizing disease	3	-

Preparation of mastic caps

A UV source device (Jost/Ba-ro, Type FDLT 250/-80 × 2500) was used for sterilization of the Chios Mastic resin. Then, the sterilized mastic granules were milled to fine powder (particle size < 400 μm) by using a Hosokawa Alpine Mill (Fine Impact Mill 100 UP2). The encapsulation of powder was performed using the Profill Capsule filling System (Torpac Inc.). Capsule cells (capsugel, V caps, size 0) were made of Hpromellose (hydroxypropyl methylcellulose) and each contained 0.37 (± 0.02) g of mastic powder.

Intervention trial protocol

Dissolution time was measured according to standard methods[20] and was found to last approximately 7 min. Patients and healthy controls were subjected to a 4-wk supplementation with mastic caps (6 caps/d, 2.2 g in total) over a period from June 2005 to January 2006. Dietary assessment was accomplished applying Food Frequency Questionnaire (FFQ) and 24 h recalls. Dietary instructions were given to both healthy controls and patients as to maintain consumption of food rich in anti-inflammatory and antioxidant ingredients as poor as initially assessed by FFQ and 24 h recall interviews. Assessment of compliance during the trial was tested applying 24 h recalls twice a week. Mastic, either in the form of gum or as a sweet or bread ingredient, and fish oil, either crude or in the form of supplement, was not allowed in either group. The daily energy intake was evaluated by means of 24 h recalls. Blood samples were obtained for plasma isolation and subjected to CRP and albumin measurements prior and after the trial. At the same time points, plasma cytokine and antioxidant potential measurements were performed. Body weight was measured using electronic scales initially and at the end of the trial.

Disease activity index evaluation

The Crohn's Disease activity was evaluated by means

of the CDAI[21]. The CDAI incorporates eight related variables: the number of liquid or very soft stools per day, the severity of abdominal pain or cramping, general well being, the presence or absence of extraintestinal manifestations of CD, the presence or absence of an abdominal mass, the use of antidiarrheal drugs, hematocrit, and body weight. Scores range from 0 to 600 with higher scores indicating more severe disease activity. A score of 151 to 200 corresponds with mild disease activity; moderate disease has a score of 201 to 400, and scores of 401 or greater represent severe disease activity.

Biochemical measurements

CRP concentrations were analyzed immunoturbidimetrically on a Beckman Synchron CX5 fully automated chemistry analyzer. Albumin was measured by means of the bromocresol green method on the same analyzer.

Cytokine assays

Plasma cytokines from patients with CD and controls were assessed by quantitative enzyme-linked immunosorbent assays (ELISA) (R & D Systems Abingdon, UK) according to the manufacturer's instructions. Sensitivity limits of TNF-α, IL-6, and MCP-1 ELISAs are, respectively, 1.6 pg/mL, 0.70 pg/mL and 5.0 pg/mL. Plasma cytokines from patients with CD and controls were assessed in duplicate.

Plasma total antioxidant potential assay

Total antioxidant potential (TAP) in plasma was assessed by a colorimetric, quantitative assay for TAP in aqueous samples (OxisResearch Portland, USA) according to the manufacturer's instructions. The results of the assay were expressed as mmol/L of uric acid equivalents. The sensitivity of the assay is 30 μmol/L uric acid equivalents.

Statistical analysis

Results were expressed as mean ± SE. The Mann-Whitney Test was used for comparing differences between patients and controls prior the intervention. Differences reported primarily and at the end of the study within individual groups, were tested for significance by the Wilcoxon signed ranks test. Calculated $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Alterations of CDAI and induction of remission

The CDAI score was assessed at baseline and after the 4 wk treatment with mastic. All patients receiving mastic showed a reduction of the CDAI as compared to pretreatment values. The reduction of the mean CDAI value was statistically significant (from 222.9 ± 18.7 to 136.3 ± 12.3, $P = 0.05$) (Figure 1). The two main elements of CDAI showing the most striking improvement were the number of liquid stools per day and the score of general well being.

Nutritional risk index

One of the clinically useful measures of nutritional status in CD is the Nutritional Risk Index (NRI), which is calculated based on serum albumin levels and body weight using the following equation: NRI = [1.519 × albumin (g/L)] + [0.417 × (current weight/usual weight) × 100]. A NRI > 100 denotes absence of nutritional risk. NRI values between 97.5 and 99.9 correspond to a mild nutritional risk, NRI values from 83.5 to 97.5 to moderate nutritional risk, and NRI values lower than 83.5 to severe nutritional risk.

The patients' "usual weight" was the body weight at the time of remission, as reported in medical records at the hospital and confirmed by each single patient. NRI of healthy controls was normal at the start of the study and remained unchanged after the mastic supplementation (data not shown). The mean NRI value of CD patients increased from 87.5 ± 3.7 before treatment to 91.5 ± 3.2 at the end of treatment ($P = 0.059$). This increase was evident at the end of the second week of mastic supplementation and remained constant thereafter until the end of the trial.

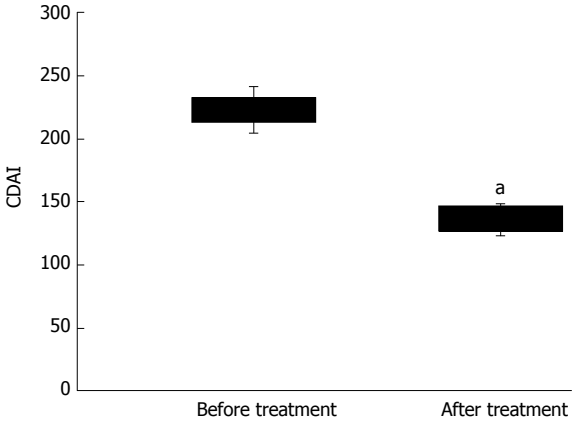

Figure 1 Crohn's disease activity index (CDAI) was decreased in patients with active Crohn's disease ($n = 10$) after 4-wk treatment with mastic caps ($^aP < 0.05$). Horizontal bars represent the mean value (± SE).

CRP

Prior to mastic treatment, CRP levels were significantly higher in CD patients (40.3 ± 13.1 mg/mL) than in healthy controls (2.4 ± 0.7 mg/L) ($P = 0.002$). Treatment with mastic caps of healthy controls resulted in no modifications in CRP values (2.3 ± 0.6 mg/L), which remained at concentrations ⩽ 5.0 mg/mL in all individuals. In CD patients, mean CRP levels were significantly decreased after treatment (from 40.3 ± 13.1 mg/mL to 19.7 ± 5.5, $P = 0.028$) (Figure 2).

IL-6 plasma concentration

IL-6 was below detection in healthy controls prior to therapy, while in patients it was significantly elevated compared to controls ($P = 0.034$). As with CRP, IL-6 in controls remained unaltered, while in patients it decreased significantly (from 21.2 ± 9.3 pg/mL to 7.2 ± 2.8 pg/mL, $P = 0.027$) (Figure 3).

TNF-α plasma concentration

Patients with active CD had TNF-α plasma concentrations 10-fold higher compared to controls before therapy (27.1 ± 9.7 pg/mL *vs* 2.6 ± 1.5 pg/mL, $P = 0.009$). After

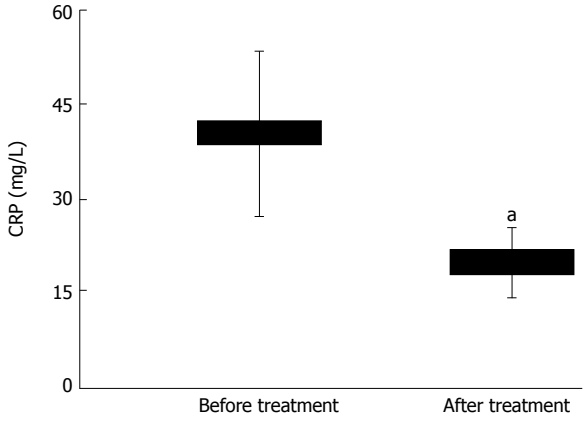

Figure 2 C-reactive protein (CRP) concentrations in patients with active Crohn's disease (n = 10) before and after 4-wk treatment with mastic caps ($^aP < 0.05$). Horizontal bars represent the mean value (± SE).

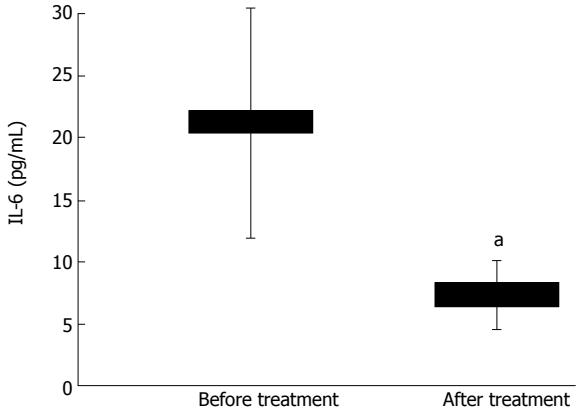

Figure 3 Plasma concentrations of interleukin-6 (IL-6) were suppressed in patients with active Crohn's disease (n = 10) after 4-wk treatment with mastic caps ($^aP < 0.05$). Horizontal bars represent the mean value (± SE).

treatment, plasma TNF-α decreased in patients, although this decrease did not reach statistical significance (27.1 ± 9.7 pg/mL to 16.4 ± 4.7 pg/mL, $P = 0.114$).

MCP-1 plasma concentration

In the case of MCP-1, patients with active CD had MCP-1 plasma concentrations 2.5-fold higher compared to controls (140.7 ± 43.9 pg/mL *vs* 57.5 ± 11.8 pg/mL, $P = 0.368$). Although not statistically significant, a decrease was observed in MCP-1 in CD patients at the end of the trial (76.6 ± 20.9 pg/ mL, $P = 0.074$).

Plasma TAP

TAP was significantly different between the two groups before mastic treatment (healthy controls, 0.4 ± 0.06 *vs* CD patients, 0.15 ± 0.09 mmol/L uric acid, $P = 0.003$). As shown in Figure 4, TAP was significantly increased in individual groups after mastic treatment (controls, 0.4 ± 0.06 *vs* 0.5 ± 0.05 mmol/L uric acid, $P = 0.025$; CD patients, 0.15 ± 0.09 *vs* 0.57 ± 0.15 mmol/L uric acid, $P = 0.036$).

Side-effects

No patient exhibited any side effects. However, during the third day of treatment, one female patient with CD of the small and large bowel reported an abrupt onset of constipation. She was advised to reduce the dose for two days. After that, she continued treatment without further complaints. No other untoward effect was reported.

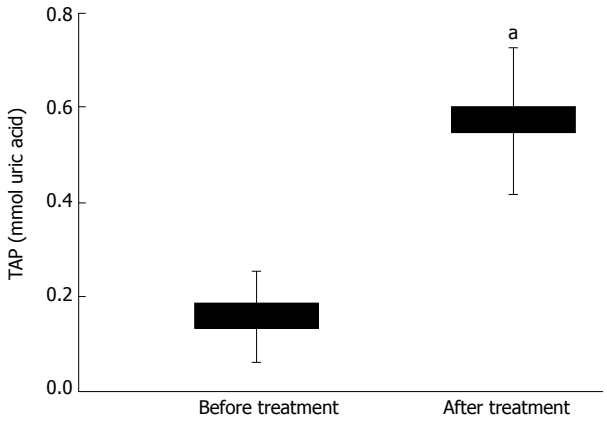

Figure 4 Plasma total antioxidant potential (TAP) was upregulated in patients with active Crohn's disease (n = 10) after 4-wk treatment with mastic caps ($^aP < 0.05$), indicating absorption of antioxidants and an improved *in vivo* antioxidant status. Horizontal bars represent the mean value (± SE).

DISCUSSION

Chios mastic has been previously shown to exert various biological properties *in vitro*[12], in experimental animal models[18] and in humans[14]. In the current study, we demonstrated that mastic was effective in the regulation of inflammation, evaluated by CRP, IL-6, TNF-α and MCP-1 in plasma, as well as in the regulation of oxidative stress, evaluated by TAP. In more details, mastic treatment significantly decreased the CDAI, which probably occurred through decrease of the pro-inflammatory IL-6, inducing remission in seven out of ten patients. Another important observation was that mastic resulted in improvement of the nutritional status, as shown by NRI.

Nutritional support in patients with CD has a primary role in inducing remission and malnutrition is very common in CD. While several factors, such as malabsorption and increased resting energy expenditure in underweight patients, may contribute to malnutrition[22], decreased oral intake is the primary cause. The methods used to support patients with CD are enteral and parenteral nutrition, in terms of protein-calorie intake. NRI is one of the most useful measures of nutritional status and points out severely malnourished patients when less than 83.5[23]. Hereby we show that NRI in patients supplemented with mastic was increased, however not significantly, perhaps due to the limited number of subjects. Particularly, NRI was increased in nine out of ten patients supplemented with mastic, two of whom experienced no nutritional risk (data not shown). The main element of NRI showing improvement was body weight gain. Based upon the fact that daily energy intake was unchanged during the trial (data not shown), increase in body weight and in NRI is due to the fact that mastic treatment resulted in decrease of liquid stools and therefore improvement in nutrient absorption.

The observed decrease in NRI in one of the patients was due to body weight loss, despite the fact that the number of liquid stools decreased. The daily energy intake of this young patient was gradually reduced and, according to her statement long after the end of the protocol, she was on a diet for weight loss.

The importance of IL-6 in patients with CD has been well documented. In patients with active CD, mRNA for IL-6 is overexpressed in the inflamed mucosa[24] and IL-6 is thought to play a crucial role in the pathogenesis of CD. Elevated IL-6 in plasma of patients with CD has been previously described[25]. Accordingly, we report that in patients with CD plasma concentration of IL-6 was significantly higher versus the control group. Significant decrease in IL-6 with mastic treatment was observed in patients following a decrease in plasma CRP (Figure 2). Because IL-6 is the main cytokine factor responsible for hepatic induction of acute phase proteins in CD, respective decrement in CRP is reasonable. In view of the fact that (1) oleoresins consist of triterpenes[26] with established anti-inflammatory and antioxidant effects[19,27] and (2) mastic contains antioxidant phenolic compounds[28], it is more likely that the plasma IL-6 decrease observed in CD patients was due to these compounds.

TNF-α showed an unsignificant (P = 0.114) 1.6-fold decrease in CD patients. On the other hand, the difference in TNF-α concentrations between patients and controls at baseline was significant. The data reported about TNF-α in CD are somewhat contradictory. Whereas some groups were able to demonstrate increased concentrations of TNF-α in CD compared to healthy controls[29], others were not[30]. Because TNF-α induces MCP-1 secretion via the activation of nuclear factor-kappa B[31], it is likely that the slight decrease in MCP-1 was due to the lower activation of the nuclear factor-kappa B pathway secondary to the decrease in TNF-α.

Oxidative stress has been proven to upregulate IL-6 gene expression[32]. We show that mastic treatment resulted in increase of plasma TAP in CD patients (Figure 4) as well as in controls. Plasma is a heterogenous solution of diverse antioxidants and an increase in the antioxidant capacity indicates absorption of antioxidants and an improved *in vivo* antioxidant status[33]. Whether the antioxidant triterpenes and phenolics contained in mastic[12] are absorbed or act on the exposed gastrointestinal mucosa, remains uncertain. Generally, our knowledge on the absorption and bioavailability of polyphenols is still limited, and the few studies in humans show that some are well absorbed and others hardly absorbed[34]. The unabsorbed may remain in the lumen and become available for fermentation in the colon. A substantial proportion of the gastrointestinal mucosa is therefore exposed to these compounds, or to their bacterial and systemic metabolites[35]. However, phenolic compounds do not seem to be absorbed as well as vitamins C and E, and hence their concentrations can be much higher in the lumen of the gastrointestinal tract than are ever achieved in plasma or other body tissues, making the action in the gastrointestinal tract more likely. Even less are the data on the absorption of triterpenes. Glycyrrhetinic acid, the triterpene derivative of glycyrrhizin, has been shown to be bioactive in experimental gastric lesion models[36] and has also been detected in the serum of experimental animals[37].

In conclusion, subjecting CD patients with mild to moderate activity to mastic treatment seems to improve the clinical features of the disease and to regulate inflammation and antioxidant status. The use of natural products as primary treatment in CD should attract wider support and research, with increasing awareness of the harm of the long-term use of corticosteroids. Whether it is time for gastroenterologists to embrace the concept that natural products, such as mastic, may be beneficial to CD needs further research in larger cohorts.

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