Coffee intake and gastroesophageal reflux: Relationship with clinical, endoscopic and functional features

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Abstract. *Background and Aim:* Coffee consumption seems to play a role in gastroesophageal reflux (GERD). The purpose of this study was to investigate the effect of coffee intake on GERD, in comparison with other clinical conditions. *Methods:* A total of 449 patients were distributed into three groups. Group 1 (GERD): 239 patients; Group 2 (cholelithiasis): 116 subjects; Group 3 (dyspeptic): 94 patients. In the GERD group symptoms were categorized and related to coffee intake. Serum pepsinogens I and II (PGI and PGII) were measured by immunoassay in group 1 and group 3. *Results:* All GERD patients showed erosive esophagitis at endoscopy. Cholelithiasis in group 2, was diagnosed by an abdominal ultrasound. Subjects of group 3 fulfilled the Rome III criteria for functional dyspepsia. All subjects filled out a questionnaire about their GI symptoms and coffee intake. Two hundred and ninety-two subjects consumed coffee daily, of which, 148 from group 1, 77 from group 2 and 67 from group 3. Coffee consumption was not different in the three groups. PG I level increased according to daily coffee consumption in GERD and dyspeptic patients. Symptoms of GERD patients worsened as the amount of coffee intake a day increased. *Conclusions:* Coffee intake was distributed in GERD and the other two control groups, without statistical significance. A relationship was found between coffee and PGI levels, both in GERD and dyspeptic patients. Accordingly, symptoms in GERD patients worsened as the amount of coffee consumed increased, particularly when consumption exceeded 4 cups per day. (www.actabiomedica.it)

Key words: coffee intake, gastroesophageal reflux disease, serum pepsinogens

Introduction

Coffee is a pharmacologically active, widely consumed and beloved beverage all over the world, which has been suggested for a long time to affect the gut-brain axis with controversial outcomes. In some studies, a coffee-mediated increased gastric acid secretion (1,2) has been associated with GI troubles, such as gastroesophageal reflux, epigastric pain, and heartburn (3). However, results from clinical and epidemiological trials have shown that coffee consumption has protective effects on GI function with no associations with gastric ulcer, duodenal ulcer, reflux esophagitis, and non-erosive reflux disease (4).

The mechanism of action of coffee on digestive processes and coffee effects on the gastro-intestinal tract and the brain-gut axis, have been developed in two detailed and recent reviews (5,6). The knowledge on some aspects remains limited mainly because concentrations of the different components of coffee are

strongly affected by various factors such as the coffee type and origin, the roasting process and the method of preparation, which largely vary among different countries.

Among gastrointestinal disorders that are reported to be affected by coffee consumption, we have focused our attention mainly on reflux esophagitis. Gastroesophageal reflux disease, commonly known as GERD, is a condition in which the stomach's contents move back up into the esophagus resulting in symptoms and/or complications. A comprehensive review of the literature focusing on GERD from 2012 to 2022 has been reported in a meta-analysis published in 2022, based on 8,964 publications (7).

The increasing incidence of GERD could be caused by several risk factors including age, obesity, hiatus hernia, genetic or hereditary, life-style, lack of physical activity. Smoking and consumption of various types of food are also believed to induce GERD, however, the role of widely consumed beverages, like coffee, in the development of GERD and/or worsen symptoms, is still controversial (8-16).

The current study aimed to investigate the habits of coffee consumption on a total of four hundred and forty-nine patients, all of which experienced disorders on the upper gastrointestinal tract. They were divided into three different groups, according to their symptoms and the diagnosis achieved by endoscopic/ultrasound examination. We evaluated the effects of coffee intake on the individuals of the three groups by means of a structured questionnaire, the tools Global Symptomatic Score (GSS) and Visual Analogue Scale (VAS), and serum pepsinogens measurement.

Pepsinogens serology has been proposed by several Authors, including our Group (17-19), as a useful non-invasive test (defined as "serological biopsy"), aimed at providing a gastric function serum profile. Pepsinogens are aspartic proteinases synthesized/secreted by the gastric chief cells and they have a major role in the digestive process (20). Pepsinogen I (PGI) is only produced/secreted by the chief cells of the oxyntic glands in the gastric fundus and corpus. As both parietal cells and chief cells are located within the oxyntic glands, PGI is considered a reliable proxy of the stomach's acid-secreting capacity. Pepsinogen II (PGII) is produced/secreted by glands in the mucus-secreting antral and cardia compartments, and by the chief cells mainly included in the oxyntic glands (21,22).

Both pepsinogens are autocatalytically activated when the acidity level drops below pH 5, leading to the exposure of the active site, and they are rapidly inactivated by the post-pyloric alkaline pH. While both pepsinogens are excreted mainly into the stomach lumen, very small amounts (about 1%) spread into the bloodstream, enabling their serological detection.

Methods

Study population

This study was carried out on a total of 449 patients; they were divided into three different groups, based on the GI disorder experienced by all of them.

The first group included 239 consecutive patients, 124 males and 115 females, mean age of 47 years, range 23-71 years, with typical gastroesophageal reflux symptoms; they were recruited as GERD group. All of them underwent esophago-gastro-duodenoscopy (EGD), from January 2018 to November 2021, in north-east Italy region. EGDs were performed by expert endoscopists; in case of any visible lesion and/or mucosa abnormality, gastric biopsies were taken according to updated Sydney system (23). In case of erosive esophagitis seen on EGD, it was graded from A to C according to the Los Angeles (LA) classification (24).

The clinical outcome of all participants was assessed by means of the tools Global Symptomatic Score (GSS) and Visual Analogue Scale (VAS). The GSS was graded as follows: grade (a) in case of 1-4 score; grade (b) in case of 5-7 score; grade (c) in case of 8-10 score. Symptoms perception (severity and frequency) has been graded using VAS, ranging 0-10, where 0 means "absence of symptoms" and 10 represents the "worst possible symptom". Both GSS and VAS were collected in a semi-structured way at baseline and after one month.

All patients were off-therapy (proton pump inhibitors (PPI) or histamine-2 receptor antagonists) at least over the preceding four weeks.

The second group included 116 consecutive patients: 41 males and 75 females, mean age 59 years, range 34-75 years, with cholelithiasis, as resulting by abdominal ultrasound, taken for upper GI complains, excluding typical GERD symptoms (heartburn, regurgitation).

The third group included 94 consecutive patients: 39 males and 55 females, mean age 48 years, range 29-64 years, who suffered from dyspeptic symptoms. All of them underwent EGD and/or abdominal ultrasound and biochemical assessment, as well as fulfilled Rome III criteria.

Questionnaire survey

In the present study, a face-to-face semi-structured interview was conducted during the health checkup, on coffee intake habits. Subjects who drank american coffee and/or decaffeinated coffee were excluded.

GERD patients were also asked to fill out a questionnaire at the same interview, consisting of questions about their symptoms. The questionnaire included baseline information (age, sex) and the following questions:

1. Do you suffer from any of the following symptoms?
   Epigastric pain, acid regurgitation, burning mouse, chest pain, cough, globus sensation.
2. If yes, how often? How severe are the symptoms? (recorded by Visual Analogue Scale, VAS, from 0 to 10).
3. How many cups of coffee do you drink every day? The answers to this question were categorized into three groups: drinking 1-2 cups of coffee per day, 3-4 cups of coffee per day, more than 4 cups of coffee per day.
4. Did you feel the development of symptoms or their aggravation, after drinking coffee?

Serum pepsinogens determination

Serum pepsinogens I and II were measured for patients of GERD group and group 3, by an enzyme-linked immunosorbent assay (Biohit, Helsinki,

Finland) according to the manufacturer's instructions. Normal values were considered: 30-165 mg/L for PGI and 2-10 mg/L for PGII.

Statistical methods

All measured parameters are expressed as mean values with standard deviations. Statistical analysis was performed using the student's t test. Categorical variables are presented as sample numbers with percentages and were compared using the 2 or Fischer's exact tests. Correlations between symptoms, severity of esophagitis and serologic tests were determined using the Spearman rank correlation test. P-values <0.05 were considered statistically significant for group comparisons. All statistical analyses were performed with the SPSS statistical software program for Windows (version 20.1)

Results

A total of 449 patients were recruited in the present study and were divided into three groups based on their clinical features. Table 1 shows the data in detail, together with the subject habits in coffee consumption.

Group 1 consisted of 239 patients, mean age was 47 years; they all reported having gastroesophageal reflux symptoms, mainly epigastric pain, and regurgitation, and/or others, such as chest pain, cough, burning mouth, globus sensation. Therefore, it was otherwise named GERD group.

GERD patients underwent an upper gastrointestinal endoscopy which showed erosive esophagitis in all cases; it was graded from A to C according to the Los Angeles (LA) classification (24). The results were as follows: 201 patients (84%) had erosive esophagitis classified as LA-A, 24 patients (10%) were LA-B and 14 patients (6%) were LA-C; in our study population there was no patient with LA-D esophagitis.

Within group 1, 148 participants (62%) drank coffee regularly, 91 subjects (38%) did not. Among the patients who drank coffee regularly, only about half of them (54%) made moderate use of it (1-2 cups a day), while 28% of subjects used to drink 3-4 cups a day and 18% of subjects drank even more than 4 cups a day.

Table 1. Clinical features and coffee intake habits (in cups/day) in the three groups of patients.

449 patients, grouped according to clinical features	Cups of coffee a day N (%) patients		
	1-2 cups/day	3-4 cups/day	>4 cups/day
Group 1 n=239: GERD patients with erosive esophagitis*; 148 of them (62%) drank coffee regularly	80 (54%)	41 (28%)	27 (18%)
Group 2 n=116: cholelithiasis patients; 77 of them (66%) drank coffee regularly	55 (72%)	17 (22%)	5 (6%)
Group 3 n=94: dyspeptic patients with no organic lesions, control; 67 of them (71%) drank coffee regularly	46 (68%)	15 (23%)	6 (9%)
p–value	n.s.	n.s.	0.01

Abbreviations. GERD: gastroesophageal reflux disease; n.s.: not significant.

*Diagnosis was endoscopically established.

The severity of esophagitis was not significantly different between coffee drinkers and non-drinkers. Similarly, for patients who drank coffee regularly, no significant difference was observed based on the amount of coffee consumed (not shown).

GERD patients were asked to fill out a questionnaire, besides answering to a face-to-face semi-structured interview during the health checkup, consisting of questions about their symptoms. The GSS results obtained of response to the questionnaire by the 148 patients who drank coffee every day, are detailed in Table 2. There was no significant difference in the distribution of patients belonging to (a), (b), or (c) GSS grade (53, 46, 49 patients, respectively). Across the three different grades, only the percent of subjects drinking 3-4 cups of coffee each day is constant (23%-24%), while the percent of subjects drinking only 1-2 cups of coffee a day is higher among the ones reporting a GSS of grade (a) of symptoms. Accordingly, if we consider a coffee consumption exceeding 4 cups per day, the percentage of subjects describing the worst symptomatology, GSS of grade (c), is significantly higher than those who reported moderate symptoms, GSS of grade (a) (24% vs 12%, respectively, Table 2).

Among 116 subjects of group 2, mean age was 59 years; they had cholelithiasis, as resulting by abdominal ultrasound, taken for upper GI complains. None of the patients suffered of biliary colic. In this group, 77 individuals (66%) drank coffee regularly, 39 subjects

Table 2. Global Symptomatic Score in 148 patients of group 1, exhibiting GERD and erosive esophagitis, as a function of coffee consumption.

Global Symptomatic Score in GERD patients of group 1, drinking coffee regularly (n=148)	Cups of coffee a day (%) patients		
	1-2	3-4	>4
Grade (a) – 53 patients	65%	23%	12%
Grade (b) – 46 patients	58%	24%	18%
Grade (c) – 49 patients	52%	24%	24%
p–value	0.05	n.s.	0.01

Abbreviation. GERD: gastroesophageal reflux disease.

(34%) did not (Table 1). The majority of individuals (72%) reported consuming coffee only 1-2 cups a day.

Among 94 subjects of group 3, mean age was 48 years; they suffered from functional dyspepsia, according to the Rome III classification (25). All these patients underwent EGD and/or abdominal ultrasound examination, showing no organic lesions. Therefore, it was otherwise named "control group", with respect to the GERD group. 67 individuals (71%) drank coffee regularly, 27 subjects (29%) did not. In this group 3 as well the majority of subjects drank coffee in moderation (1-2 cups a day), with only 9% of subjects that can be considered heavy coffee drinkers (>4 cups/day).

Pepsinogens serology

Serum pepsinogens measurement was considered an adequate strategy to explore the status of the gastric mucosa in group 1 and group 3 of patients, concerning coffee consumption habits.

Table 3a summarizes serological values of PGI and PGII pepsinogens that were tested in GERD patients and in dyspeptic patients. Subjects who drank coffee regularly were grouped with the ones who did not.

Data show higher levels of both pepsinogens in GERD patients of group 1 (PGI, 81 mg/L vs 74 mg/L; PGII, 8.1 mg/L vs 7.6 mg/L) although the difference is not statistically significant.

Table 3b shows the PGI and PGII values, considering only the patients who drank coffee regularly, in both GERD group 1 and in dyspeptic patients of group 3; the results are divided according to the amount of coffee consumption per day.

In the case of serum PGI, within each group of patients, the value increased as a function of the number of cups of coffee consumed (group 1, range 71 mg/L - 83 mg/L; group 3, range 66 mg/L - 81 mg/L). If we compare PGI levels between the two groups, a moderately higher value is observed in GERD patients, with respect to dyspeptic patients, mainly at low coffee consumption (1-2 cups/day, 71 mg/L *vs* 66 mg/L), while the difference faded in case of 3-4 cups of coffee consumed a day (76 mg/L *vs* 73 mg/L). For subjects who were heavy coffee consumer (>4 cups a day) the PGI values were even more similar each other (83 mg/L *vs* 81 mg/L).

Regarding serum PGII levels, only GERD patients exhibited a weak increase according to the amount of coffee consumed (range 7.9 mg/L − 8.2 mg/L),

Table 3a. Serum pepsinogen PGI and PGII values in group 1 (GERD patients) and in group 3 (dyspeptic patients with no organic lesions, control). Subjects who drank coffee regularly are grouped together the ones who did not.

	PGI mg/L	PGII mg/L
Group 1 (n=239) GERD patients with erosive esophagitis	81 ± 33	8.1 ± 3.2
Group 3 (n=94) Dyspeptic patients with no organic lesions, control	74 ± 28	7.6 ± 3.8
p-value	n.s.	n.s.

Table 3b. Serum pepsinogen PGI and PGII values as a function of coffee intake (in cups a day) in group 1 (GERD patients) and in group 3 (dyspeptic patients, control); only subjects who drank coffee regularly were considered here.

	Cups of coffee a day						
	1-2		3-4		> 4		
	PGI mg/L		PGI mg/L		PGI mg/L		*p-value*
Group 1 (n=148)* GERD patients with erosive esophagitis	71 ± 32		76 ± 29		83 ± 26		0.01
Group 3 (n=67)** Dyspeptic patients with no organic lesions, control	66 ± 21		73 ± 26		81 ± 32		0.01
	PGII mg/L		PGII mg/L		PGII mg/L		
Group 1 (n=148)* GERD patients with erosive esophagitis		7.9 ± 3.1		8.0 ± 2.9		8.2 ± 3.2	n.s.
Group 3 (n=67)** Dyspeptic patients with no organic lesions, control		7.3 ± 2.9		6.9 ± 2.4		7.1 ± 3.0	n.s.

*148 patients (62% of 239 total) and **67 patients (71% of 94 total) consumed coffee regularly, *see Table 1 for details*.

although the difference is not statistically significant. Also in this case, a higher value of PGII is observed in GERD patients with respect to dyspeptic patients, in each range of coffee consumption per day.

Discussion

In the present study, we investigated the possible effect of coffee intake on some GI disorders, with a specific focus on gastroesophageal reflux disease, and on symptoms by means of a validated questionnaire and VAS. This work also identified the frequency of coffee consumption, and it was found that the most common coffee consumption frequency was 1-2 cups per day, in all three groups of subjects.

The relationship between dietary habits (large-volume meals, rapid food intake, eating between meals, late-evening meals) did not show statistical significance in affecting GERD, while irregular dietary intake was suggested to be one of the risk factors for GERD, associated with reflux-related symptoms (8,14,16). Regarding the role of coffee in the development of GERD and/or worsening symptoms, so far, the results are controversial (8-16).

It is generally difficult to evaluate the cause and effect between dietary habits and GERD, because patients with reflux symptoms may tend to avoid certain foods that would provoke their symptoms. Besides this, the symptoms of GERD, irritable bowel syndrome and functional dyspepsia are often overlapping each other. Researchers would define GERD in the epidemiological study using the self-reporting of at least weekly regurgitation or heartburn or both, increasing the possibility of overestimation. In this regard, subjects with erosive esophagitis may be considered the preferred study population when evaluating the relationship between dietary habits and GERD.

Taking into consideration that 91 subjects of this group were not drinking coffee, the results indicated that caffeine does not appear to play a major role in the development of GERD, according to some previous studies (4,9). Based on the Los Angeles classification, following endoscopy in patients of the group1, coffee intake did not influence the severity of erosive esophagitis.

In some cases, GERD seems related to an increased gastric acid secretion, being caffeine (as a bitter alkaloid) suggested as one of the main substances inducing this event. As a large body of literature examined the reliability of serological assessments of pepsinogens (PGI and PGII) in reflecting the morphology and function of the gastric mucosa, we used this non-invasive blood test to obtain information regarding gastric secretion (PGI) and inflammation of gastric mucosa (PGII).

In this study, GERD patients of group 1 had slightly higher levels of both serum pepsinogens than dyspeptic control individuals of group 3. In the case of serum PGI, the increase in levels as a function of the amount of coffee consumed, in both group 1 and group 3 of patients, indicated subsequent increase of gastric acid secretion. If we compare PGI levels between the two groups 1 and 3, a higher value is observed in GERD patients of group 1, concerning dyspeptic patients of group 3, mainly at low coffee consumption (1-2 cups/day), while this difference almost disappeared in case the subjects were heavy coffee consumer. This finding suggested that a higher coffee consumption indeed increased gastric acid secretion, regardless of the patient's clinical status.

Also, in the case of dyspepsia, the pathophysiological explanation of the disease involves multiple mechanisms that interact with each other resulting in symptoms. Some triggering factors, such as life-style, dietary factors including coffee intake, psychological events have been related to dyspepsia, despite the contradictory scientific output. It is thought that coffee should influence dyspepsia due to gastric acid secretion induced by compounds in coffee such as caffeine and chlorogenic acid. Our results of serum pepsinogen I levels in some dyspeptic subjects of group 3 confirmed an increase in gastric acid secretion as a function of the amount of coffee consumption.

Pepsinogen II values, a marker of gastric mucosal inflammation, were compatible with the absence of the patient's inflammatory lesions, not only in GERD patients but also in all the individuals belonging to group 3, also taking into account that cut-off levels vary among studies. These results were not affected by coffee consumption.

From the self-reported scale questionnaire, which was developed for our study and was used to evaluate the severity of symptoms in GERD patients, it turned out that there was an almost equal distribution of individuals reporting GSS grade (a) or (b) or (c). This result may be affected by differences in symptom perception and interpretation among individuals. Nevertheless, it might be of interest to note that among the 53 GERD patients who reported a GSS of grade (a), namely the lowest severity of symptoms, 65% of them consumed 1-2 cups of coffee each day and only 12% were heavy coffee consumers. Differently, among the 49 GERD patients who reported a GSS of grade (c), namely the highest severity of symptoms, only 52% of them consumed 1-2 cups of coffee each day and 24% were heavy coffee consumers. The reproducibility and responsiveness of GSS in upper gastrointestinal symptoms are well established.

Accordingly, the VAS tool in most cases indicated a worsening of symptoms as a function of the amount of coffee consumption per day (not shown). These results are consistent with several physiological studies which have shown a decrease in lower esophageal pressure and an increase in esophageal acid exposure in response to ingestion of a variety of food items.

We support the hypothesis that inconsistent findings of the literature regarding the association between coffee intake and gastrointestinal disease, GERD included, might be attributed to the different types of coffee (including roasting process, temperature, filtered or not) and/or to the different study population in terms of genetics, age, lifestyle, social and economic condition, culture.

Our study presents several strengths compared to other ones: (a) a high number of participants; (b) the questionnaire has been administered by a face-to-face single professional, therefore no question was not fully understood by the respondents; (c) GERD diagnosis was established by the presence of erosive esophagitis as resulting from esophago-gastro-duodenoscopy; (d) in the case of GERD patients, the questionnaire has been administered at the first diagnosis of erosive esophagitis, ad it was further validated within two-three weeks during the health control.

However, there are limitations that should be acknowledged: (a) the possible simultaneous consumption of alcohol and/or smoking, have not been considered; (b) there is no specific details about the type of consumed coffee, e.g. caffeine content and roasting process employed; (c) other drinks sources of caffeine (i.e. Coke, Red Bull) were not taken into consideration; (d) within each group of patients results are presented for the entire sample, male and female are not divided; in this respect a previous study indicated no main significant effect of gender; (e) it was not possible to standardize the habits; for example, after-meal coffee consumption can be a confounding variable for the decreased pressure of the lower esophageal sphincter (LES).

Conclusions

In summary, this study highlights the effects of coffee consumption on some gastrointestinal disorders, mainly gastroesophageal reflux, evaluating the relationship between clinical features, endoscopic surveys, reported symptoms, and serum pepsinogens measurement.

We found no statistically significant difference as regards coffee consumption in GERD patients in comparison with the two control groups. Accordingly, coffee intake is not related to the severity of erosive esophagitis.

Pepsinogen I level increased as the number of cups of coffee consumed a day increased, in GERD and dyspeptic patients, suggesting an increase in acid secretion in both cases. Differently, the PGII level showed no significant modification.

From a clinical point of view, symptoms perception in GERD patients worsened as the amount of coffee consumed a day, increased. In particular, the data suggest that intake of more than 4 cups of coffee a day represents a cut-off for a specific worsening of symptoms.

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