High prevalence of functional dyspepsia in nonalcoholic fatty liver disease: a cross-sectional study

Érika Cristina Lima1, Maria do Carmo Friche Passos1, Silvia Marinho Ferolla1, Raissa Soares Neves da Costa2, Quelson Coelho Lisboa3, Lucas Ismael Dias Pereira4, Mateus Jorge Nardelli4, Vitor Nunes Arantes4, Teresa Cristina de Abreu Ferrari4, Claudia Alves Couto6

School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil

Abstract

Background: Gastrointestinal (GI) symptoms are frequent complaints from individuals with nonalcoholic fatty liver disease (NAFLD). Dyspepsia is a universal clinical symptom and is among the most common GI complaints observed in the general population, but its prevalence in the population with NAFLD has not been previously investigated.

Objective: To compare the prevalence of functional dyspepsia (FD) between patients with NAFLD and controls without liver disease.

Design and setting: Cross-sectional study at the Outpatient Liver Clinic, University Hospital, Belo Horizonte, Brazil.

Methods: We included 96 NAFLD patients and 105 controls without liver disease. All participants were assessed for GI symptoms in accordance with the Rome III criteria. Evaluation methods included a questionnaire for FD (validated in Brazil), laboratory tests and upper GI endoscopy.

Results: Mean age and sex were similar between the groups. The NAFLD group presented higher frequency of proton-pump inhibitor usage (31.3% vs 4.8%; P < 0.001) and prevalence of FD (25.0% versus 12.4%; P = 0.021). The symptom frequencies were as follows: postprandial distress, 22.9% versus 11.4% (P = 0.030); postprandial fullness, 18.8% versus 10.5% (P = 0.095); early satiation, 8.3% versus 5.7% (P = 0.046); epigastric pain or burning, 18.8% versus 5.7% (P = 0.004), in NAFLD patients and controls, respectively. Multivariate analysis demonstrated that female sex (odds ratio, OR 6.97; 95% confidence interval, CI 1.51-32.12; P = 0.013) and NAFLD diagnosis (OR 2.45; 95% CI: 1.14-5.27; P = 0.021) were independently associated with FD occurrence.

Conclusion: FD occurs more frequently in individuals with NAFLD than in controls without hepatic disease.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently considered to be a public health problem in many countries, affecting both adults and children. This condition is characterized by hepatic steatosis, which is detected through ultrasound (US) or histological examination of the liver in individuals without a history of excessive alcohol consumption and with no other causes of liver disease.1 NAFLD can progress to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocarcinoma. Obesity, insulin resistance, type 2 diabetes mellitus (DM) and other components of metabolic syndrome are common related comorbidities.2 The global incidence of NAFLD is unknown since it depends on the population studied and on the methods used to diagnose this condition (e.g. liver biopsy, magnetic resonance spectroscopy or US). Despite these limitations, the prevalences of NAFLD and NASH in the general population in Western countries have been estimated to reach 20%-30% and 1%-3%, respectively.1,2

NAFLD is considered to be a silent disease with asymptomatic evolution until its advanced stages. Studies have demonstrated a lack of specific symptoms in 45%-100% of patients.3-5 The diagnosis is made unintentionally in asymptomatic patients through detecting elevated serum aminotransferase levels or steatosis on US performed as a routine test or during investigation of other comorbidities related to NAFLD. However, more recently, it has been suggested that NAFLD patients may present with multiple symptoms related to the gastrointestinal (GI) tract. For example, a high proportion of the patients with NAFLD that was incidentally detected...
through US examination initially sought medical attention due to the presence of functional GI symptoms. Moreover, patients with functional dyspepsia (FD) who underwent US have also been described as having high prevalence of fatty liver. Nevertheless, published data regarding the prevalence of GI symptoms specifically in the NAFLD population are scarce.

Dyspepsia is one of the most frequent GI symptoms observed in the general population. It is defined as a digestive disorder characterized by a set of symptoms related to the upper GI tract, such as pain, burning or discomfort in the upper abdomen, which may be associated with early satiety, postprandial nausea, vomiting, bloating or a feeling of abdominal distention. The Rome III consensus defines FD as the presence of one or more of the following: epigastric pain or epigastric burning, bothersome postprandial fullness and early satiety with no evidence of a structural disease (including upper endoscopy evaluation) that would explain the symptoms. Patients with these symptoms but without any structural disease upon diagnostic evaluation probably have FD, even though according to the Rome III guidelines, these criteria should be met during the last three months with symptom onset at least six months before the diagnosis.

**OBJECTIVE**

Considering the current increasing burden of NAFLD and the lack of knowledge regarding the characterization of GI symptoms in this population, we conducted this study to test the hypothesis that individuals with NAFLD have higher prevalence of FD than do subjects without fatty liver disease.

**METHODS**

**Study population and data collection**

This cross-sectional study included 201 subjects who were prospectively selected between August 2015 and December 2016. The patients were consecutively recruited from the Outpatient Liver Clinic, University Hospital, Belo Horizonte, Brazil, after they had been diagnosed with NAFLD. This institution is a referral center within the Brazilian public healthcare system for treating liver diseases. A control group was also formed, and this included 105 individuals without known liver disease. These subjects were the companions of patients treated in the Outpatient Liver Clinic, and they were selected based on their clinical history of no liver diseases. The local ethics committee approved the study (CAAE 26228014.7.0000.5149) on March 12, 2014, and all patients signed an informed consent statement. The sample was obtained according to convenience after inclusion of prospective patients’ inclusion, since the prevalence of FD among NAFLD subjects was unknown.

The diagnosis of NAFLD was established in accordance with the criteria of international guidelines. The inclusion criteria comprised (a) steatosis on US and/or liver biopsy (performed based on clinical judgment); (b) exclusion of other causes of liver disease (i.e. alcoholic disease, autoimmune disorders, viral hepatitis, hemochromatosis, Wilson’s disease and alpha-1-antitrypsin deficiency); (c) no history of prior gastric or jejunoileal bypass and no exposure to hepatotoxins; (d) no use of steatogenic medications within the past six months; and (e) 18 years of age or older. The inclusion criteria for controls were that they needed to be adults aged between 18 and 75 years and without any history of liver disease. The exclusion criteria for both groups were the presence of a diagnosis of decompensated liver cirrhosis, use of oral contraceptives or nonsteroidal anti-inflammatory drugs, corticosteroid treatment or history of organic GI diseases.

**Clinical and laboratory investigations**

Demographic characteristics, anthropometric data, use of proton-pump inhibitors and prevalence of comorbidities were evaluated in all patients. Anthropometric data comprised weight (kg), height (m), waist circumference (cm) (measured midway between the lower limit of the rib cage and the iliac crest, with the participant in a standing position) and body mass index (BMI), which was calculated as weight/height² (kg/m²). For analysis purposes, obesity was defined as BMI ≥ 30 kg/m².

Metabolic syndrome was defined in accordance with the criteria adopted by the International Diabetes Federation: central obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women), along with two or more of the following conditions: hypertriglyceridemia (≥ 150 mg/dl), low high-density lipoprotein (HDL) cholesterol levels (< 40 mg/dl in men and < 50 mg/dl in women), hypertension (systolic blood pressure ≥ 130 mmHg and diastolic ≥ 85 mmHg) and fasting glucose ≥ 100 mg/dl.

All patients who had GI symptoms underwent upper GI endoscopy to investigate the presence of structural disease. We excluded patients with findings suggestive of structural diseases that may cause dyspeptic symptoms, such as peptic ulcers, erosive duodenitis, intestinal metaplasia or gastric mucosal atrophy. Since erosive esophagitis and gastroesophageal reflux disease (GERD) do not usually cause dyspeptic symptoms, they were not excluded. Nonspecific findings such as enanthematous gastritis/pangastritis and hiatal hernia were described. Esophageal varices were considered to be manifestations of portal hypertension related to progressive steatohepatitis, as long as a diagnosis of NAFLD was previously present.

*Helicobacter pylori* infection was tested by means of histopathological assessment, and individuals with positive tests were treated for its eradication. Patients with persistent dyspeptic symptoms after six months, despite adequate *H. pylori* treatment proved through a respiratory test, were diagnosed as presenting FD.

The laboratory assessment included total cholesterol and fractions, triglycerides, fasting blood glucose and insulin,
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RESULTS

Characteristics of the patients

The present study included 96 patients with NAFLD with a mean age of 55.9 ± 12.7 years and 105 controls with a mean age of 55.2 ± 12.8 years. The demographic characteristics, anthropometric data and prevalence of comorbidities are shown in Table 1.

Six patients were not included, based on the following exclusion criteria: four patients had Crohn's disease (two NAFLD subjects and two controls) and two patients had previously undergone gastroduodenal anastomosis (NAFLD group). Upper gastrointestinal endoscopy revealed peptic ulcers and/or erosive duodenitis in three patients in the NAFLD group. These patients were not included.

There was no difference between the groups regarding sex distribution or median age. NAFLD patients presented significantly higher frequencies of obesity, hypertension, DM, hypercholesterolemia, low HDL-cholesterol levels, metabolic syndrome and use of proton-pump inhibitors than did the controls (Table 1). In the whole sample, 35 patients had been using omeprazole; 30 NAFLD patients (13 with GERD, 10 with FD, seven with both conditions and 14 who were using this drug for other indications) and five control individuals (two had GERD, none had FD and three were using this drug for other indications).

DM was observed in 42.1% of the NAFLD patients. NAFLD fibrosis score analysis demonstrated that, out of the 96 NAFLD patients, 41 (42.7%) did not have significant fibrosis and 13 (13.5%) presented significant fibrosis; in 42 (43.8%) patients, the stage of fibrosis could not be determined from the score.

Functional gastrointestinal symptoms

All the patients with dyspeptic symptoms underwent upper endoscopy in order to map any presence of organic diseases, as shown in Table 2 (five control individuals did not have this test.

Table 1. Demographic, anthropometric and clinical data on the NAFLD patients and controls

| Variable                      | Groups                  | P-value |
|-------------------------------|-------------------------|---------|
|                               | NAFLD (n = 96)          | Control (n = 105) |         |
| Female sex                    | 78 (81.3)               | 82 (78.1) | 0.579†  |
| Age (years)                   | 59 (49.5-64.0)          | 58 (48.5-64.0) | 0.638†  |
| BMI (kg/m²)                   | 32 (28.36)              | 26 (23-29) | < 0.001† |
| Obesity (BMI ≥ 30)            | 62/94 (66)              | 22/104 (21.2) | < 0.001† |
| Central obesity               | 93/96 (96.9)            | 48/105 (45.7) | < 0.001† |
| Hypertension                  | 67/95 (70.5)            | 36/105 (34.3) | < 0.001† |
| Diabetes                      | 40/95 (42.1)            | 14/105 (13.3) | < 0.001† |
| Hypertriglyceridemia          | 49/90 (54.4)            | 13/91 (14.3) | < 0.001† |
| Low HDL cholesterol           | 43/88 (48.9)            | 11/91 (12.1) | < 0.001† |
| Metabolic syndrome            | 71/95 (74.7)            | 13/105 (12.4) | < 0.001† |
| Proton-pump inhibitor use     | 30/96 (31.3)            | 5/105 (4.8)  | < 0.001† |

Data are expressed as absolute numbers (percentages) and medians (interquartile ranges). NAFLD = nonalcoholic fatty liver disease; BMI = body mass index; HDL = high-density lipoprotein; †chi-square test; ‡Fisher’s exact test; §Mann-Whitney U test.
because they refused to undergo the procedure). Although FD and epigastric burning or pain occurred more frequently in the NAFLD patients, the frequencies of Helicobacter pylori infection, gastritis and pangastritis were similar in the two groups.

Out of the 27 NAFLD patients who underwent upper endoscopy, eight were diagnosed with Helicobacter pylori (29.6%) and were treated with conventional therapy. After six months of treatment, three of these patients achieved resolution of the dyspeptic symptoms, while the other five had persistent symptoms, despite undergoing a respiratory Helicobacter pylori test that confirmed that the treatment had been adequate. Patients with resolution after Helicobacter pylori eradication were not considered to have had FD.

Figure 1 shows the frequency and type of FD in the NAFLD individuals and controls, respectively: FD, 24 (25.0%) and 13 (12.4%) (P = 0.021); postprandial distress syndrome, 22 (22.9%) and 12 (11.4%) (P = 0.030); postprandial fullness, 18 (18.8%) and 11 (10.5%) (P = 0.095); early satiation, 8 (8.3%) and 6 (5.7%) (P = 0.466); and epigastric burning or pain, 18 (18.8%) and 6 (5.7%) (P = 0.004).

For better characterization of the patients with FD, we compared the individuals with and without FD inside each of the groups (i.e. NAFLD and controls) according to age, sex and features of metabolic syndrome (Table 3). Although the overall NAFLD group presented higher frequency of obese patients (Table 1) than the control group, when the subjects in each group were separated according to the presence or absence of FD, the frequencies of DM, central obesity and other metabolic features were similar among those with NAFLD, and also inside the control group.

Multivariate analysis was performed in order to investigate predictors for FD occurrence in the whole population studied, by adding the variables of age, sex and NAFLD diagnosis to a logistic regression model. After adjustment, the variables independently associated with FD occurrence were female sex (OR 6.97; 95% CI 1.51-32.12; P = 0.013) and NAFLD diagnosis (OR 2.45; 95% CI 1.14-5.27; P = 0.021).

The NFS categories were not associated with any functional gastrointestinal symptom or disorder: FD (P = 0.689), postprandial

Table 2. Comparison between endoscopic findings among NAFLD patients and controls with dyspeptic symptoms

| Variable                        | NAFLD (n = 27) | Control (n = 9) | P-value |
|---------------------------------|----------------|----------------|---------|
| Peptic ulcers                   | 0 (0.0)        | 0 (0.0)        | 1.000†  |
| Erosive duodenitis              | 0 (0.0)        | 0 (0.0)        | 1.000†  |
| Erosive esophagitis             | 5 (18.5)       | 0 (0.0)        | 0.302†  |
| Enanthematous gastritis         | 7 (25.9)       | 4 (44.4)       | 0.409†  |
| Enanthematous pangastritis      | 14 (51.9)      | 1 (11.1)       | 0.051†  |
| Esophageal varices              | 2 (7.4)        | 0 (0.0)        | 1.000†  |
| Hiatal hernia                   | 2 (7.4)        | 1 (11.1)       | 1.000†  |
| Helicobacter pylori infection   | 8 (29.6)       | 1 (11.1)       | 0.266†  |

Data are expressed as absolute number (percentage); †Fisher’s exact test.
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A heterogeneous group of pathophysiological mechanisms has been implicated in the pathogenesis of FD, including delayed gastric emptying, antral hypomotility, impaired intestinal motility, decreased gastric accommodation, increased visceral sensitivity, abnormal sensitivity to carbohydrates, poor fatty acid duodenal digestion, infiltration of the digestive tract by immune cells and psychological factors. Despite years of intense research, many controversies about the role of these factors and their causal relationship with FD symptoms remain to be elucidated.20

Although the pathogenesis of NAFLD has not been fully elucidated, it is well known that this condition is strongly associated with insulin resistance, obesity and dyslipidemia.1 A heterogeneous group of pathophysiological mechanisms has been implicated in the pathogenesis of FD, including delayed gastric emptying, antral hypomotility, impaired intestinal motility, decreased gastric accommodation, increased visceral sensitivity, abnormal sensitivity to carbohydrates, poor fatty acid duodenal digestion, infiltration of the digestive tract by immune cells and psychological factors. Despite years of intense research, many controversies about the role of these factors and their causal relationship with FD symptoms remain to be elucidated.20

Although the pathogenesis of NAFLD has not been fully elucidated, it is well known that this condition is strongly associated with insulin resistance, obesity and dyslipidemia.1

Additionally, previous studies demonstrated that FD is associated with central obesity and DM. DM patients frequently report GI symptoms such as postprandial fullness, heartburn, bloating, abdominal pain, early satiety, vomiting and nausea. These symptoms were previously attributed to diabetic gastropathy as an expression of autonomic neuropathy; however, more recent data have suggested that those symptoms are probably due to multifactorial mechanisms.21,22 Indeed, controversies regarding the association of DM with GI symptoms still exist. Some studies23,24 did not show any differences in the prevalence of GI symptoms between individuals with and without DM, except for lower prevalence of heartburn in individuals with type 1 DM. In contrast, in other investigations,25,26 subjects with DM reported significantly more GI symptoms than did control individuals without DM. However, those authors did not use the Rome III criteria for diagnosing FD. We did not find any association between FD and DM within the NAFLD group, or among the controls (Table 3). Female sex has also been associated with FD in diabetic and control populations.26

It has been suggested that obesity may cause dyspeptic symptoms by means of different mechanisms, such as alterations in the function of GI neuropeptides;27 excess visceral adiposity, which may increase intra-abdominal pressure; and secretion of adipokines and proinflammatory cytokines by visceral adipose tissue.28

### Table 3. Comparison between patients with and without functional dyspepsia, according to age, sex and features of metabolic syndrome

| Variable              | NAFLD (n = 96) | Control (n = 105) | P-value |
|-----------------------|---------------|-------------------|---------|
|                       | FD (n = 24)   | No FD (n = 72)    |         |
| **Female**            |               |                   |         |
| Female                | 23 (95.8)     | 55 (76.4)         | 0.037** |
| Age (years)           | 56 (42-63)    | 60 (53-65)        | 0.140†  |
| Central obesity       | 23 (95.8)     | 70 (97.2)         | > 0.999 |
| Hypertension          | 19 (79.2)     | 48 (67.6)         | 0.283†  |
| Diabetes              | 10 (41.7)     | 30 (42.3)         | > 0.999 |
| Hypertriglyceridemia  | 16 (66.7)     | 33 (45.8)         | 0.091†  |
| Low HDL-c             | 15 (62.5)     | 28 (38.9)         | 0.036** |
| Metabolic syndrome    | 20 (83.3)     | 51 (70.8)         | 0.026** |

NAFLD = nonalcoholic fatty liver disease; FD = functional dyspepsia; HDL-c = high-density lipoprotein cholesterol. Data are expressed as number (percentage) and median (interquartile range); †chi-square test; ‡Fisher’s exact test; *Mann-Whitney U test.
However, the epidemiological data linking obesity to functional GI disorders are inconsistent.\textsuperscript{39} Although it is well established that obesity is associated with GERD, it remains unclear whether obesity is a risk factor for common functional GI disorders.\textsuperscript{30}

Recent studies have demonstrated an association between high BMI and increased risk of FD among females.\textsuperscript{31,32} In the current study, we found an association between female sex and FD, thus corroborating the results from previous studies. Interestingly, one study identified a positive correlation between visceral adiposity and FD. Regarding GI symptoms, only epigastric pain was found to be associated with visceral adiposity.\textsuperscript{33} Those results were different from ours, as our NAFLD patients and controls with FD did not present higher frequency of central obesity, considering each group individually (Table 3).

Our study had limitations that should be noted. Firstly, there was subjectivity in applying the questionnaire and there are inherent clinical difficulties in making assertive diagnoses of functional disturbances. On the other hand, the Rome III questionnaire has been validated in Brazil. Additionally, a specific team was trained for individual and standardized administration of questionnaires. This strength is relevant in comparison with other observational studies in which the questionnaires were administered online or by telephone, or were handed to patients to be returned later.\textsuperscript{31,34}

Furthermore, we used the Rome III criteria instead of Rome IV because our team already had experience with its administration; and because Rome IV only presents minor changes in relation to Rome III. These changes were an attempt to increase the specificity of appropriate patient inclusion in clinical trials, whereas in clinical practice this precision may not be required.\textsuperscript{35}

Lastly, the controls did not undergo abdominal ultrasonography for diagnosing NAFLD. Thus, the study results may constitute an underestimation, considering that after excluding possible controls with undiagnosed NAFLD, the association between FD and the group with diagnosed fatty liver could even have been stronger than we found. Further studies are needed to confirm this.

CONCLUSION
In conclusion, the present study provides new evidence regarding the association between FD and NAFLD. The prevalence of FD was higher among individuals with NAFLD. Further studies are required in order to validate these observations and to establish optimal strategies for managing dyspeptic symptoms in these individuals.

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Address for correspondence:
Claudia Alves Couto
Departamento de Clínica Médica da Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG)
Av. Professor Alfredo Balena, 190
Belo Horizonte (MG) — Brasil
CEP 30130-100
Tel. (+55 31) 3409-9746
E-mail: clalcouto@gmail.com