Fatty liver disease and the risk of erosive esophagitis in a sample of iraqi patients: a cross sectional study

Enfermedad del hígado graso y el riesgo de esofagitis erosiva en una muestra de pacientes iraquíes: un estudio transversal

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Abstract

Objectives: To investigate an association between fatty liver disease (FLD) and erosive esophagitis. Aim of Study: To look for the presence of association between fatty liver disease (FLD) and erosive esophagitis in a sample of Iraqi patients. Materials and Methods: This was a cross-sectional study of asymptomatic patients did esophagogastroduodenoscopy (OGD) in two large gastroenterology centers between April 2019 and May 2020. Erosive esophagitis was classified according to Los Angeles (LA) classification and FLD was diagnosed by ultrasonography and fibroscan (Ultrasound Attenuation Parameter UAP). the anthropometric and laboratory data of the patients were analyzed with chi square test and phi coefficient. Results: In 110 patients, the total number of patients were classified according to OGD results into two groups, erosive esophagitis and non-erosive reflux disease (NERD). Again, the total number of patients classified into two groups, 40 (36.4%) patients found to have FLD were classified as fatty liver group and 70 (63.6%) patients found not to have FLD and classified as non-fatty liver disease group. The percentage of erosive esophagitis is higher in FLD group 21/40(52.5%) than in non-FLD group 19(47.5%), and the risk factors were investigated and correlated to each group by specific statistical equations. Conclusion: There is a significant association between FLD and erosive esophagitis and FLD is an independent risk factor for erosive esophagitis.

Keywords: Fatty Liver Disease, Erosive Esophagitis, Iraqi Patients, A Cross Sectional Study.

Resumen

Investigar una asociación entre la enfermedad del hígado graso (FLD) y la esofagitis erosiva. OBJETIVO DEL ESTUDIO: Buscar la presencia de asociación entre la enfermedad del hígado graso (FLD) y la esofagitis erosiva en una muestra de pacientes iraquíes. MATERIALES Y MÉTODOS: Estudio transversal de pacientes asintomáticos sometidos a esofagogastroduodenoscopia (OGD) en dos grandes centros de gastroenterología entre abril de 2019 y mayo de 2020. La esofagitis erosiva se clasificó según la clasificación de Los Ángeles (LA) y la EFL se diagnosticó mediante ecografía y fibroscan (parámetro de atenuación de ultrasonido UAP). Los datos antropométricos y de laboratorio de los pacientes se analizaron con prueba de chi cuadrado y coeficiente phi. RESULTADOS: En 110 pacientes, el número total de pacientes se clasificó de acuerdo con los resultados de OGD en dos grupos, esofagitis erosiva y enfermedad por reflujo no erosiva (ERNE). Nuevamente, el número total de pacientes clasificados en dos grupos, 40 (36,4%) pacientes que tenían EHF se clasificaron como grupo de hígado graso y 70 (63,6%) pacientes que no tenían EHF y se clasificaron como grupo de enfermedad de hígado no graso. El porcentaje de esofagitis erosiva es mayor en el grupo con FLD 21/40 (52,5%) que en el grupo sin FLD 19 (47,5%), y los factores de riesgo se investigaron y correlacionaron con cada grupo mediante ecuaciones estadísticas específicas. CONCLUSIÓN: Existe una asociación significativa entre la FLD y la esofagitis erosiva y la FLD es un factor de riesgo independiente para la esofagitis erosiva.

Palabras clave: enfermedad del hígado graso, esofagitis erosiva, pacientes iraquíes, un estudio transversal.

Introduction

Gastro-esophageal reflux disease (GERD) is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications[1]. The most typical symptoms of GERD are heartburn and regurgitation, additional symptoms, such as dysphagia and chest pain are also common, extra-digestive symptoms such as cough and laryngitis, are often associated[2-4]. Among the complications, reflux esophagitis is the most common, evident by mucosal breaks or erosions in the esophageal mucosa. Non-erosive reflux disease (NERD) patients have reflux symptoms of sufficient frequency/severity to impair their life without esophagitis[5].

The increased prevalence of GERD has occurred in parallel with the dramatic increase in obesity[6]. Studies have consistently reported an association between higher body mass index (BMI) and GERD[7-11] and found that both obesity (BMI >30 kg/m²) and overweight (BMI 25-30 kg/m²) are associated with GERD[12-14].

The reflux of gastric content into the esophagus is normally prevented by the esophagogastric junction (EGJ), making the anatomical and functional integrity of the EGJ essential[15].

Dyslipidemia and obesity are approved risk factors for GERD, due to their effects on lower esophageal sphincter[16-21]. Increased intra-abdominal fat associated with obesity increases intragastric pressure, which increases the gastroesophageal pressure gradient and frequency of Transient lower esophageal relaxation (tLESRs), thereby predisposing gastric contents to migrate into the esophagus. [22] Patient with GERD have overexpressed cytokines in the mucosa of the esophagus[9]. Obesity triggers esophageal mucosal injury because a variety of cytokines, such as IL-6 and TNF-α are produced by adipose tissues and macrophages[17,23].

Nonalcoholic fatty liver disease (NAFLD) is characterized by fat accumulation in the liver in the absence of excessive alcohol consumption (less than 20 g/day) and exclusion of other secondary causes of hepatic steatosis[16,18,24,25].

Primary NAFLD is closely associated with other features of metabolic syndrome, particularly insulin resistance (IR)[19,20,26]. Secondary causes of NAFLD can be related to nutrition (i.e., rapid weight loss, malnutrition), drug-induced toxicity (i.e., methotrexate, tamoxifen, chemotherapies), metabolic conditions (i.e., lipodystrophy, abetaproteinemia), and other causes (i.e., bypass surgery, bacterial over growth, celiac disease, etc.).

NAFLD represent a histopathological spectrum ranging from simple hepatic steatosis to steatohepatitis characterized by necroinflammatory changes which increases the risk for progression to advanced fibrosis and cirrhosis [18, 21].

The degree of hepatic steatosis in NAFLD is graded based on the percent of total hepatocytes that are involved:

A-Grade 1 is defined as 5%-33% of parenchyma involvement by steatosis,

B-Grade 2 is 34%-66%,

C-Grade 3 >67%.

According to the histological feature scoring system for the diagnosis and grading the severity of NAFLD, accumulation of greater than 5% hepatic fat is scoring the minimal requirement for the histological diagnosis of NAFLD[17].

Hepatic fat accumulation is the hallmark of NAFLD while steatohepatitis is the infiltration of the fatty liver with necroinflammatory cells and associated cell injury [23].

Patient with NAFLD are usually asymptomatic; general malaise or fatigue appears to be the most prevalent complaint in symptomatic individuals. The most common physical finding in subject with NAFLD is obesity, which might be present in the majority of patients[19,20,27].

In the absence of significant alcohol use and a negative serological work-up for common etiologies of liver diseases, the most likely diagnosis is NAFLD[28-30].

Since liver biopsy is invasive, costly, and might not change the management of most cases, a number of noninvasive approaches have been investigated in the diagnosis and staging of NAFLD, the fatty liver index (FLI) is computed from BMI, waist circumference, triglyceride, and Ύ-glutamyl-transpeptidase[31], a score of greater than 60% has an 86% specificity in diagnosing steatosis. Liver fat score is calculated on the basis of the presence of metabolic syndrome, type II diabetes, fasting serum insulin, AST and AST/ALT ratio, and predict the presence of hepatic steatosis with 86% sensitivity and 71% specificity[32].

There were many investigations which tried to find methods to identify NASH including imaging evaluations and blood tests but still these procedures could not diagnose it well[33]. Consequently, investigators are trying to find noninvasive valuable procedure in the diagnosis of liver stiffness/fibrosis. In this regard, application of Fibroscan®/Fibrotouch® (transient elastometer) is a device that can examine liver stiffness[34,35]. Diagnosis of liver stiffness and fibrosis by this method was reported previously[36,37.] Thus, serial evaluation of liver stiffness can provide evidence about the progression of liver diseases like NASH[14]. Transient elastography was first described in France[38], then in other parts of the world[39,40].

Adipocytokines that play an important role in the pathogenesis of NAFLD include adiponectin, TNF-α, and IL-6. Primary NAFLD is closely associated with other features of metabolic syndrome which characterized by obesity, diabetes, hypertension and hypertriglyceridemia[29,41]. There are

increase in the prevalence of FLD, GERD as well as their risk factors[42-44], but there were only a few studies which investigated the relationship between GERD and FLD, so, we were investigated the association between erosive esophagitis diagnosed by OGD and FLD diagnosed by ultrasonography and confirmed by UAP measurements in this study.

The study subjects were patients who had unsatisfactory response to trial of PPI, and those with alarm symptoms of GERD such as dysphagia, odynophagia, gastrointestinal bleeding, early satiety and weight loss, examined by OGD in period between April 2019 to May 2020 for the presence of erosive esophagitis, and then staging according to Los Angeles (LA) classification system into four grades[45]. Medical history, laboratory tests, abdominal ultrasonography and UAP by FibroTouch® device were all performed for each patient.

The exclusion criteria include the followings:

(1) History of liver diseases, such as acute or chronic viral hepatitis, autoimmune liver disease, haemochromatosis and Wilsons disease,

(2) Liver cirrhosis of any causes.

(3) Diagnosed cases with Hepatocellular carcinoma or hepatic metastasis.

(4) Alcoholics, defined as exceeding 14 units per week of alcohol for both men and women.

Methods

This was a cross-sectional study. All the patients, after examination by OGD using Olympus C60 endoscope and under local anesthesia, were divided to erosive esophagitis and NERD. Then classified again according to ultrasonography and Fibroscan findings (FibroTouch®) device, into two groups: FLD group (Those with Ultrasound Attenuation Parameter (UAP) is > 240 dB/m (>11% fatty changes (Grade S1 and above)) and non-FLD group (UAP < 240 dB/m (Grade S0)). The data included in analyses were about sex, age, BMI, smoking and medical history. The anthropometric and laboratory data included systolic and diastolic blood pressure (SBP and DBP), fasting blood sugar (FBS), serum lipid profile, liver enzymes (aspartate transaminase, alanine transaminase, alkaline phosphatase and gamma-glutamyltransferase) and serum bilirubin. Obesity was defined as BMI 25 or more, high SBP 140mmHg or more, high DBP 90mmHg or more, high FBS 126mg/dl or more. FLD was mainly diagnosed by Fibrosacn machine (FibroTouch®). Erosive esophagitis was classified using Los Angeles (LA) classification system by OGD. According to this system, esophagitis is scored into four grades[45]:

(a) Grade A is defined as mucosal breaks confined to the mucosal fold, each no longer than 5 mm,

(b) Grade B corresponds to at least one mucosal break longer than 5mm confined to the mucosal fold but not continuous between two folds,

(c) Grade C is characterized by mucosal breaks that are continuous between the tops of mucosal folds but not circumferential and

(d) Finally, grade D is represented by extensive mucosal breaks engaging at least 75% of the esophageal circumference.

Statistics

For statistical analysis, the IBM SPSS statistical system version 26 was used. Chi square was used to look for the presence of correlations between results, and phi coefficient was used to look for the strength of these correlations. P values <0.05 were considered statistically significant. Phi value ranged between zero to one, (0: no correlation, 0.1: small correlation, 0.3: medium correlation, 0.5: large correlation).

FLD and risk factors correlations in all patients (n=110) are illustrated in table 1. Among 110 patients, 40 (36.4%) were arranged as FLD group and 70 (63.6%) were arranged as non-FLD group. The mean age in FLD group was 41.2 with SD 5.5, and in non-FLD group was 40.4 with SD 5.8, there was no significant correlation between age and FLD, also, there was no recognized increase in FLD with age.

The female to male ratio in FLD group was (1.5:1), with medium correlation between FLD and gender. The percentage of obesity was higher in FLD group than non-FLD group with significant correlation with FLD group. The smoker percentage was higher in FLD group than in non-FLD group with significant correlation between the FLD and smoking. The SBP percentage was higher in FLD group than in non-FLD group and higher than DBP proportion in the same group with significant correlation between FLD and SBP, and again it was significant correlation regarding DBP. The FBS elevation percentage was higher in FLD group than in non-FLD group with significant correlation between FBS and FLD. The TCH elevation percentage was higher in non-FLD group than in FLD group with significant correlation between FLD and TCH elevation. According to LA classification, there were higher percentage of grade A cases in both groups, grade B was higher in non-FLD group than in FLD group, small percentage of grade C in both groups, and there were no cases with grade D.

Table 1. FLD and risk factors correlations of all patients (n=110)

Variables	FLD group	Non-FLD group	P value	**Phi value**
N	40(36.4%)	70(63.6%)		
Age(year)			0.500	**0.00**
Mean	41.2 ± 5.5	40.4 ± 5.8		
Gender Male Female	 16(40%) 24(60%)	 51(72.9%) 19(27.1%)	0.001	**0.30**
BMI(kg/m²) Healthy weight Obese	 5(12.5%) 35(87.5%)	 33(47.1%) 37(52.9%)	0.000	**0.35**
Smoker	22(55%)	12(17%)	0.000	**0.39**
High SBP mmHg	26(65%)	24(34.3%)	0.002	**0.29**
High DBP mmHg	11(27.5%)	7(10%)	0.017	**0.22**
Elevated FBS (mg/dl)	27(67.5%)	25(35.7%)	0.001	**0.30**
Elevated TCH (mg/dl)	36(90%)	9(12.9%)	0.000	**0.75**
Elevated TG (mg/dl)	28(70%)	0(0.0%)	0.000	**0.77**
Low HDL (mg/dl)	20(50%)	0(0.0%)	0.000	**0.62**
Elevated LDL (mg/dl)	11(27.5%)	0(0.0%)	0.000	**0.44**
High TCH/HDL ratio	36(81.8%)	8(18.2%)	0.003	**0.77**
Elevated AST (IU/L)	40(100%)	20(28%)	0.004	**0.4**
Elevated ALT (IU/L)	40(100%)	15(21%)	0.002	**0.3**
Elevated ALP(IU/L)	40(100%)	26(37.%)	0.004	**0.4**
Elevated GGT(IU/L)	40(100%)	13(18.5%)	0.002	**0.4**
Normal TSB(mg/dl)	40(100%)	70(100%)		
Erosive esophagitis	21(52.5%)	23(32.9%)	0.040	**0.19**
LA classification				
Grade A	11(52.4%)	12(52.2%)		
Grade B	8(38.1%)	10(43.5%)		
Grade C	2(9.5%)	1(4.3%)		
Grade D	0%	0%		

Healthy body weight: BMI (18.5-24.9), obese: BMI ≥25. High BP: SBP ≥140, DBP ≥90. Elevated FBS ≥126. Elevated TCH ≥200. Elevated TG ≥150. Low HDL <40. Elevated LDL>130. High TCH/HDLratio>4. Elevated AST > 40. Elevated ALT > 40. Elevated ALP > 112. Elevated GGT > 30. Normal TSB (0-1). BMI : body mass index, SBP: systolic blood pressure ,DBP: diastolic blood pressure, FBS: fasting blood sugar, TCH : total cholesterol, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphstase, GGT: gamma-glutamyltransferase, TSB: total serum bilirubin, LA: Los Angeles.

Erosive esophagitis and risk factors correlation in all patients (n=110) as illustrated in table 2. All patients again arranged into two groups, erosive esophagitis 44(40%), and NERD 66 (60%). There was no significant correlation between the age and erosive esophagitis, and there was no recognized increase in erosive esophagitis. There was higher prevalence of male than female in both erosive esophagitis and NERD, with male to female ratio 1.3:1 in erosive esophagitis and 1.75:1 in NERD, but there was no significant association between erosive esophagitis and gender. Significant association was found between erosive esophagitis and smoking, but was not so with BMI, SBP, DBP, FBS and TG. There was significant association between erosive esophagitis and each of high TCH, low HDL, high LDL, and elevated TCH/HDL ratio. There was significant correlation between erosive esophagitis and FLD.

Table 2. erosive esophagitis and risk factors correlations in all patients (n=110)

	Erosive esophagitis group	NERD group	P value	Phi value
N	44(30.3%)	66(45.5%)		
Age(year)				
Mean	41.73±4.9	40.03±6.1	0.120	0.00
Gender Male Female	 25(56.8%) 19(43.2%)	 42(63.6%) 24(36.4%)	0.400	0.06
BMI(kg/m²) Obese	32(48.5%)	18(40.9%)	0.400	0.07
Smokers	35(79.5%)	22(33.3%)	0.004	0.38
High SBP(mmHg)	18(40.9%)	32(48.5%)	0.400	0.07
High DBP(mmHg)	17(15.9%)	11(16.7%)	0.900	0.01
High FBS(mg/dl)	30(68%)	25(37%)	0.005	0.35
High TCH(mg/dl)	27(61.4%)	18(27.3%)	0.000	0.34
High TG(mg/dl)	13(29.5%)	15(22.7%)	0.400	0.07
Low HDL(mg/dl)	12(27.3%)	8(12.1%)	0.040	0.19
High LDL(mg/dl)	11(25%)	0(0%)	0.000	0.40
High TCH/HDL ratio	27(61.4%)	17(38.6%)	0.000	0.35
FLD	21(52.5%)	19(47.5%)	0.040	0.19

Obesity: BMI≥25. High blood pressure: SBP≥140, DBP≥90. High FBS≥126. High TCH ≥ 200.High TG≥150.Low HDL<40.High LDL>130. High TCH/HDLratio >4. BMI:body mass index .SBP :systolic blood pressure, DBP: diastolic blood pressure.FBS :fasting blood sugar.

Discussion

Our study demonstrated that FLD group was significantly associated with the increased risk of erosive esophagitis. GERD is a condition in which refluxed acidic gastric contents result in troublesome symptoms or complications[1]. GERD is related to a variety of symptoms, such as heartburn (most common), regurgitation and difficulty of swallowing[46].

GERD develops when the anti-reflux barrier comprising the lower esophageal sphincter (LES) and the crucial portion of a hiatus do not function properly[50]. LES function is reduced by several factors, such as high BMI, intra-abdominal pressure, intragastric pressure, inspiratory intrathoracic pressure and hiatal hernia. High-fat diet and caloric intake increase weight and obesity, which reduce the intrinsic LESP and increase the frequency of transient LES relaxation; these consequently lead to GERD[51,52]. Therefore, obesity is a risk factor of GERD. In addition, patients with GERD have overexpressed cytokines in the mucosa of the esophagus. Obesity triggers oesophageal mucosal injury because a variety of cytokines are produced by adipose tissues and macrophages[53,54]. The prevalence of FLD ranges from 25% to 45% world-wide. FLD includes alcoholic FLD and NAFLD. The pathophysiology of NAFLD involves multifactorial mechanisms affected by environmental, genetic and metabolic factors[55]. Visceral adipose tissues alter the metabolism of lipid and glucose. As a result, hepatocyte fat accumulates, inflammatory milieu injures the liver and other tissues generate. Lipid toxicity, apoptotic process, oxidative stress and endoplasmic reticular stress lead to liver damage and progressive fibrosis[56]. Increased BMI and obesity are documented risk factors of NAFLD[55]. From previous studies, we have known that obesity was a risk factor of GERD and NAFLD. In this regard, the present study investigated whether FLD is a risk factor of GERD. In addition, a recent study reported that NAFLD was strongly associated with GERD[44].

However, this study has some limitations, including its small sample size further, only patients with gastrointestinal problems were included, not the general population. Conversely, the present study included numerous subjects for health check-up examination and reported that obesity (BMI ≥25 kg/m2), high blood pressure, high fasting glucose and erosive oesophagitis were significantly higher in the FLD group than in the non-FLD group. In the multivariate analysis, the risk factors of erosive oesophagitis were FLD group, male sex and obesity. Therefore, our study suggests that FLD is a risk factor of GERD which is consistent with those of previous studies[47-50].

In conclusion, the present study reports that FLD is an independent risk factor of erosive oesophagitis in sample of Iraqi patients. The mechanism and pathophysiology between fatty liver and erosive oesophagitis should be further evaluated in future studies and it is highly recommended to make a multicentric research about the same subject.

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