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Evaluation of Gallbladder Motilityin Patients With Functional Gallbladder Disorder

Salem M. Awami

Department of medicine, Faculty of medicine, Omar AL-Mukhtar University, Al-Bayda- Libya

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Abstract: Rome IV defines Functional gastrointestinal disorders (FGID) as disorders of gut-brain interaction. It is a group of disorders classified by gastrointestinal symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing. Patients with Gallbladder Functional disorder (GBFD) may have abnormal gastric emptying and colonic transit, suggesting a possible generalized gastrointestinal motility disorder. The presentation of functional gallbladder disorder mimics classic symptoms of biliary pain ،27 patients and 27 healthy volunteers (7 males and 20 females) in each group, age between 21 and 48 years were included into the study, and diagnosis of functional gallbladder disorder was based on Rome III criteria. All patients were given a standard test fatty meal, and Gallbladder volume was calculated manually by using the ellipsoid formula (Dodd's formula). The pre-meal and post-meal gallbladder volumes and ejection fraction (EF) of the gallbladder (GB) were estimated. The patients and control groups were compared for age, gender, and body mass index. The body mass index in our control and patients was high indicating a prevalence of overweight in both groups. This study demonstrated that fatty meal ultrasound is a cheap, easy to handle, and physiologic. GBFD patients have decreased emptying of gallbladder compared to healthy subjects. GBFD should be considered in patients presented with recurrent right upper quadrant abdominal pain, decreased emptying of gallbladder in the absence of visualized gallstones on abdominal ultrasound, and meeting the Rome III criteria.

Keywords: Irritable bowel syndrome, IBS, Rome III diagnostic criteria, abdominal pain or discomfort, Functional gastrointestinal disorders, (FGID).

INTRODUCTION

Functional gastrointestinal disorders are due to disturbances in sensory and/or motor gastrointestinal function, which may overlap across anatomic regions leading to a generalized functional abnormality of the smooth muscle of the gastrointestinal tract, the Gallbladder, the urinary bladder, and even of the bronchial tree (Drossman 1999). Rome IV defines Functional GI disorders as follows: "Functional GI disorders are disorders of gut-brain interaction. It is a group of disorders classified by Gastrointestinal symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing (Whitehead *et al.,* 2017). The presentation of functional gallbladder disorder mimics classic symptoms of biliary pain, which manifests as steady, severe epigastric or right upper quadrant pain that might radiate through to the back and right infrascapular regions, lasting for at least thirty minutes but less than 6 hours. It can be associated with symptoms of nausea and vomiting and may awaken the patient from sleep. It has been noted that patients with functional gallbladder disorder may have abnormal gastric emptying and co-

***Corresponding Author:** Salem Awami, salemawami@yahoo.comFaculty of Medicine, Omar AL-Mukhtar University, El-Bayda, Libya

lonic transit, suggesting a possible generalized gastrointestinal motility disorder. The diagnosis begins with the exclusion of other likely causes including functional dyspepsia, ischemic heart disease, sphincter of Oddi dysfunction, common bile duct obstruction, and peptic ulcer disease. Patients usually have blood work that is normal, normal liver and pancreatic biochemistries, and negative diagnostic imaging(Hansel and DiBaise 2010).

Table(1): the Rome III diagnostic criteria for functional gallbladder disorder published by Behar et al 2006.

It must include episodes of pain located in the epigastrium and/or right upper quadrant and all of the following findings:
• Gallbladder is present • normal liver enzymes, conjugated bilirubin, and amylase/lipase • episodes lasting ≥30 minutes • recurrent symptoms occurring at different intervals (not daily) • The pain builds up to a steady level • The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit • The pain is not relieved by bowel movements • The pain is not relieved by postural change • The pain is not relieved by antacids • exclusion of other structural diseases that would explain the symptoms
Supportive criteria: The pain may present with one or more of the following findings:
• Pain is associated with nausea and vomiting • Pain radiates to the back and/or right infra subscapular region • Pain awakens the patient from sleep in the middle of the night

The gallbladder ejection fraction (GBEF) is abnormal in patients with functional gallbladder disorder. However, many of the studies supporting the use of the GBEF for diagnosis are not conclusive (DiBaise *et al.,* 2011). Diagnosis of functional gallbladder disorder is based on characteristic symptoms and abnormal gallbladder function resulting in low gallbladder ejection fraction (GBEF). Oral cholecystography was the first imaging modality used to assess gallbladder dyskinesia depending on visual X-ray film assessment of gallbladder contraction after fatty meal. Other method of assessment of gallbladder contractility in terms of ejection fraction (EF) is calculated from a hepatoiminodiacetic acid (HIDA) scan. Although ultrasound is considered the modality of choice for evaluating gallstones (Cooperberg and Burhenne 1980), it currently has a limited application in evaluating functional biliary disease, such as gallbladder dyskinesia. Most researchers define a normal EF as >35% (Francis and Baillie 2011), but the Rome III criteria use a cutoff of 40%. A patient who has an EF <40% and meets the other guideline criteria is diagnosed with functional gallbladder disorders (FGBD) (Goussous *et al.,* 2017). Surgical gallbladder removal (cholecystectomy) results in pain relief in more than 90% of the individuals with gallbladder dyskinesia(Mahid *et al.,* 2009).

Therefore, our study is aimed to investigate gallbladder motility in patients with functional gallbladder disorder diagnosed by Rome III diagnostic criteria for functional gallbladder disorder published by(Behar *et al.,* 2006); and in healthy subjects using a real time ultrasonography measurement.

Patients and methods: 27 patients and 27 healthy volunteers (7 males and 20 females) in each group, age between 21 and 48 years were included into the study, and diagnosis of functional gallbladder disorder was based on Rome III criteria. Table (1). All subjects gave informed consent for the study. All subjects with functional gallbladder disorder had normal results of the following tests: complete blood count, erythrocyte sedimentation rate, stool hemoccult test, stool culture, stool test for ova and parasites, urinalysis, blood chemistry, thyroid function tests, and studied

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for anti-tissue transglutaminase IgA and IgG antibodies for Coeliac Disease.

Exclusion criteria: It includes: gallstone disease, history of cholecystectomy, diseases that influence gallbladder functions (e.g. diabetes mellitus, thyroid diseases). Also patients being prescribed drugs known to affect secretion or gallbladder motility were excluded. Gallbladder measurements were performed by the ultrasound machine with a 3.5 MHz convex transducer. The gallbladder was measured in three dimensions, one longitudinal (D1) and cross-sectional diameter (D2) and depth (D3), and the volume was calculated manually by using the ellipsoid formula (Dodd's formula): Volume = (D1 cm x D2 cm x D3 cm) X π /6 = volume ml. All patients were studied after 12-hours of fasting and 45 min after eating. All patients were given a standard test fatty meal to stimulate gallbladder contraction: one egg, butter cube (30 g), and a single bread slice (Kishk *et al.,* 1987, Irshad *et al.,* 2011).The pre-meal and post-meal gallbladder volumes were substituted into the following formula to calculate the ejection fraction (EF) of the gallbladder (GB). EF (%) = fasting GB volume – postprandial GB volume ÷ fasting GB volume %.

Statistical analysis: All analyses, descriptive Statistics, analysis of variance (ANOVA), and Correlations (Pearson) were done using Windows-based Minitab Statistical Package (version 11.12), and P values 0.05 were considered as significant.

RESULTS

The patient and control groups were comparable for age, gender, body mass index. The body mass index in our control and patient was high indicating a prevalence of overweight in both groups, although the mean body mass index in control group is insignificantly lower than patient group (ANOVA p: 0.104) (WHO 854 (1995), (WHO 894 (2000.) table (2). The fasting gallbladder volume (FGV) was similar in patient and control groups (18.1 ± 3.0 ml vs. 18.1 ± 2.6 ml, ANOVA p 0.962), whereas the Postprandial gallbladder volume PGV was lower in control group than in the patient group (6.6 ± 0.423 ml vs. 8.4 ± 0.542 ml, ANOVA p = 0.012).

Table (2): The characteristic features of study and control groups (BMI body mass index, FGBV fasting gallbladder volume, PGBV Postprandial gallbladder volume)

Variable	N (Female/Male)	Mean	SE Mean	Min	Max
Age Control	27 (20/7)	37.41 ±	1.61	21.00	48.00
Age Patient	27 (20/7)	38.19 ±	1.65	21.00	48.00
BMI Control	27 (20/7)	29.74 ±	1.24	17.40	45.50
BMI Patient	27 (20/7)	32.74 ±	1.33	20.10	53.40
FGBV in control	27 (20/7)	18.11 ±	0.60	12	24
FGBV in patient	27 (20/7)	18.20 ±	0.50	14	23
PGBV in control	27 (20/7)	06.60 ±	0.423	04	13
PGBV in Patient	27 (20/7)	08.40 ±	0.60	04	15

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Table (3) : Descriptive Statistics of results of Gallbladder Ejection Fraction (*EF*) measurements

Variable	N	Mean ± SE Mean	EF< average	EF< 40%
EF Control	27	62.60 ± 2.03	09 (33%)	3 (11%)
EF Patient	27	53.78 ± 2.57	10 (37%)	8 (30%)
EF Control Female	20	61.29 ± 2.65	08 (40%)	3(15%)
EF Control Male	07	66.33 ± 1.44	01 (14%)	0 (00%)
EF Patient Female	20	52.64 ± 3.14	09 (45%)	7 (35%)
EF Patient Male	07	57.03 ± 4.37	01 (14%)	1 (14%)

The mean EF of gallbladder in control group was higher than that in the patient group (62.6% vs. 53.87%, ANOVA P: 0.010), and this was also true in comparisons of patient and control female (61.29% vs. 52.641%, ANOVA P:0.042); but insignificant difference of GBEF was found among patient and control males (66.33% vs. 57.03%, ANOVA P: 0.066). Nine out of 27 (33 %) of control group were below average GBEF, and one out of 27 (3.7%) of control group was below or equal to 35% of GBEF. Ten out of 27 (37 %) of patient group were below average GBEF, and five out of 27 (18%) of patient group were below or equal to 35% of GBEF. Table (3) There was a strong negative correlation between EF and BMI in both groups ($P < 0.01$), and a significant negative correlation between EF and age in patient group ($P < 0.05$); Table (4)

Table (4): Correlations (Pearson) between EF and age, BMI in both groups (EF, Ejection fraction, BMI, Body mass index)

Correlations (Pearson)		
gallbladder EF and BMI in Control	= -0.541**	P= 0.004
gallbladder EF and BMI in Patient	= -0.643**	P= 0.000
Age and EF in Control	= 0.072	P= 0.722 NS
Age and EF in patient	= -0.482*	P= 0.011

* Correlation is significant at the 0.05 level (2-tailed).
* * Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

In this study, we investigated the motility of gallbladder by using real time ultrasonography in FGBD patients and none FGBD control, we used fatty meal as a stimulant of indigenous cholecystokinin (CCK), and the gallbladder emptying study was based on a geometric formula (Çay *et al.,* 2006). There was no difference in basal volumes of the gallbladder between the control group (mean 18.1 ml) and the patients (18.2 ml). This result is lower than that in a study by (Palotta *et al.,* 1994), they found in their study in Italy on 150 healthy volunteers a mean fasting GBV of 23.8 cm3 (±12.5). This slight difference could be attributed to the relatively younger age of our study group (Palasciano *et al.,* 1992) have found in a sonographic population study among Italians that gallbladder volume significantly increased with age in healthy non-obese males.Endogenous cholecystokinin (CCK) stimulates hepatic bile secretion, gallbladder

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contraction, and relaxes the sphincter of Oddi. However, postprandial gallbladder contraction is characterized by an immediate cephalic phase regulated by a sequence of excitatory cholinergic vagal nerves, and rate of gastric emptying and endogenous cholecystokinin. Therefore, all these factors could play a role in gallbladder motility in health and disease (Funch-Jensen *et al.,* 2006). The mean differences in the fasting and postprandial gallbladder volume and ejection fraction were lower in the patient group compared to controls (P: 0.010). The cutoff of GBEF equal to 40%, which set by Rome III is met by 30% of patients and 11% of control (none of male control has value <40%) (Table III). This might explain the possibility of a statistical association of functional gallbladder disorder and gallbladder hypomotility.In our study, there is a strong significant negative correlation between BMI and gallbladder ejection fraction (Sari *et al.,* 2003). Table IV, gallbladder dysfunction denote a condition where the gallbladder empties insufficiently in a patient with biliary symptoms without demonstrable organic substrate such as gallstones. Some researches claim that functional gallbladder disorder is initiated by fatty infiltration of the gallbladder wall, causing increasing levels of inflammation and steatocholecystitis that lead to poor motility (Goldblatt *et al.,* 2006, Tsai 2009). The relative risk of gallstone formation appears to rise as body weight increases, and this positive correlation with increasing BMI is more pronounced when BMI exceeds 30 kg/m² (Kim and Popkin 2006). The limitations of our study were the lack of clear cutoff value of gallbladder ejection fraction, and USG is highly operator-dependent. The gallbladder has various configurations at fasting, and changes its shape during contraction resulting in inaccuracies in ultrasonographic estimation of gallbladder volume and contractility (Hurrell *et al.,* 1994). It would be difficult to discriminate stone impaction from sphincter of Oddi dysfunction on fatty-meal ultrasonography (Varghese *et al.,* 2000). In conclusion, this study demonstrated that fatty meal ultrasound is a cheap, easy to handle, and physiologic. Gallbladder Functional disorder (GBFD) patients have decreased emptying of gallbladder compared to healthy subjects.

GBFD should be considered in patients presented with recurrent right upper quadrant abdominal pain, decreased emptying of gallbladder in the absence of visualized gallstones on abdominal ultrasound, and meeting the Rome III criteria (Jung *et al.,* 2017).

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تقييم حركية الحوصلة المرارية في المرضى الذين يعانون من اضطراب المرارة الوظيفي

سالم محمد العوامي

قسم الامراض الباطنة كلية الطب البشري، جامعة عمر المختار، البيضاء. ليبيا

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المستخلص: عرف اجتماع روما الرابع اضطرابات الجهاز الهضمي الوظيفية كاضطرابات في تفاعل الأمعاء مع الدماغ، واضاف التعريف أنها مجموعة من الاضطرابات المصنفة من قبل أعراض الجهاز الهضمي المتعلقة بأي مزيج مما يلي: اضطراب حركة الجهاز الهضمي، فرط الحساسية الحشوية، وتغيير كل من الغشاء المخاطي والمناعة، والجراثيم المعوية، وتفاعل الجهاز العصبي المركزي للمرضي. المرضى الذين يعانون من اضطراب المرارة الوظيفي قد يكون إفراغ المعدة والقولون غير طبيعي، مما يشير إلى احتمال تعميم اضطراب حركية الجهاز الهضمي. عرض اضطراب المرارة الوظيفي يحاكي الأعراض الكلاسيكية لألم القناة الصفراوية، تم تضمين 27 مريض و27 متطوعا أصحاء (7 ذكور و20 إناث) في كل مجموعة، تتراوح أعمارهم بين 21 و48 سنة في الدراسة، واستند تشخيص اضطراب المرارة الوظيفي على معايير اجتماع روما الثالث. أعطيت جميع المرضى وجبة اختبار الدهون القياسية، وتم حساب معدل انقباض وافراغ الحوصلة المرارية يدويا باستخدام الصيغة الإهليلجية (صيغة دود) بعد اجراء صورة الموجات الصوتية. تم تقدير حجم المرارة قبل وبعد وجبة طعام خاص ومن ثم تم حساب معدل افراغ الحوصلة المرارية، في مجموعتين مقارنة من المرضى الذين يعانون من اضطراب المرارة الوظيفي والذين لا يعانون؛ وكانت كلتا المجموعتين متقاربة في العمر والجنس ومؤشر كتلة الجسم. كان مؤشر كتلة الجسم في كلتا المجموعتين مرتفع، مما يوحي بانتشار زيادة الوزن في كلتا المجموعتين. المناقشة والخلاصة: أظهرت الدراسة أن اختبار وظيفة وانقباض الحوصلة الصفراوية باستخدام الموجات فوق الصوتية تحت تأثير وجبة طعام خاص معدة من الدهون هي سهلة وفسيولوجية ورخيصة، ونتج في هذا الاختبار انخفاض معدل تفريغ المرارة عند المرضي مقارنة مع الأشخاص الأصحاء. ومن هذا نستنبط بأن المرضى الذين يعانون من اضطراب المرارة الوظيفي يعانون من الام متكررة في الربع العلوي الأيمن للبطن، وانخفاض معدل إفراغ المرارة في غياب حصى في المرارة بعد استعمال الموجات فوق الصوتية، وتلبية معايير اجتماع روما الثالث.

الكلمات المفتاحية: اضطرابات الجهاز الهضمي الوظيفي، اضطرابات المرارة الوظيفية، انقباض الحوصلة الصفراوية، الموجات فوق الصوتية، وجبة دهنية.

*سالم محمد العوامي salemawami@yahoo.com قسم الامراض الباطنة كلية الطب البشري، جامعة عمر المختار، البيضاء. ليبيا.