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RESEARCH ARTICLE

Evaluation of gallbladder contractility and Doppler findings in patients with irritable bowel syndrome; a case-control study

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ABSTRACT

Background: Irritable Bowel Syndrome (IBS) is a common gastrointestinal disorder causing abdominal pain, altered bowel habits and bloating without structural issues. Gallbladder dysfunction may be linked to IBS due to disrupted cholecystokinin release. This study aims to assess gallbladder function and related hemodynamic parameters using Doppler ultrasound in IBS before and after meals.

Method: In this case-control study, we investigated gallbladder function differences between constipation-predominant IBS (C-IBS) patients and healthy volunteers. Participants underwent ultrasonography to measure gallbladder parameters before and after consuming a predefined meal. Gallbladder volume, wall thickness and resistance index (RI) of cystic and superior mesenteric arteries (SMA) were assessed. Student t-test and paired t-test were used to compare case and control groups and pre- and post-meal data, respectively.

Results: A total of 34 people (18C-IBS and 16 healthy control) were included. The mean (Standard deviation) of gallbladder fasting volume was measured 24.74 (8.85) and 29.73 (9.65) cubic millimeter for case and controls, respectively. Postprandial volume was 11.34 (5.66) and 16.9 (6.16) cubic millimeter for case and controls respectively. We observed a statistically significant difference in emptying fractions (EF) between groups (p value = 0.009). IBS patients had a smaller fasting SMA RI (p value = 0.016) but the fraction of change after meal was not significant (p value = 0.10). The cystic artery RI did not reach statistical significance between the fasting and post-meal values (p value = 0.067).

Conclusion: IBS patients have a higher emptying fraction and lower change in SMA RI compared to healthy controls. Further studies with larger sample size, inclusion of patients with different coexisting conditions and subtypes of IBS and combining colon transit study with gallbladder ejection fraction evaluation can be used to further provide more meaning to this study.

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Irritable bowel syndrome; gallbladder; superior mesenteric artery; cystic artery

Introduction

Irritable Bowel Syndrome (IBS) is a prevalent functional gastrointestinal disorder characterized by abdominal pain, altered bowel habits, and bloating without any identifiable structural or biochemical abnormalities [1]. It is estimated that around 10 to 15% of the American population is affected by IBS, and the annual occurrence rate is about 1 to 2% and is believed to affect patients' quality of life similar to organic disorders such as IBD [2, 3]. Functional gastrointestinal disorders (FGIDs), including IBS, are caused by disorders of GI functioning, namely altered gut sensitivity, motility, microbiota, immune functioning, visceral hypersensitivity, altered GI secretion, presence and degree of bile acid malabsorption, microbial dysbiosis, and alterations to the gut-brain axis [4]. There have been reports of altered movements in the whole GI tract of patients with IBS [5]. While the primary manifestations of IBS pertain to the colon, there are also extra-colonic symptoms including early satiety, heartburn [6, 7], nausea, and vomiting, as well as somatic symptoms such as fibromyalgia [8] and autonomic cardiovascular disorders [9]. Among its subtypes, constipation-predominant IBS (C-IBS) is recognized for its distinct clinical presentation, involving infrequent and difficult passage of stools [10].

A hypothetical general abnormality impacting the smooth muscle and/or autonomic nervous system has been proposed as a potential explanation for all of these associations [11]. The gallbladder plays a vital role in the digestion of fats, as it stores and concentrates bile produced by the liver, which is then released in response to meals [12]. Moreover, malfunctions in the release of cholecystokinin (CCK) have been detected in individuals with IBS, potentially giving rise to the development of functional disorders in other associated organs, especially the gallbladder [13]. The autonomic nervous system and CCK have a critical role in the appropriate functioning of the gallbladder [14, 15].

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There are limited studies on gallbladder function in IBS patients. Moreover, so far, no study has been conducted to specifically evaluate the function of the gallbladder through Doppler ultrasound parameters of its supplying arteries. Moreover, the dynamic nature of gallbladder function, influenced by factors such as meal consumption and hormonal changes, necessitates a more robust investigation to elucidate its role in C-IBS. Color Doppler imaging proves beneficial for appraising blood flow in the arteries supplying the gallbladder and the entire GI tract [16]. The selection of the cystic and superior mesenteric arteries as the target vessels for RI measurements is based on their essential roles in supplying blood to the gallbladder and intestines, respectively. Despite lack of a definitive treatment, management of the symptoms can relieve the symptoms of these patients and improve their quality of life [17]. Therefore, the purpose of this study is to investigate the emptying fraction (EF) and contractility of the gallbladder, as well as the Doppler parameters of the cystic and superior mesenteric arteries (SMA) in patients with IBS before and after meals.

Methods and materials

The present study is a case-control study conducted for 11 months (between December 2020 to October 2021) in the X hospital, X University of Medical Sciences, X, X. According to past studies as well as to the number of referrals, 34 people (18 patients with constipation-predominant IBS (C-IBS) and 16 healthy volunteers) were included in the study. The cases were randomly selected from the clinically diagnosed IBS patients with body mass index (BMI) of less than 30 k_{g/m^2} referring to the gastroenterology clinic of the hospital. The diagnosis of IBS was based on the Rome IV criteria and Bristol Stool Form Index [18] and was ascertained by a gastroenterologist. The exclusion criteria were the presence of gallstone, a previous history of cholecystectomy, diseases that affect the function of the gallbladder (such as diabetes mellitus, thyroid dysfunctions, electrolyte imbalances, and other systemic diseases), the use of drugs that affect the function of the gallbladder (like anticholinergics), and diseases affecting gastric emptying (such as diabetes mellitus, smooth muscle disorders, neurological disorders, and gastric outlet obstruction). Participants were instructed not to smoke, consume alcohol or drink caffeine for 24 h before the study to avoid the potential impacts of these substances on gallbladder motility. All patients had a normal physical examination, complete blood count, erythrocyte sedimentation rate, thyroid function test, liver function test, and renal function test results with normal sigmoidoscopy reports. Moreover, test results for occult blood screening, parasites, and parasite eggs were negative for all the participants. Due to the evidence of changes in gallbladder function during the different phases of the menstrual cycle, women of reproductive age were studied in the luteal phase [19]. For blinding, after obtaining the written consent, they were given a special form with a code which was unbeknown to the radiologist. Data was gathered and entered to SPSS by another investigator not involved in the clinical aspect of this project. After 12 h of fasting, the functional parameters of the gallbladder including the volume of the gallbladder in the fasting state, the thickness of the gallbladder wall, and the resistance index (RI) of the cystic and superior mesenteric arteries were measured and recorded.

All the participants were examined by an expert radiologist using real-time ultrasonography technique with a Samsung WS80A ultrasound machine and Convex C2-8A probe. The gallbladder's dimensions were assessed in three separate planes, including one longitudinal (D1) and two cross-sectional diameters (D2 and D3). The volume computation was performed using the ellipsoid equation ($\pi/6 \times D1 \times D2 \times D3$) [20] (Figure 1). The mean gallbladder volume was determined based on a series of three consecutive measurements of the organ's volumes.

The minimum amount of fat for gallbladder function studies is 10-12 gr, so all the participants had a prepared 100-g chocolate bar containing 36 gr carbohydrate and 27 gr fat. The measured parameters in the fasting state were assessed again 45 min after having the meal. The gallbladder ejection fraction (EF) was calculated using the following formula [20, 21]:

$$EF = \left(\begin{array}{l} \text{gallbladder volume in fasting state} - \text{gallbladder volume} \\ \text{after meal} / \left(\text{gallbladder volume in fasting state} \right) \end{array} \right)$$

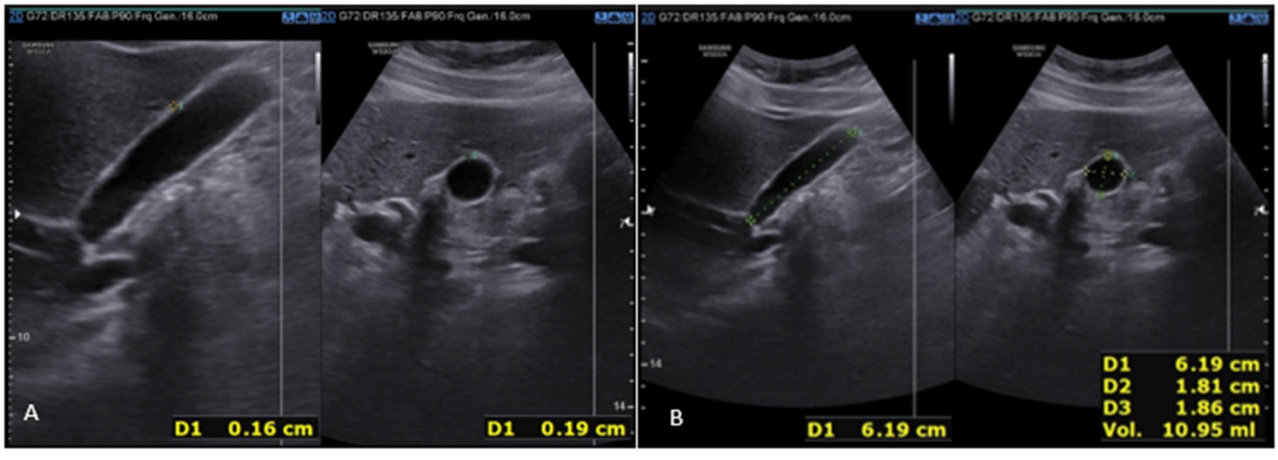

Figure 1. Measuring the thickness (A) and volume (B) of the galbllader using two longitudinal and transeverse views.

Color Doppler imaging, utilizing the left lateral position, identified blood flow signals in the cystic artery situated along the long axis of the gallbladder wall where it was best visualized with color Doppler (Figure 2).

Angle correction less than or equal to 60° was made with the artery in longitudinal dimension. After detecting an appropriate arterial waveform, RI was computed with an automatic method selecting maximum peak systolic volume and end-diastolic volume. For calculating the RI of the superior mesenteric artery, the pulsed Doppler sampling gate was positioned approximately 2 centimeters from the origin of the superior mesenteric artery. The axial length of the Doppler sampling gate was modified to range between 3 and 7 millimeters, depending on the vessel diameter. Adjustments were made to the transducer position and sampling volume to achieve the minimal angle of insonation in relation to the superior mesenteric artery. Four RI measurements were conducted during each examination and the resulting values were averaged. In order to characterize the waveform of blood flow signals employing the pulsed Doppler technique, a 2-millimeter sampling width was established and the angle of the flow signal was frequently adjusted as needed. Fraction of change in the resistance indices were calculated using a similar formula to gallbladder EF formula.

The entirety of the statistical analysis was performed in SPSS version 27 (IBM Corp., Armonk, N.Y., USA). Comparisons of the continuous variables between the groups were conducted using student t-test and for difference before and after meal with paired t-test. Difference in gender distribution was compared with Fisher's Exact Test. Data are presented as mean ± standard deviation (SD). P-values below 0.05 were considered statistically significant.

This study was approved by the ethics committee of X University of Medical Sciences and written informed consent was obtained from all the participants after fully explaining the study and its goals. No additional fees were imposed on the participants.

Results

In this case-control study, a total of 34 people (18 patients diagnosed with constipation-predominant IBS and 16 healthy people as the control group) were included. The demographic characteristics of the population are shown in Table 1.

The mean volume of the gallbladder, its wall thickness, and the RI of the cystic and superior mesenteric arteries in the fasting state and post-prandially in both groups were measure and are summarized in Table 2, Figures 3–7. Overall, after the meal, gallbladder volume was decreased and gallbladder wall thickness was increased in both groups. Moreover, cystic and superior mesenteric arteries' RI both decreased after eating.

In the case group, the gallbladder volume showed a significant difference before and after the meal (p value = 0.00003). The difference in gallbladder wall thickness between the fasting and post-meal measurements was not significant (p value = 0.403). The cystic artery RI also demonstrated a significant difference before and after the meal (p value = 0.036). However, there was no significant difference in the Superior mesenteric artery RI between the pre- and post-meal values (p value = 0.644).

In the control group, the gallbladder volume and wall thickness showed a significant difference before and after eating (p value = 10^{-5} and $<10^{-5}$ respectively). The cystic artery RI did not reach statistical significance between the fasting and post-meal values (p value = 0.067). A significant difference was observed in the superior mesenteric artery RI between the fasting and post-prandial measured values (p value = 0.00003).

The between-group analysis revealed significant differences in the post-meal gallbladder volume, pre- and post-meal gallbladder wall thickness, and fasting superior mesenteric artery RI values. Furthermore, the gallbladder EF indicated significantly greater values in the case group compared to the control group (Table 3).

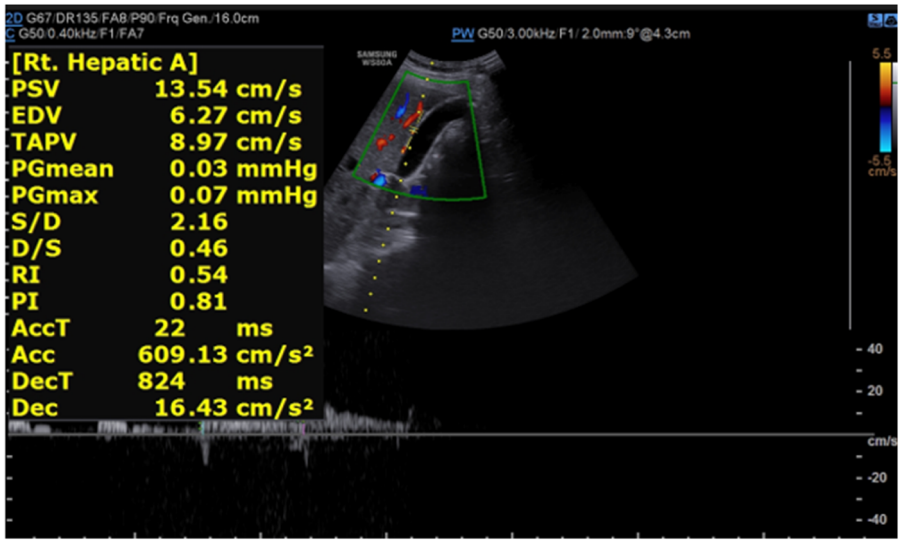

Figure 2. Measuring resistance index of the cystic artery near long axis of the gallbladder wall.

Table 1. Demographic characteristics of case and control groups.

		Case	Control	Total	*p*-value for the difference between groups
Age	Mean	32.94	30.13	31.62	0.199
	S.D	8.047	3.931	6.513	
	Minimum	18	24	18	
	Maximum	45	38	45	
Gender	M/F	9/9	5/11		0.315

*S.D: Standard deviation.

Table 2. Gallbladder volume, wall thickness, and cystic and SMA arteries RI before and after meal for all the patients.

	Before the meal		After the meal		
	Mean	S.D	Mean	S.D	*p*-value
Gallbladder volume	27.09	9.44	13.95	6.46	$<10^{-5}$
Gallbladder wall thickness	1.85	0.37	2.63	0.45	$<10^{-5}$
Cystic artery resistance index	0.71	0.072	0.66	0.079	0.04
Superior mesenteric artery resistance index	0.83	0.059	0.80	0.052	0.013

*S.D: Standard deviation.

Discussion

In the present study, we studied the gallbladder function in a group of IBS and healthy subjects by real-time ultrasound in fasting and post-prandial states. Moreover, this study was the first study to assess the gallbladder motor function through color Doppler ultrasound indices. Despite the similar fasting volume measurement in both groups, there is a larger decrease in volume in IBS patients compared to control group. This is also reflected in EF data, as patients have more EF than controls. These results show the more degree of response of the gallbladder in IBS to eating stimuli. These results are in concordance with previous studies which showed that EF of the gallbladder was higher in IBS patients (84%) when compared with controls (55%, $p<0.001$) [22]. Cystic artery RI measured in the case group was significantly reduced after the meal. However, such significance was not observed in control group. Regarding the RI of the superior mesenteric artery, the results were complete the opposite of

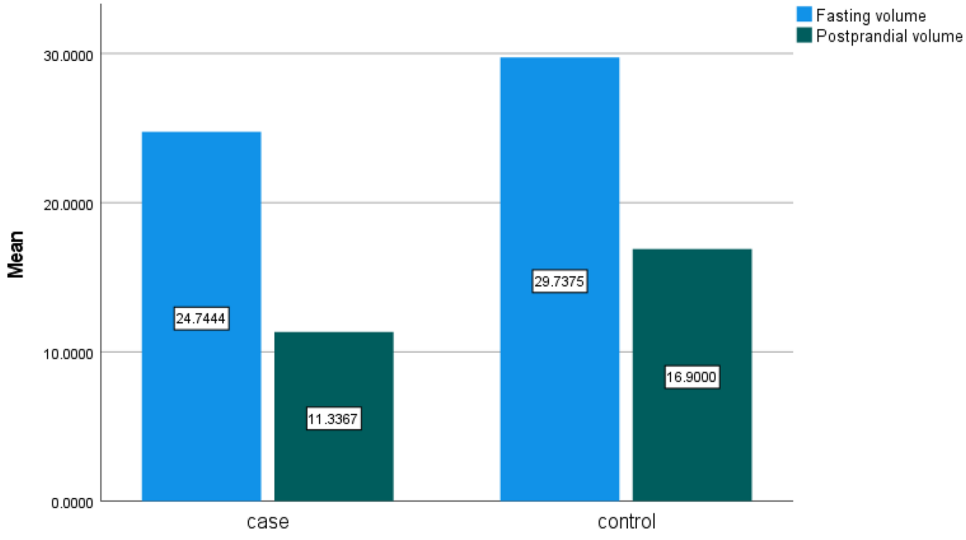

Figure 3. Comparison of fasting and postprandial gallbladder volume in cases and controls.

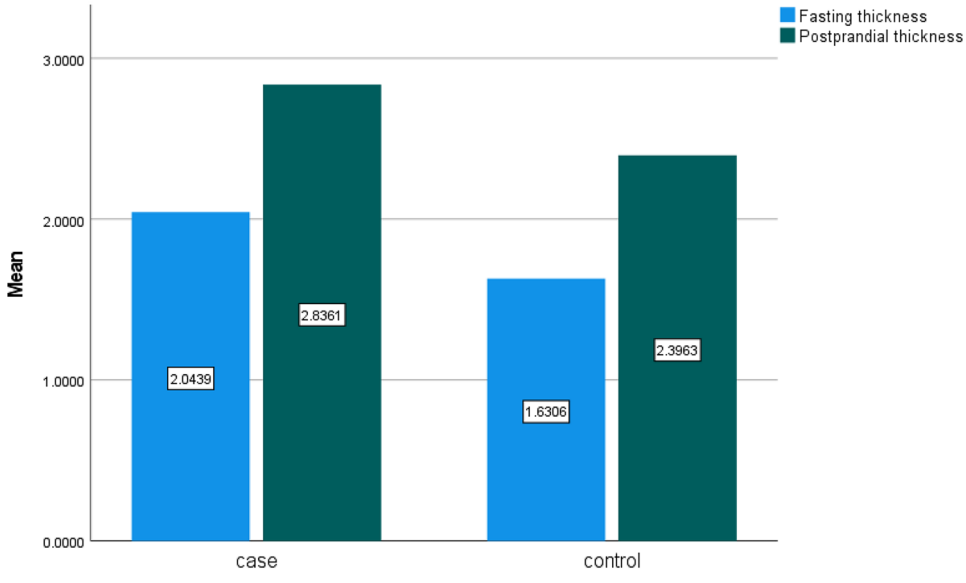

Figure 4. Comparison of fasting and postprandial gallbladder thickness in cases and controls.

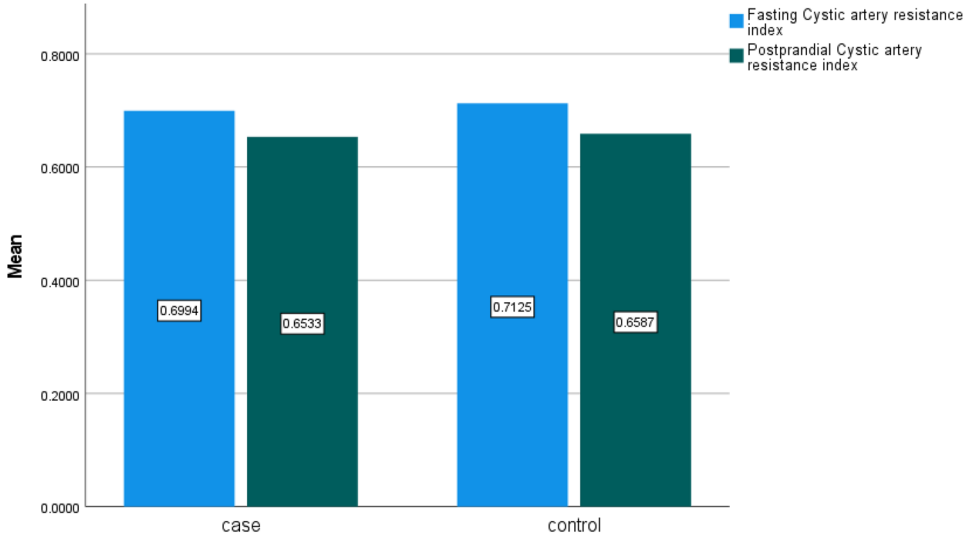

Figure 5. Comparison of fasting and postprandial cystic artery resistance index in cases and controls.

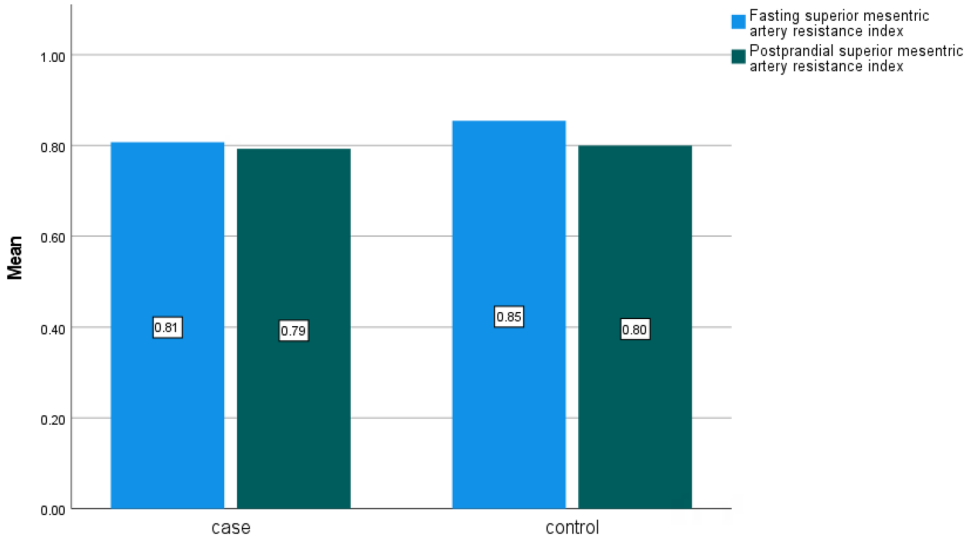

Figure 6. Comparison of fasting and postprandial superior mesenteric artery resistance index in cases and controls.

cystic artery. Fraction of change in these indices were not statistically significant between groups.

There are previously studied hormonal and neuronal pathways known to play a role in mediating SMA RI and blood flow after having a meal. Cholinergic nervous reflex mediated by acetylcholine has been shown to role in postprandial mesenteric blood flow and pretreatment with atropine can reduce the flow response to meal stimulation. Some hormones such as octapeptide, gastrin 17, secretin, and glucagon have been investigated for their role in regulating postprandial SMA blood flow. However, the study found that these hormones only show a significant increase in flow parameters when infused at pharmacologic doses and not in physiologic doses [23]. Glucagon-like peptide 2 (GLP-2) is an intestinotrophic hormone that has been found to influence mesenteric blood flow. A study showed that GLP-2 infusion increased mesenteric blood flow in healthy volunteers, which was similar to the changes seen after a standard meal [24]. It's been shown that low vagal tone, as a component of the parasympathetic nervous system, has a role in IBS patients mediating peripheral inflammation [25]. Hod et al. showed that increased serum cholinesterase activity is associated with IBS diarrhea-predominant symptoms through decreased inflammatory inhibition [26]. Further research is needed to determine the specific factors altered in IBS patients and their role in SMA hemodynamic alterations.

There is no previous study on Doppler variables of cystic and superior mesenteric arteries in IBS patients, so we can't compare the results and come to an exact conclusion. In the study by Hansen et al. having meals reduced the mean RI of SMA in healthy individuals, which increases the blood flow to the bowel helping in the better digestive functioning of the gastrointestinal system [27]. We couldn't find the exact explanation for the absent reduced postprandial RI of SMA in IBS patients, but, maybe the high resistance of vessels and resultant hypoxia and ischemic processes are one of the culprits of pain and discomfort after having meals in these patients.

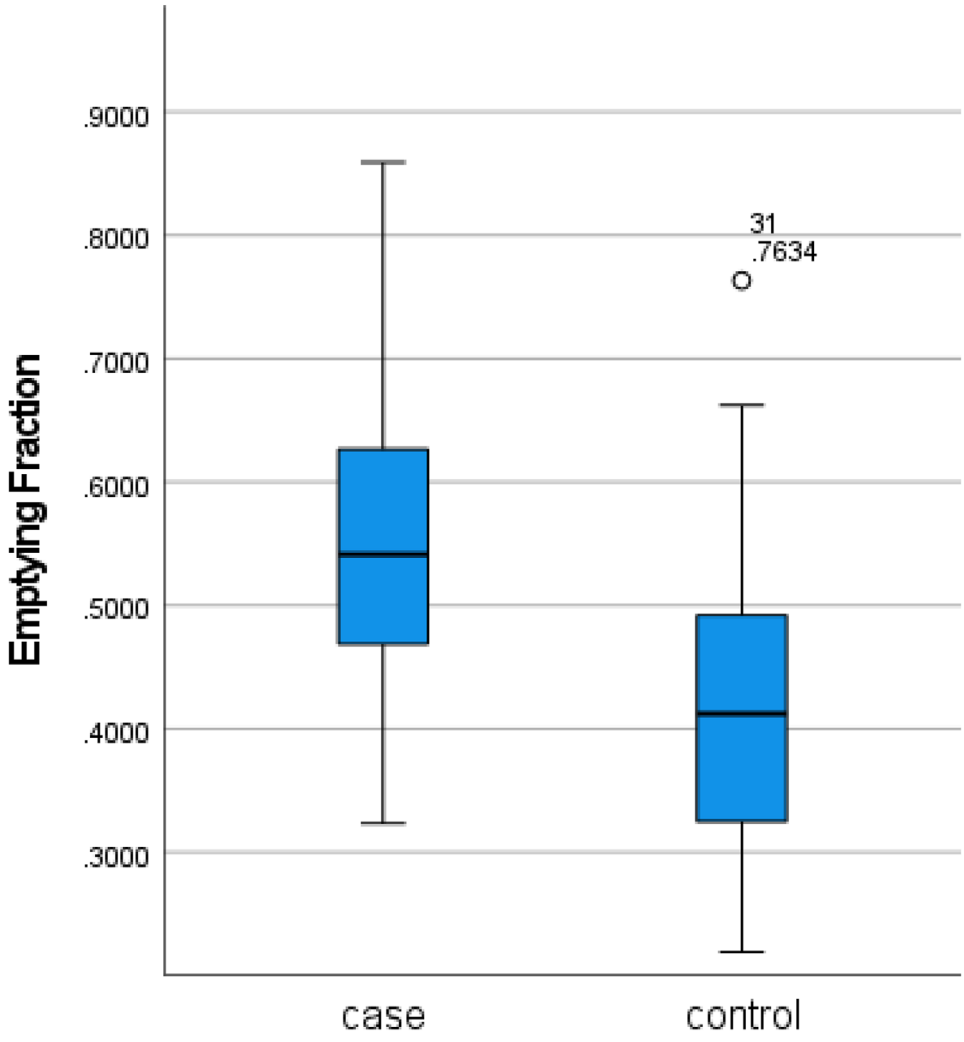

Figure 7. Comparison of gallbladder emptying fraction in cases and controls.

Table 3. Difference of measured and calculated variables for each group before and after meal.

		case		control		
		Mean	S.D	Mean	S.D	*p*-value
Gallbladder volume	Fasting	24.7444	8.8547	29.7375	9.6492	0.125
	After meal	11.3367	5.6653	16.9000	6.1583	0.010
Gallbladder wall thickness	Fasting	2.0439	0.3310	1.6306	0.2832	0.0005
	After meal	2.8361	0.4216	2.3963	0.3698	0.003
Cystic artery resistance index	Fasting	0.6994	0.0769	0.7125	0.0687	0.607
	After meal	0.6533	0.0864	0.6588	0.0726	0.845
Superior mesenteric artery resistance index	Fasting	0.81	0.06	0.85	0.04	0.016
	After meal	0.79	0.06	0.80	0.05	0.693
Gallbladder emptying fraction		0.5573	0.1339	0.4259	0.1417	0.009
Fraction of change in gallbladder wall thickness		0.41	0.27	0.50	0.30	0.387
Fraction of change in cystic artery resistance index		−0.06	0.12	−0.07	0.15	0.941
Fraction of change in Superior mesenteric artery resistance index		−0.01	0.11	−0.06	0.05	0.100

*S.D: Standard deviation.

There is a scarcity of research endeavors exploring gallbladder function in patients diagnosed with IBS, and the reports that do exist display inconsistencies. Several studies have established that there is no discernible distinction between the function of the gallbladder in individuals with IBS and those who are regarded as healthy volunteers [28, 29]. The initial study that assessed the motor function of the gallbladder in twelve patients with IBS revealed that fasting gallbladder volume (FGV) and residual volume after maximum contraction were greater in IBS patients compared to controls [30]. However, the maximum percentage of gallbladder emptying and the time required for maximum contraction were similar to those seen in the control group [30]. Another study conducted by Sood et al. [13] demonstrated increased FGV levels in IBS cases, along with lower EF values, in comparison to healthy individuals. Furthermore, no remarkable difference was detected in FGV or EF of the gallbladder between patients with C-IBS or diarrhea-predominant IBS (D-IBS) [13]. Gultier et al. observed that FGV did not exhibit any significant differences between the IBS cases and the controls [31]. However, the EF of the gallbladder was substantially greater in the IBS-affected subjects when compared to the healthy controls, similar to the findings of the present study and Güçlü et al.'s [22]. In addition, there were not any

notable differences between the FGV and the EF of the gallbladder between the two distinct subgroups of individuals diagnosed with IBS [31]. On the other hand, O'Kane et al. [32] have reported a tendency towards a decline in the bile ejection rate and a delay in the emptying of the gallbladder in C-IBS patients.

It is commonly acknowledged that the regulation of gallbladder function is controlled by neuroendocrine hormones. Also, the cholinergic system, which is part of the autonomic nervous system, plays a dual role in gallbladder function by assisting with contraction during food intake and digestion while also preventing increased gallbladder tonicity during the inner digestive phase [33, 34]. Typically, the process of gallbladder emptying is under the control of both neural and hormonal mechanisms. During gallbladder contraction, the Oddi sphincter must simultaneously relax to allow for the discharge of bile [14, 35], and defects in this coordinated process may interfere with proper gallbladder emptying. Cholecystokinin (CCK) functions as the primary physiologic mediator of gallbladder contraction and relaxation of the sphincter of Oddi. CCK has a fundamental role in not only stimulating pancreatic and biliary secretions but also in the regulation of gastrointestinal motility by inhibiting gastric emptying and colonic transit as CCK receptors can be found throughout the gastrointestinal tract [35]. Studies have indicated that individuals diagnosed with IBS exhibit an intensified and extended release of CCK post-meal, and this has been suggested as a contributing factor to the pathophysiology of IBS [36–38]. Furthermore, it has been observed that in contrast to healthy subjects, patients with C-IBS show an increased sensitivity of their gallbladders to CCK infusion, while those with D-IBS show a reduced response [39]. Studies have indicated that small bowel transit is slower in individuals with C-IBS [40], whereas it is faster in those with D-IBS [41]. Consequently, CCK-1 receptor antagonists are currently in the developmental stage as a treatment option for C-IBS. Clinical investigations have demonstrated that CCK-1 receptor antagonists can boost gastric emptying and suppress gallbladder contraction, which can hasten the transit of waste through the colon in healthy volunteers and individuals with IBS [42, 43]. Another crucial factor in the regulation of gallbladder emptying is the autonomic nervous system. Several studies have proposed that the autonomic nervous system could affect visceral sensations and the modulation of gastrointestinal motility through changes in afferent reflex mechanisms [11]. The augmented occurrences of dysmenorrhea, respiratory symptoms, and urinary frequency observed in individuals with IBS indicate potential autonomic instability in these patients [6, 44].

To limit the potential confounding factors in our study we excluded many patients with different medical conditions and comorbidities. Despite seeing rather consistent results in our data, generalizability of our study is very limited and future studies with multicenter design and larger sample sizes are required to evaluate this subject in different subtypes of IBS and for patients with other coexisting conditions. Furthermore, the observed response might be affected by our choice of meal and different substances might elicit varying responses. Another point to improve in future studies would be inclusion of colonic transit study, CCK levels in serum and HIDA scan assessment of gallbladder in the study design. This would better help control for and assess other variables that could potentially affect gallbladder function.

Conclusion

There is alteration in gallbladder motility, its emptying fraction and cystic artery resistance, and blood flow to the gastrointestinal tract in IBS. Further research regarding etiological factors mediating these disturbances can be helpful in developing therapeutic strategies for these patients.

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Disclosure statement

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