

Comorbid disorders of esophagus in patients with irritable bowel disease

Hossam Mahmoud Abdelwahab^{a*}, Bishoy Shehata^a, Nabila Faiek Amin Mousa^a^aInternal Medicine Department, Faculty of Medicine, Assiut University, Assiut, Egypt**Abstract**

Background: Irritable bowel syndrome (IBS), Gastroesophageal reflux disease and functional oesophageal disorders may overlap and share the same pathophysiologic mechanisms.

Objectives: The purpose of the study is to assess the incidence of variant esophageal disorders that can overlap IBS using different diagnostic modalities.

Patients and methods: In this study, 100 IBS patients with esophageal symptoms were examined in the Department of Gastroenterology. All underwent esophagogastroduodenoscopy, ECG, barium swallow, abdominal ultrasound, esophageal motility studies, and 24-hour PH monitoring. Diagnosis of IBS and evaluation of esophageal symptoms was established according to Rome IV criteria.

Results: 27% of cases were diagnosed as ERD (Erosive Reflux Disease) depending on the presence of reflux esophagitis in upper endoscopy, 24% of cases were diagnosed as NERD (Non-Erosive Reflux Disease) depending on the absence of esophagitis in upper endoscopy and presence of acid reflux in 24-hour pH monitoring. While in 49% of cases, upper endoscopy and 24-hour pH-monitoring were normal, they were diagnosed as Functional Esophageal Disorders (FED). In our study, FED was the most prevalent among different IBS subtypes. Female gender was most predominant in different IBS subtypes except IBS-C (Irritable Bowel Syndrome - Constipation). FED was prevalent at a younger age than NERD and ERD. However, NERD and ERD were prevalent at higher BMI (Body Mass Index) than FED.

Conclusion: There is a high frequency of overlap between IBS and variant esophageal disorders i.e. ERD, NERD, and FED as they share many pathophysiological mechanisms.

Keywords: Irritable bowel syndrome; Esophageal reflux; Functional esophageal disorders.

*Correspondence: h.mahmoud@aun.edu.eg

DOI: 10.21608/svuijm.2024.261138.1771

Received: 1 November, 2023.

Revised: 17 November, 2023.

Accepted: 24 November, 2023.

Published: 10 February, 2024

Cite this article as: Hossam Mahmoud Abdelwahab, Bishoy Shehata, Nabila Faiek Amin Mousa (2024). Comorbid disorders of esophagus in patients with irritable bowel disease. *SVU-International Journal of Medical Sciences*. Vol.7, Issue 1, pp: 294-303.

Introduction

In the practice of gastroenterologists, IBS is the most common functional condition. The frequency of it in the general population is about 9.2% (Oka et al.,2020). Its frequency in women is more than in men and in young is more than in population older than 50 years (Chang ,2004); (Lovell & Ford, 2012).

Gastroesophageal reflux disease (GERD) is one of the common gastrointestinal diseases (Boulton & Dettmar, 2022). It can be classified as ERD (Erosive Reflux Disease) and NERD (Non-Erosive Reflux Disease) depending on endoscopic picture (Fass , 2007). According to Rome IV, there might be difficult to differentiate between GERD and reflux hypersensitivity or functional heartburn. However, esophageal pH monitoring can help to differentiate between these three disorders. In ones who have abnormal acid exposure with or without symptom–reflux association, the diagnosis of GERD can be done. Also, the diagnosis can be functional heartburn, if there is normal acid exposure and negative symptom–reflux association. If there is normal acid exposure associated with positive symptom–reflux association, those patients can be diagnosed with reflux hypersensitivity (Aziz et al.,2016).

It has been shown in some studies, that a patient's symptoms from several functional gastrointestinal disorders may overlap (Mayer et al.,2015). The frequency with which esophageal problems manifest in IBS patients has been assessed by different researchers. So, they are found in 15–80% of cases, based on the different publications (Morozova et al.,2020; Nedelcut et al.,2018).According to the results of a population study, a combination of IBS and GERD was noted in 21% of cases (Lee et al.,2019). In another study, it has been noted that In 77% of instances, IBS was associated with functional heartburn, and in 33% of cases, it was linked to GERD and a hypersensitive oesophagus (also known as heartburn associated with reflux). (De Bortoli et al.,2016). There are also many epidemiological studies that show the common presence of IBS and GERD (Pimentel et al.,2002; Talley et al.,2003).Therefore, these disorders may share a similar pathophysiologic mechanism. One of the theories that explain this association suggests that there is an overlap between IBS and GERD. This

theory depends on the presence of certain genetic sequences and similar motility disturbances in patients with IBS and GERD (Dickman et al.,2006; Lembo et al.,2007).

The other theory says that IBS symptoms are part of GERD manifestations. This is supported by the improvement of lower abdominal symptoms after medical or surgical treatment of GERD (Guillemot et al.,2005). The pathophysiology of functional esophageal disorders may result from visceral hypersensitivity and hypervigilance (Sperber et al.,2021).

Traditionally, the diagnosis of a combination of functional disorders of the esophagus and intestine was based on data obtained from X-ray and endoscopic methods. However, modern research has shown the importance of using 24h pH monitoring in this group of patients. Thus, many authors have noted the undoubted advantages of this method in the diagnosis of esophageal disorders (Nedelcut et al.,2018; Triadafilopoulos et al.,2018). Unfortunately, there are very few publications on this subject, and the data collected from them is quite confusing. (Garros et al.,2016; Frazzoni et al.,2018), which indicates the need to continue research in this direction.

Patients and Methods

This study included 100 patients [of which 45 were male and 55 females] with an established diagnosis of IBS. All of them were complaining from esophageal symptoms in the form of heartburn, Globus sensation, non-cardiac chest pain, dysphagia, and regurgitation. None of them had any of exclusion criteria listed below.

IBS diagnosis has been based on the IV revision of the Rome criteria which is recurrent abdominal pain on average at least one day a week in the last three months, associated with 2 or more of the following criteria: association with the change in frequency of stool, form of stool, and/or related to defecation (Lacy et al.,2016).

All patients underwent esophagogastroduodenoscopy with esophageal biopsies for exclusion of oesinophilic esophagitis (PENTAX:EG-29I10, EG-34I10), ECG, barium swallow, abdominal ultrasound, esophageal motility studies (Solar™ GI High-Resolution Manometry), 24-hour PH monitoring and

symptom-associated probability (SAP) was calculated depending on the result of pH monitoring. (chongqing jinshan science & technology (group) co. ltd, MMs-0Z1P).

Criteria for excluding patients in the study: patients who refused to contribute to this study; history of thoracic, esophageal, or gastric surgery; the presence of duodenal or gastric ulcer or cancer on upper endoscopy; eosinophilic esophagitis; conditions that prevent the installation of a nasal gastric tube (nasopharyngeal malformation, severe lumen-facial trauma); pregnancy and breastfeeding; as well as mental disorders state and disability.

Functional esophageal disorders were assessed according to the IV revision of the Rome criteria. This includes functional chest pain, functional heart pain, reflux hypersensitivity, Globus (**Aziz et al.,2016**).

Consent has been obtained from the participant patients . all study protocols were approved by the institutional review board of the Faculty of Medicine Assiut university under IRP number 17101298.

Statistical analysis

Statistical analysis: SPSS (statistical package for social science; SPSS Inc., Chicago, IL, USA) version 22 was used for all statistical computations. When data were not normally distributed, they were statistically represented using the mean \pm standard deviation (\pm SD), or in terms of median and range, frequencies (number of instances), and relative frequencies (percentages) as applicable. Comparison of quantitative variables was done using the ANOVA test or Kruskal Wallis test according to the distribution of studied variables. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. The P-value is always 2-tailed sets significant at 0.05 levels.

Results

Our study involved 100 IBS patients aged 21 to 60 years complaining of esophageal symptoms and did not have any of the exclusion criteria including eosinophilic esophagitis which excluded by endoscopy and biopsy. Symptoms of IBS among the studied participants are given in (**Table.1**).

Table 1. Symptoms of IBS among the studied participants

IBS symptoms	N	(%)
• Colicky abdominal pain	100	(100.0)
• Subtypes of IBS	100	(100.0)
▪ Diarrhea	38	(38.0)
▪ Constipation	34	(34.0)
▪ Mixed	28	(28.0)
• Related to defecation	57	(57.0)

Qualitative data are presented as number (percentage)

The results of the study revealed that 27 patients (27%) had ERD that was diagnosed by upper endoscopy as visible breaks on lower esophagus. However, no pathology was detected during upper endoscopy in 73 patients (73%). when conducting a daily pH monitoring on those 73 patients, 24 patients (24%) were found to have large reflux and increased exposure to acids in the esophagus (high DeMeester score). This made it possible to diagnose this group of patients as NERD. In the last 49 patients (49%) who have low DeMeester scores, they were diagnosed as having FED.

In those 49 patients who diagnosed as FED, when symptoms-associated probability (SAP) was calculated, it has been positive in 9 patients and negative in 40 patients. Those 9 patients with positive SAP were diagnosed as having hypersensitivity to reflux. In patients with negative SAP, the diagnosis was established based on the leading symptom: functional heartburn was diagnosed in 27 patients complaining mainly from heartburn, functional Globus in 9 patients with a lump sensation in throat, and functional chest pain in 4 patients with non-cardiac chest pain (**Fig.1**).

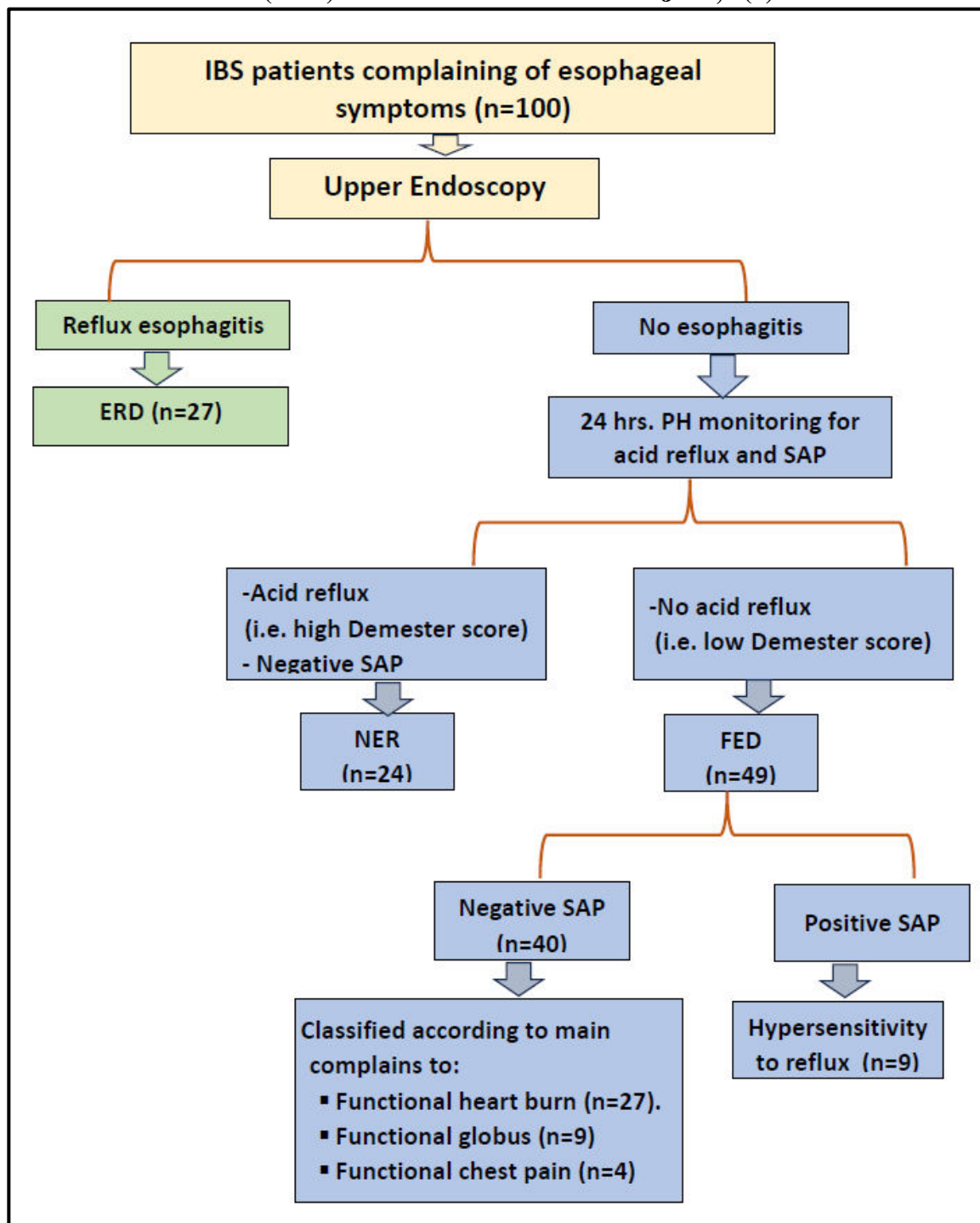


Fig.1. Approach to find diagnosis of IBS patients complaining of esophageal symptoms.

ERD: Erosive reflux disease, NER: Non erosive reflux, SAP: Symptoms associated probability
, FED: Functional esophageal disorders

So, as a result of the comprehensive examination, including upper endoscopy, 24h pH monitoring, and esophageal motility studies, it was revealed that comorbid disorders of the esophagus in patients with IBS were: ERD in 27%

of cases, NERD in 24%, FED - in 49% (while in 27% of cases they are represented by functional heartburn, in 9% by hypersensitivity to reflux, in 9% by a lump in the throat, and in 4% by functional chest pain; (**Fig.2**).

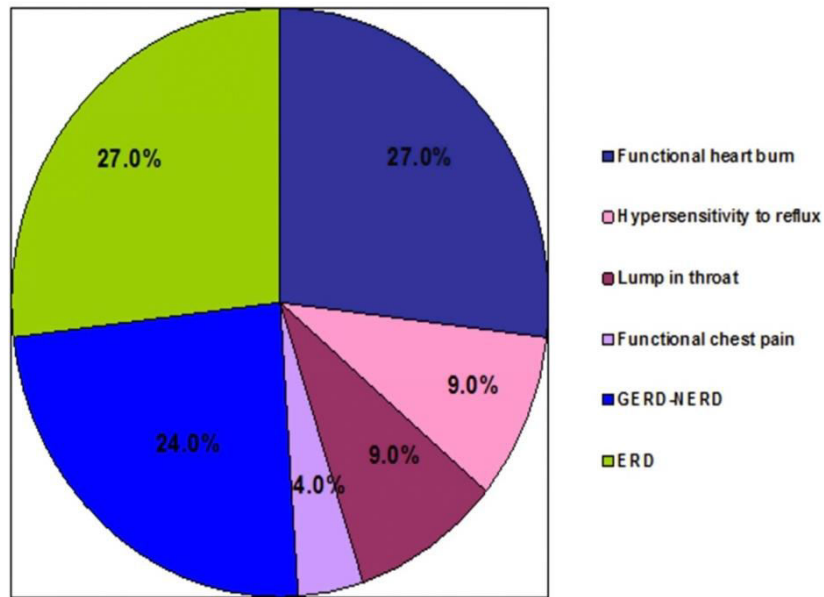


Fig.2 .Pie graph showing the distribution of the final diagnosis of esophageal disorders among the studied IBS cases

Laboratory details of the studied 100 patients with IBS showed the mean number of WBCs, HB, and PLTs was 6.42 ± 1.59 , 13.54 ± 1.15 , 299.18 ± 62.74 respectively. The mean number of chemistry was 4.03 ± 1.30 mmol/L

for BUN, 77.08 ± 17.10 $\mu\text{mol/L}$ for creatinine, 22.06 ± 17.86 U/L for AST, 28.61 ± 36.71 U/L for ALT, 139.62 ± 3.06 mEq/L for sodium, and 4.10 ± 0.35 mEq/L for potassium. The mean number of ESR was 4.14 ± 2.29 . (**Table. 2**)

Table 2. Laboratory details of the studied 100 patients with IBS

Laboratory details	Mean \pm SD	Median (range)
CBC		
▪ WBCs	6.42 ± 1.59	6.1 (3.7 - 10.0)
▪ HB	13.54 ± 1.15	13.5 (12.0 - 16.0)
▪ PLTs	299.18 ± 62.74	314 (158 – 511)
Kidney function		
▪ Urea	4.03 ± 1.30	3.80 (1.70 - 7.50) (mmol/l)
▪ Creatinine	77.08 ± 17.10	78.0 (45.0 - 120.0) (umol/l)
Liver test profile		
▪ AST	22.06 ± 17.86	18.0 (8.0 - 111.0) (U/L)
▪ ALT	28.61 ± 36.71	21.0 (10.0 - 254.0) (U/L)
▪ ALP	96.59 ± 104.40	80.0 (40.0 - 804.0) (U/L)
Coagulation profile		
▪ PT	11.55 ± 1.07	11.4 (10.0 - 15.0)
▪ PC	99.73 ± 13.98	98.0 (58.0 - 131.0)
▪ INR	0.93 ± 0.17	1.0 (0.60 - 1.30)
Electrolytes		
▪ Na	139.62 ± 3.06	140.0 (128.0 - 145.0)

▪ K	4.10 ± 0.35	4.1 (3.5 - 4.9) (mEq/L)
Inflammatory markers		
▪ ESR	4.14 ± 2.29	4 (1 – 10)
▪ CRP, n (%)		
- Negative	100 (100.0)	
Stool analysis, n (%)		
- Normal	100 (100.0)	

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage).

As regard different types of IBS either IBS-D (irritable bowel syndrome with diarrhea), In IBS-C (irritable bowel syndrome with constipation), IBS-M (irritable bowel syndrome with mixed diarrhea and constipation), the results revealed that FED show increased occurrence in different types of IBS with significant difference between these types (P Value = 0.0039). Also, It

is noted slight increase in female gender in patients with IBS-D and IBS-C when comparing with IBS-M making significant difference regarding sex (P Value = 0.003). Age of studied groups of IBS and Body Mass Index (BMI) show no significant difference between our patients. (**Table.3**)

Table 3. Demographic and clinical data for all studied patients (n=100)

Variable name	IBS-D (n=38)	IBS-C (n=34)	IBD-M (n=28)	P Value
Age (years)				0.844
• Mean ± SD	36.50 ± 12.22	35.53 ± 9.49	34.96 ± 10.51	
• Median (range)	39 (13 – 54)	33 (23 – 59)	32 (22 – 60)	
BMI (kg/m²)				0.104
• Mean ± SD	27.36 ± 4.97	26.17 ± 3.88	25.04 ± 3.99	
• Median (range)	27.9 (18 – 36)	25.7 (19.5 – 33.2)	23.6 (20 – 32.4)	
Sex				0.003*
• Male	10 (26.3)	16 (47.1)	19 (67.9)	
• Female	28 (73.7)	18 (52.9)	9 (32.1)	
Final diagnosis				0.039*
• FED	18 (47.4)	14 (41.2)	17 (60.7)	
• NERD	14 (36.8)	8 (23.5)	2 (7.1)	
• ERD	6 (15.8)	12 (35.3)	9 (32.1)	

IBS-D: irritable bowel syndrome with diarrhea. IBS-C: irritable bowel syndrome with constipation. IBS-M: irritable bowel syndrome with mixes diarrhea and constipation. BMI: body mass index. FED: functional esophageal disease. NERD: non-erosive reflux disease. ERD: erosive reflux disease. Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage). Significance defined by p<0.05.(ANOVA test& Chi-square test)

It is worth mentioning that there was statistically higher age in ERD than NERD or FED groups. When comparing them regarding BMI and sex, there is no significant difference. It

was noted also that various esophageal symptoms show no significant difference between these groups with slight increase of heartburn symptoms. (**Table. 4**)

Table. 4. Comparison of the studied demographic and clinical data according to the final diagnosis of the IBS studied participants (n=100)

Variable name	FED (n=49)		NERD (n=24)		ERD (n=27)		P Value
Age (years)							0.002*
• Mean \pm SD	31.88 \pm 10.45		38.54 \pm 9.55		40.26 \pm 10.21		
• Median (range)	32 (13 – 60)		36 (27 – 54)		42 (26 – 59)		
BMI (kg/m²)							0.005*
• Mean \pm SD	24.93 \pm 4.41		27.58 \pm 3.90		27.67 \pm 4.21		
• Median (range)	23.7 (18 – 36)		26.7 (21 – 33)		28.4 (19.5 – 33.5)		
Sex							0.051
• Male	16	(32.7)	14	(58.3)	15	(55.6)	
• Female	33	(67.3)	10	(41.7)	12	(44.4)	
Esophageal symptoms							
• Heartburn	36	(73.5)	22	(91.7)	23	(85.2)	0.143
• Globus sensation	9	(18.4)	6	(25.0)	8	(29.6)	0.517
• Non cardiac chest pain	4	(8.2)	0	(0.0)	4	(14.8)	0.126
• Dysphagia	7	(14.3)	4	(16.7)	6	(22.2)	0.695
• Regurgitation	35	(71.4)	19	(79.2)	21	(77.8)	0.717

BMI: body mass index. Quantitative data are presented as mean \pm SD and median (range), qualitative data are presented as number (percentage). Significance defined by $p < 0.05$. (Anova test & Chi-square test)

Discussion

In accordance with the set goal, esophageal disorders were studied in IBS patients aged 21 to 60 years. From 2020 to 2022 in the Department of Gastroenterology at Assiut university hospital; 100 patients of IBS were examined. For esophageal symptoms, 27% OF them had erosive reflux disease, this can be correlated with previous research that showed the prevalence of gastroesophageal reflux-type symptoms in IBS was 42% (**Lovell and Ford ,2012**).

The study of esophageal disorders in IBS patients revealed that ERD was detected in 27% of IBS patients with esophageal symptoms. NERD was diagnosed in 24% of patients. It is noted that NERD in IBS can manifest itself not only with heartburn, but also with Globus sensation, regurgitation, dysphagia, or chest pain of non-cardiac origin. The diagnosis of FED was established in 49% of patients (27% of them

represented by functional heartburn, 9% by hypersensitivity to reflux, 9% by a lump in the throat and 4% by functional chest pain). The revealed spectrum of changes suggests that failure of proton pump inhibitor therapy in part of patients with GERD symptoms in combination with IBS may be due to its intersection with FED, the treatment of which has not yet been developed.

Previous research showed that IBS/NERD overlap was 42% and IBS/ERD overlap was 38% (**Martinucci et al.,2011**). Other study revealed overlapping between IBS and functional heartburn is more frequent than IBS/GERD overlapping (**De Bortoli et al.,2016**). **Neumann et al (2008)** investigated the frequency of IBS symptoms in GERD patients subdivided into Barrett's oesophagus (BE), NERD, and ERD. They found that IBS was prevalent along the whole GERD range, with 44% in ERD, 63% in NERD, and 21%

in Barrett's esophagus (BE) patients having it.. **Martinucci et al (2011)** observed that IBS overlaps with functional heart burn (FH), ERD, and NERD with a rate of 66%, 17%, and 39.5% respectively. Data collected from our research and results from previous studies, one can conclude that IBS overlaps with ERD, NERD, and FED. Also, this overlapping can be more frequent between IBS/ FED than IBS/ERD and IBS/NERD. However, there are some data from southeast Asia showed that IBS symptoms have had an association with NERD, but not with ERD (**Nam et al.,2013**). This may be due to differences in risk factors and demographic distribution of esophageal disorders. **Nedelcut et al** showed that FEDs overlapping IBS was the most in FH, then Functional globus, and less in Functional chest pain in athletes (**Nedelcut et al.,2018**). The importance of these overlaps appears in treatment such as when **Monnikes et al** treated patients with IBS/ERD with pantoprazole, they observed only 4.7% continued to have IBS symptoms (**Mönnikes et al.,2012**). Some authors demonstrated treatment with combined lactulose and itopride hydrochloride Among individuals suffering from combined GERD and IBS-C leads to improving GERD symptoms and esophageal PH normalization (**de Bortoli et al.,2014**).

In studying the prevalence of esophageal disorders among IBS subtypes presenting with esophageal symptoms, FED is the most prevalent among different IBS subtypes. However, NERD was the second most prevalent esophageal disorder in IBS-D and the last prevalent in IBS-C and IBS-M after FED and ERD.

Analysis of gender effect on the studied IBS subtypes showed a significant predominance of female gender in IBS-D and IBS-C. However, the male gender was predominant in IBS-M. In comparison with most previous epidemiological data that showed that the female gender has been predominant among different IBS subtypes (**Shinozaki et al.,2008; Houghton et al.,2016**). This needs further researches.

An attempt was made to analyze the effect of gender, age, and BMI differences on the prevalence of esophageal disorders in patients with IBS. Analysis of our data demonstrated the absence of gender differences in the prevalence of esophageal disorders in patients with IBS, since

the significance of differences between all groups was statistically insignificant. However, **Nedelcut et al (2018)** showed FEDs/IBS overlap is more in female than males in athletes. Also, Some authors demonstrated combined GERD and IBS-C is more common in females (**de Bortoli et al.,2014**). This point needs more research. In our research, there was a significant difference in the age where FED was prevalent at a younger age than NERD and ERD. previous research shows that GERD occurs more predominant at middle and older age (**Eusebi et al.,2018; Ness-Jensen et al.,2012**). Although, there are increases in the prevalence of GERD in younger ages in the last decades e.g. people aged range 30-39 (**Yamasaki et al.,2018**). According to the calculated BMI, NERD and ERD were prevalent at higher BMI than FED in our study. Previous research showed that GERD is directly related to obesity (**Chang et al,2014**). Also, the prevalence of GERD increases as BMI increases (**Zvenyach and Pickering 2017**).

Conclusion

There is a high frequency of overlap between IBS and variant esophageal disorders i.e. ERD, NERD, and FED based on results of upper endoscopy, esophageal motility studies, and 24h pH monitoring. Moreover incidence of FED was higher than ERD or NERD in IBS patients. This can be explained by many pathophysiological mechanisms. It is recommended to do similar studies on larger numbers of patients.

Declarations

- Ethics approval and consent to participate: All study protocols were approved by the institutional review board of the faculty of medicine, Assiut University, Egypt under the IRP number 17101298. Consent has been obtained from the participant patients.
- Consent for publication: "Not applicable".
- Availability of data: All data used and analyzed during this study are available from the corresponding author on reasonable request.
- Competing interests: The authors declare that they have no competing interests.

- Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
- Authors' contributions:-
 - DR. Hossam Mahmoud Abdelwahab: Conceived and designed the analysis, Contributed data and analysis tools.
 - Bishoy Shehata: Collected data, performed the analysis.
 - Prof. Nabila Faiek Amin Mousa: Conceived and designed the analysis, wrote the paper.
 - All authors read and approved the final manuscript.
- Acknowledgements: "Not applicable"

References

- **Oka P, Parr H, Barberio B, Black CJ, Savarino E V, Ford AC (2020).** Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *lancet Gastroenterol Hepatol.* 5(10):908–17.
- **Chang L(2004).** Epidemiology and quality of life in functional gastrointestinal disorders. *Aliment Pharmacol Ther.* 20:31–9.
- **Lovell RM, Ford AC (2012).** Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol.* 10(7):712–21.
- **Boulton KHA, Dettmar PW(2022).** A narrative review of the prevalence of gastroesophageal reflux disease (GERD). *Ann Esophagus.* 5(7).
- **Fass R(2007).** Erosive esophagitis and nonerosive reflux disease (NERD). comparison of epidemiologic, physiologic, and therapeutic characteristics. *J Clin Gastroenterol.* 41(2):131–7.
- **Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F(2016).** Esophageal disorders. *Gastroenterology*,150(6):1368–79.
- **Mayer EA, Labus JS, Tillisch K, Cole SW, Baldi P(2015).** Towards a systems view of IBS. *Nat Rev Gastroenterol Hepatol.* 12(10):592–605.
- **Morozova YN, Pogromov AP, Mnatsakanyan MG, Tashchyan O V, Kolosova KY(2020).** Esophageal disorders in patients with irritable bowel syndrome. *Ter Arkh.* 92(2):19–23.
- **Nedelcut S, Leucuta D-C, Dumitrascu DL (2018).** Overlapping of functional esophageal disorders and irritable bowel syndrome, in musicians and athletes. *Rev Bras Med do Esporte.* 24:69–72.
- **Lee SY, Lee KJ, Kim SJ, Cho SW(2009).** Prevalence and risk factors for overlaps between gastroesophageal reflux disease, dyspepsia, and irritable bowel syndrome: a population-based study. *Digestion*,79(3):196–201.
- **De Bortoli N, Frazzoni L, Savarino E V, Frazzoni M, Martinucci I, Jania A, et al (2016)** Functional heartburn overlaps with irritable bowel syndrome more often than GERD. *Off J Am Coll Gastroenterol ACG.* 111(12):1711–7.
- **Pimentel M, Rossi F, Chow EJ, Ofman J, Fullerton S, Hassard P, et al(2002).** Increased prevalence of irritable bowel syndrome in patients with gastroesophageal reflux. *J Clin Gastroenterol.* 34(3):221–4.
- **Talley NJ, Dennis EH, Schettler-Duncan VA, Lacy BE, Olden KW, Crowell MD(2003).** Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea. *Am J Gastroenterol.* 98(11):2454–9.
- **Dickman R, Feroze H, Fass R (2006).** Gastroesophageal reflux disease and irritable bowel syndrome: a common overlap syndrome. *Curr Gastroenterol Rep.* 8(4):261–5.
- **Lembo A, Zaman M, Jones M, Talley NJ(2007).** Influence of genetics

on irritable bowel syndrome, gastro-oesophageal reflux and dyspepsia: a twin study. *Aliment Pharmacol Ther.*,25(11):1343–50.

- **Guillemot F, Ducrotté P, Bueno L(2005).** Prevalence of functional gastrointestinal disorders in a population of subjects consulting for gastroesophageal reflux disease in general practice. *Gastroentérologie Clin Biol.*,29(3):243–6.
- **Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al (2021).** Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. *Gastroenterology*,160(1):99–114.
- **Triadafilopoulos G, Zikos T, Regalia K, Sonu I, Fernandez-Becker NQ, Nguyen L, et al (2018).** Use of esophageal pH monitoring to minimize proton-pump inhibitor utilization in patients with gastroesophageal reflux symptoms. *Dig Dis Sci.*,63(10):2673–80.
- **Garros A, Mion F, Marjoux S, Damon H, Roman S (2016).** Factors associated with nonresponse to proton pump inhibitors therapy in patients referred for esophageal pH-impedance monitoring. *Dis Esophagus.*,29(7):787–93.
- **Frazzoni L, Frazzoni M, de Bortoli N, Tolone S, Martinucci I, Fuccio L, et al (2018).** Critical appraisal of Rome IV criteria: hypersensitive esophagus does belong to gastroesophageal reflux disease spectrum. *Ann Gastroenterol.*,31(1):1.
- **Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al (2016).** Bowel disorders. *Gastroenterology*,150(6):1393–407.
- **Lovell RM, Ford AC (2012).** Prevalence of gastro-esophageal reflux-type symptoms in individuals with irritable bowel syndrome in the community: a meta-analysis. *Off J Am Coll Gastroenterol ACG*,107(12):1793–

801.

- **Martinucci I, De Bortoli N, Di Fluri G, Mismas V, Gambaccini D, Leonardi G, et al (2011).** Diagnosis of NERD in a population of patients with and without IBS: a pH-MII study. *Dig Liver Dis.*,43):S168.
- **Neumann H, Mönkemüller K, Kandulski A, Malfertheiner P(2008).** Dyspepsia and IBS symptoms in patients with NERD, ERD and Barrett's esophagus. *Dig Dis.*,26(3):243–7.
- **Nam SY, Ryu KH, Park BJ(2013).** Irritable bowel syndrome is associated with gastroesophageal reflux symptom but not erosive esophagitis. *J Neurogastroenterol Motil.*,19(4):521.
- **Mönnikes H, Schwan T, Van Rensburg C, Straszak A, Theek C, Sander P, et al(2012).** Randomised clinical trial: sustained response to PPI treatment of symptoms resembling functional dyspepsia and irritable bowel syndrome in patients suffering from an overlap with erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.*,35(11):1279–89.
- **de Bortoli N, Martinucci I, Savarino E, et al (2014).** Proton pump inhibitor responders who are not confirmed as GERD patients with impedance and pH monitoring: who are they? *Neurogastroenterol Motil.*,26:28–35
- **Shinozaki M, Fukudo S, Hongo M, Shimosegawa T, Sasaki D, Matsueda K, et al (2008).** High prevalence of irritable bowel syndrome in medical outpatients in Japan. *J Clin Gastroenterol.*,42(9):1010–6.
- **Houghton LA, Heitkemper M, Crowell MD, Emmanuel A, Halpert A, McRoberts JA, et al (2016).** Age, gender, and women's health and the patient. *Gastroenterology*,150(6):1332–43.
- **Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC (2018).** Global

prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut*,67(3):430–40.

- **Ness-Jensen E, Lindam A, Lagergren J, Hveem K(2012).** Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: a prospective population-based cohort study, the HUNT study. *Gut*,61(10):1390–7.
- **Yamasaki T, Hemond C, Eisa M,**
-

Ganocy S, Fass R (2018). The changing epidemiology of gastroesophageal reflux disease: are patients getting younger? *J Neurogastroenterol Motil.*,24(4):559.

- **Chang P, Friedenberg F. Obesity and GERD (2014).** *Gastroenterol Clin.*,43(1):161–73.
- **Zvenyach T, Pickering MK(2017).** Health care quality: measuring obesity in performance frameworks. *Obesity*,25(8):1305–12.