

Association Of Functional Dyspepsia With Depression; Gut-Brain Axis And Mental Health

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Abstract

Objective: The current study aimed to determine the frequency and associations of depression in patients with & without Functional dyspepsia.

Method: This case-control study was conducted at the Dept. of Medicine, RIHS, Islamabad (Jan-June 2023) after ethical approval. Cases & controls (150 each) were selected from outdoor clinics according to inclusion/exclusion criteria & informed consent was obtained. The previous medical record (including findings of upper GI Endoscopy) was reviewed. Selected cases and controls were asked questions from DSM-IV Criteria of Depression. Data was analyzed by SPSS with significant $p < 0.05$.

Results: There were 72(48 %) males & 78(52%) females in each group. Mean age was 43.7 ± 13.79 years (FD patients) vs. 46.24 ± 15.27 years (controls). Mean BMI was 24.84 ± 4.18 (FD patients) vs. 25.38 ± 4.52 (controls). There was no significant difference in gender, marital status & background of both groups. There was significantly more depression in FD patients Vs. controls ($p < 0.05$). Among FD patients 57(38%) had major depression, 41(27.33%) minor depression & 52(34.66%) were not depressed. Among controls 41(27.33%) had major depression, 30(20%) minor depression & 79(52.66%) not depressed. Among FD patients, depression wasn't associated with age. Controls above 40 years had significantly higher major depression ($p < 0.001$). Female gender & unemployment were significantly associated with depression in both groups ($p < 0.05$). 49.3% of FD patients were employed vs. 67.3% of controls.

Conclusion: The adjustment for gender, age, marital status, BMI, background & monthly income confirmed the association between Functional dyspepsia & depression. Female gender, unemployment and low educational status are possible risk factors for depression among FD patients. As compared to normal healthy people, FD patients are likely to have depression at a younger age.

Keywords: Functional dyspepsia. Depression. DSM-IV Criteria.

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1. Introduction

Dyspepsia is a frequently observed symptom in clinical practice having multifactorial pathophysiology and a wide differential diagnosis. Among patients presenting with upper abdominal discomfort, Functional dyspepsia is the most commonly encountered diagnosis.¹ It is also labelled as a non-ulcer dyspepsia or essential dyspepsia. This includes a group of heterogeneous disorders in which there is upper abdominal pain without the presence/evidence of an ulcer.²

Upper gastrointestinal motility disorders are quite common in Pakistan and Functional dyspepsia is frequently observed in our population.³ A large number of patients present with upper abdominal pain, fullness, nausea, vomiting or heartburn. Initial evaluation is by a detailed clinical history and examination. There should be a focused clinical evaluation regarding the red flag indicators of an

underlying serious disease. A substantial number of patients are found to have normal endoscopy and liver function tests. In such patients, the disorder appears to be a functional one with sluggish emptying of the stomach resulting in the symptoms as described above. Though this condition is not serious, it can be extremely disturbing to these individuals.⁴

Psychosocial factors may influence both the generation of symptoms as well as their reporting in functional dyspepsia. In comparison to the healthy subjects, functional dyspepsia patients are observed to have higher symptom scores, comparatively poor quality of life, and greater psychiatric distress.⁵

In recent years, there has been an emerging concept of the gut-brain axis. This axis can be simplified as the two-way communication between the gut and brain. This connection is not only anatomically established, but also has the hormonal, humoral, metabolic and immunologically mediated complex interplay of

mechanisms. The current study focuses on this association between a psychiatric illness and gut manifestation that could have been one of the several components of the gut-brain axis.⁶

It is difficult to evaluate the depression in the context of medical illness. The symptoms of Depressive illness may result from or reflect the stress of coping with ongoing illness. However, it may be the sequelae of the disease process itself or the result of the medicines that are used for management. This may result from the coexistence of depressive illness with the medical condition. Depression is frequently underdiagnosed and also undertreated or not treated at all.

The terminology of “minor depression” is applied to patients who experience at least two of the defined symptoms of depression at least for two weeks duration. However, these cases don't meet the whole criteria of major depression.⁷ Despite its name, minor depression is associated with significant morbidity & disability and it does respond to pharmacologic treatment. Dyspeptic symptoms are improved significantly by treatment with antianxiety or antidepressant agents. Poorer quality of life and psychiatric distress predispose an individual to Functional dyspepsia.

The rationale of this study was to evaluate the significance of depression in patients presenting with and without Functional dyspepsia so that depression can be considered as a possible risk factor in these cases and can be evaluated and managed accordingly for a better prognosis of dyspepsia.

2. Materials & Methods

This case-control study was conducted at the Department of Medicine, Rawal Institute of Health Sciences Islamabad, Pakistan after ethical approval. The duration of the study was 6 months from 1st January to 30th June 2023. A total of 300 cases were included in this study; there were 150 cases of Functional dyspepsia and 150 healthy controls. The global prevalence of functional dyspepsia ranges from 8.4-38.3%.³ Sample size was calculated by the WHO sample size calculator

taking a 95% confidence interval, 5% precision and 26% reported regional prevalence.

Adult patients (>18 years) fulfilling Rome III criteria,⁸ of Functional dyspepsia were included. This criterion states that one or more of the following should be present; bothersome postprandial fullness, early satiation, epigastric pain, epigastric burning AND no evidence of structural disease (including upper gastrointestinal endoscopy) i.e., likely to explain the symptoms. (These criteria should be fulfilled for the last 3 months with symptoms onset at least 6 months before diagnosis of FD). The exclusion criteria were the cases with alarm symptoms i.e., unintended weight loss, persistent vomiting, progressive dysphagia, odynophagia, hematemesis, jaundice, palpable abdominal mass, lymphadenopathy, unexplained iron deficiency anaemia, family history of GI malignancy, history of previous gastric surgery, serious systemic illness or prolonged NSAID use.

Age and gender-matched controls without any of the symptoms of dyspepsia were included in the control group. The diagnosed cases of any major illness, including the known cases of depression or any other psychiatric illness were excluded from the control group. The 150 cases of Functional dyspepsia meeting the inclusion and exclusion criteria were selected by non-probability; convenience sampling in group A. The 150 age and gender-matched controls were registered in group B by convenience sampling from the attendants accompanying the patients. Informed consent was obtained. The demographic information (name, age, gender and address) was obtained. After the detailed clinical evaluation including the history of drugs (including the drugs of abuse), any obvious cause of depression i.e., loss of a loved one was also asked. Patients were examined clinically for pallor, jaundice, lymph nodes and abdominal examination. The BMI was calculated ($BMI = \text{weight (kg)} / \text{height (m)}^2$). The previous medical record was reviewed, including the findings of upper GI Endoscopy.

The selected cases and controls were then asked questions from the DSM-IV Criteria of Depression. One of the symptoms should be depressed mood or loss of interest during the same 2-week period. They were asked about impairment in social, occupational, or other important areas of functioning due to these symptoms.

All the information was recorded on a specially designed proforma.

The data was entered in SPSS version 22 and analyzed. Demographic data was presented as descriptive statistics giving mean and standard deviation for age. For Quantitative variables (age, height, weight & BMI) mean±SD was calculated & Independent sample t-test was applied for the comparison of two groups about quantitative variables (age & monthly income). Categorical Qualitative variables from DSM-IV were entered into SPSS with the outcome as depression present or absent. The chi-square test was applied to compare cases and controls. P-value<0.05 was taken as significant.

3. Results

There were 72(48%) males and 78(52%) females in each group (odds ratio=1.03, 95% CI =0.65–1.6, p-value=1). The mean age was 43.7±13.79 years for FD patients Vs. 46.24±15.27 years for controls. The predominant age group was 41-60 years among the cases as well as controls. Mean BMI±SD was 24.84±4.18 for FD patients vs. 25.38±4.52 for controls. 82.7% of FD patients were married vs. 75.3% of controls (p=0.07). 38% of FD patients had a rural background and 62% urban, while 30% of the control group had a rural

background & 70% urban (p=0.09). Among cases of FD 57(38%) had major depression and 93(62%) had no major depression. Among the patients without major depression, 41(27.33%) had minor depression and 52(34.66%) were not depressed. Among controls 41(27.33%) had major depression and 109(72.66%) had no major depression; among these 30(20%) had minor depression and 79(52.66%) not depressed. Results showed significantly higher depression in FD patients as compared to controls (p=0.032).

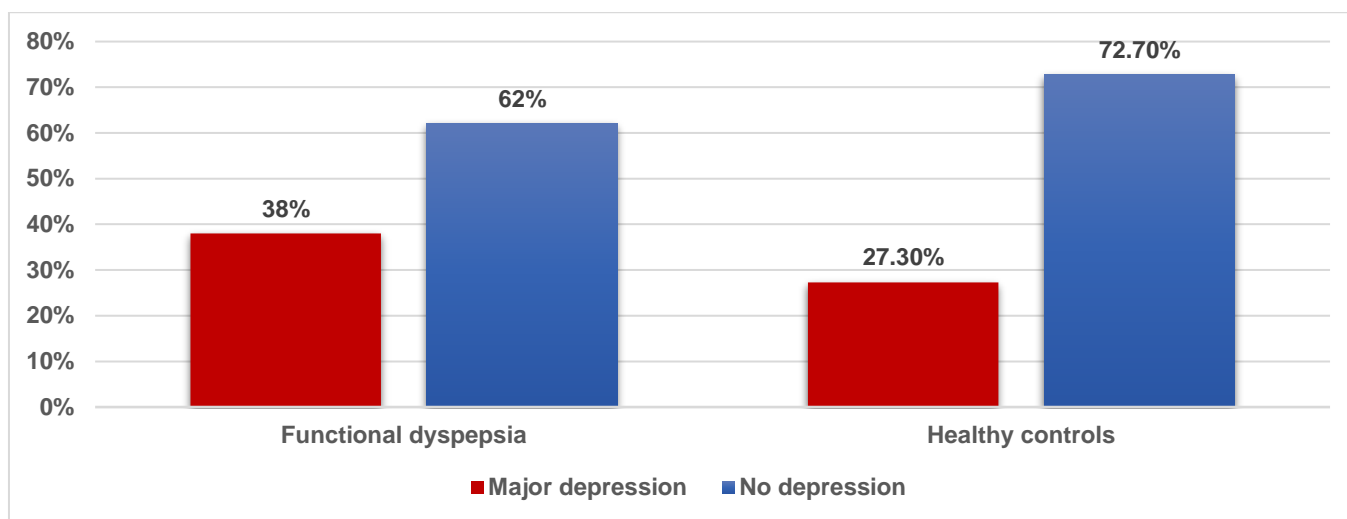
Results of the independent sample t-test showed that there was no significant association of age≥40 years with major depression in FD cases (p=0.257). However, there was significantly more depression in controls ≥40 years of age (p<0.0001). There was a significant association of major depression with the female gender in both groups (p<0.05). The employment status turned out to be lower 49.3% employed among FD patients vs. 67.3% among controls Unemployment had a significant association with depression in both groups (p<0.05).

There was not any significant statistically proven relationship between major depression and educational status, however, the mean educational level was lower 7.4 (7th standard) among FD patients vs. 12.2 (12th standard) among controls.

Variables	Amongst all n=300	Functional Dyspepsia Group A	No Dyspepsia Group B	P-value
Weight (kg)	67.95±12.17	66.55±13.14	69.36±12.20	p>0.05
BMI	25.11±4.23	24.84 ± 4.18	25.38 ± 4.52	p>0.05
Monthly income	18236±16405	17566±17178	18906±16016	p>0.05
Age (mean+ SD)	44.97 ± 14.35	43.71 ± 13.79	46.24 ± 15.27	p>0.05
Gender				
• Male	143	72 (48%)	71 (49.7%)	**1.00
• Female	157	78 (52%)	79 (50.3%)	
Marital Status				
• Single	52	24 (16%)	28 (18.7%)	**0.07
• Married	237	124 (82.7%)	113(75.3%)	
• Widow	11	2 (1.3%)	9 (6%)	
Employment				
• Employed	174	74 (49.3%)	100 (66.7%)	**0.002
• Unemployed	126	76 (50.7%)	50 (33.3%)	
Background				
• Urban	198	93 (62%)	105 (70%)	**0.09
• Rural	102	57 (38%)	45 (30%)	

(Test of significance *student-t test; **chi-square test; significant p<0.05)

Table 1: The comparison of demographic variables between FD cases and non-dyspeptic controls (n=300).



Disease	Depression		p-value
	No n=202	Yes n=98	
• Functional Dyspepsia	93 (62%)	57 (38%)	0.032
• Controls	109 (72.7%)	41(27.3%)	

*test of significance Chi-square test; significant $p < 0.05$

Table 2: The frequency of Major depression in functional dyspepsia cases Vs. healthy controls (n=300)

Disease	Depression	Gender		Total	Chi-Square (df = 1)	P-Values
		Males	Females			
Functional Dyspepsia	No	55(59.1%)	38(40.8%)	93	12.168	0.000
	Yes	17(29.8%)	40(70.1%)	57		
Controls	No	57(52.3%)	52(47.7%)	109	3.936	0.047
	Yes	14(34.1%)	27(65.8%)	41		

*Test of significance Chi-square test; significant $p < 0.05$.

4. Discussion

Functional dyspepsia is a frequently encountered problem in general medical practice. Though this condition is not serious it can be extremely disturbing and leads to frequent outdoor visits, investigations and the need for long-term medications. This has a financial and psychological burden on patients and increases the workload on the health care system. The results regarding patient satisfaction with the management of FD are variable. Sud et al reported >80% short-term symptomatic improvement.⁹ However, despite all these measures the complete long-term remission of symptoms is achieved less often. Madish et al have reported long-term remission in <20% of cases.¹⁰

Though there have been several international studies on various aspects of Functional dyspepsia and associated psychosocial factors, few studies have been conducted in Pakistan on this topic. Even internationally, while considering studies on Functional dyspepsia and Depression that have included a population-based group as a control arm, relatively fewer studies are available. Abid et al conducted a community-based study in Karachi Pakistan and evaluated 1062 households. The study found a high burden of function GI disorders (FGID) in our population i.e., 54.4% of participants and 70.2% of the FGID had functional dyspepsia.³ This shows that FD is one of the predominant reasons for upper abdominal discomfort in our population. A timely upper GI Endoscopy was suggested in patients who are not relieved by conventional dyspepsia management.

This may help us avoid the unnecessary cost of medications, laboratory and radiological investigations. Hassan et al concluded that among patients with Functional dyspepsia, 75.3% had depression.¹¹ This study was conducted in the Lady Reading Hospital, Peshawar Pakistan. The frequency of depression was comparatively higher than in our study. However, Esterita et al conducted a meta-analysis and concluded that the prevalence of depression varies from 20% to 63% in functional dyspepsia cases.¹² Hence, we may interpret that there is wide variation in the prevalence of depression in FD cases not only between various countries but also in different regions of the same country. The reasons could be differences in socioeconomic class, psychological factors, literacy, etc. In our study, cases and controls were matched based on age, gender, BMI, monthly income, marital status and background. There weren't any significant differences in the above-mentioned variables between the two groups. However, educational status was lower in the Functional dyspepsia patients, mean of 7.2 (i.e., 7th grade); as compared to normal healthy people, mean of 12 (12th grade). We may conclude that lower educational status might be an additional risk factor for Functional dyspepsia.

The employed percentage was also lower (49.3%) among FD patients as compared to the control group which had a higher employment percentage (67.3%). Also, there was a significant association between unemployment and depression among both groups. It may be considered as a bias that might have overestimated depression among FD patients in our study. However, on the other hand, it may be considered an effect of the disease itself, indicating increased psychosocial impairment in these patients. Nam et al concluded that demanding jobs and occupational climates are associated with functional dyspepsia, especially in female employees.¹³ These points towards the need to survey the employees of various fields of life. Hantoro et al found significantly impaired quality of life (QoL) in terms of health in FD cases.¹⁴ This health-related QoL impairment was frequent in females and elderly cases. The female patients with FD were affected more in their daily routine life as compared to the males. In our study, major depression was more common among females as compared to males among both the Functional dyspepsia cases and controls. To validate these gender-specific differences, further research with a larger sample size and a prospective study design is suggested.

Heidi et al conducted a population-based study and concluded that chronic uninvestigated dyspepsia was

associated with somatization and was quite difficult to treat.¹⁵ Hantoro et al,¹⁴ also found high levels of anxiety and depression in cases with long-standing dyspepsia. The FD patients reported more depressive symptoms as compared to the controls. Given these findings, it is inferred that in FD patients, the psychiatric evaluation with appropriate therapeutic intervention may be beneficial. The results of this study strengthen the concept that FD is a complex syndrome. The biopsychosocial mechanisms have a considerable role in the aetiology and clinical presentations of Functional dyspepsia. In our study, it was concluded that FD patients manifest more depressive symptoms as compared to normal healthy controls without dyspepsia. Considering the control arm of the study, amongst the healthy people without dyspepsia 27.33% had major depression; this was higher than mentioned in other studies conducted on the general population in Pakistan as mentioned below.

A community-based survey by Farooq S et al reported a high prevalence of anxiety and depression in Karachi Pakistan.¹⁶ In our study, there was 27.33% major depression in the healthy controls. This also points towards the need to conduct a multi-centre study to get the true estimates.

The World Population Review 2023 entitled Depression and the Other Common Mental Disorders - Global Health Estimates reported the prevalence of depression in Pakistan to be 4.2%. Our study reports comparatively higher major depression in FD cases, i.e., major depression was found in 38% of FD patients. Hence, we may interpret that FD cases are prone to major depression or vice versa.

A study by Sargoussi et al,¹⁷ concluded that major depressive disorder, cognitive impairment and other mental health-related disorders are associated with significantly impaired QoL (quality of life). The pharmacological, as well as psychotherapeutic intervention, leads to better outcomes in terms of QoL and recovery/remission of symptoms in patients.¹⁸ By the results of our study, we suggest that the FD cases should be managed with a multidisciplinary approach including the psychiatrist/psychologist involvement to assess for need pharmacotherapy or psychotherapy as adjusted.

The strength of the study is its design i.e., case-control. Also, there were minor demographic differences between the FD patients and controls, which shows that the cases and control groups were well-matched. However, a larger sample size might have reduced the ambiguity of statistical values, which could be considered a limitation of our study.

Possible reasons for bias in our research could be the phenomenon of recall bias which could have concerns about estimation of symptoms severity and characteristics. Another possible bias might be the difference in the employment status and the educational status between the two groups. However, this may be considered as an effect of the disease itself, indicating increased psychosocial impairment in these patients like loss of job. Furthermore, the lower educational status in the Functional dyspepsia patients might have affected the interpretation of the questionnaire. To control this bias, patients were explained the questions in their local language as well. Though these issues may have modified the findings to some extent, we may assume that they might have affected both groups equally & hence the eventual outcomes may not have been altered. Further outcomes from the study were that when we further subdivided the patients labelled as having no major depression into two groups labelled minor depression and no depression, results showed that among those Functional dyspepsia patients who didn't have major depression, 27.33% had minor depression. This percentage was lower (20%) among normal healthy people without dyspepsia.

Despite the terminology, "minor" depression has a significant association with functional impairment. A study conducted by Jamil et al in King Edward Medical University Lahore studied the association between the FD and various grades of severity of depression.¹⁹ Depression was found in all cases of FD except one and was significantly associated with EPS (Epigastric pain syndrome). This indicates the importance of identifying minor depression and reassessing patients at follow-up visits for any progression to major depression so that timely psychiatrist referral and intervention can be achieved.

Durrani et al found that a significant proportion of patients presenting to general medical clinics were suffering from unexplained vague symptoms, the predominant causes were somatization disorder, IBS, depression, hypochondriasis and conversion disorder.²⁰ Similarly, Moorthi et al stated that the psychiatric symptoms may be overlooked in several outdoor patients with underlying chronic diseases.²¹ Depressive symptoms may be the reflection of the psychological factors and stress of coping with the disease. This may be caused directly by the disease process itself or may result from certain medications prescribed for management. Also, this may simply coexist in parallel with the medical diagnosis. Our study shows a significant association between FD and depression and therefore stresses on need for awareness and training

regarding psychiatric illnesses amongst the public and the health care professionals.

5. Conclusion

With the adjustment for gender, age, marital status, BMI, background and monthly income, the association between Functional dyspepsia and depression is confirmed. Female gender, unemployment and low educational status are possible additional risk factors for depression among Functional dyspepsia patients. It was concluded that Functional dyspepsia patients are likely to have depression at a younger age as compared to healthy people. These results validate the need to assess depression in Functional dyspepsia cases and advise the recommended treatment strategies.

CONFLICTS OF INTEREST- None

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Contributions:

N.S, F.U, L.M, N.M - Conception of study

N.S, - Experimentation/Study Conduction

N.S, H.A, F.N, L.M, N.M -

Analysis/Interpretation/Discussion

N.S, F.U, H.A, F.N - Manuscript Writing

N.S, L.M, N.M - Critical Review

N.S, F.U, H.A, F.N, L.M, N.M - Facilitation and Material analysis

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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