Case-Controlled Study

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Association of vitamin D and functional dyspepsia: a case-control study

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Background: Vitamin D plays a key role in responses of brain-gut axis. It has been suggested that functional dyspepsia (FD) may be associated with decreased levels of vitamin D. Hence this study wished to find the association between vitamin D in patients with FD.
Materials and methods: This case-control study was done at a tertiary care hospital with 150 cases and 150 controls. FD was diagnosed by the ROME IV criteria. Demographic profile and serum vitamin D levels including Perceived Stress Score (PSS) and salivary amylase were determined for both cases and controls.
Results: Majority of the FD cases were males (57.3%). Post-prandial distress syndrome represented the major type of FD cases (69.3%). A higher mean BMI was found among the control group (23.2 vs. 21.2, $P < 0.05$) and higher percentage of obese individuals in the control group (42.7% vs. 29.3%, $P = 0.05$). Majority of the cases are from rural background (89.3% vs. 74%, $P < 0.001$). Comparison of PSS showed that cases had significantly higher grades of PSS than control ($P < 0.001$). However, no significant association was found in the levels of salivary amylase between the groups ($P = 0.728$). Hypovitaminosis D (< 30 ng/ml) was found significantly more among cases than controls (73.3% vs. 60%; $P < 0.05$) with an odds ratio of 1.833 (CI 95% = 1.126–2.985). After adjustment of age, place of residence and BMI, vitamin D levels were significantly associated with FD in the regression analysis.
Conclusion: This study shows significant association of vitamin D deficiency in FD patients. It also opens up new avenues for further research into the role of vitamin D supplementation to further improve the management of such cases.

Keywords: case-control study, functional dyspepsia, vitamin D deficiency

Introduction

Functional dyspepsia (FD) is an enigma in itself but a commonly prevalent problem, around 10–30%, encountered by physicians worldwide[1]. Notwithstanding of the fact that the vast facets underlying FD remains under active consideration, still certain areas delving into its etiopathogenesis is wide open. There is evidence of low-grade inflammation in duodenal mucosa including eosinophilic infiltration and T-cell mediated among others[2]. Since vitamin D has immunomodulatory properties and its role has been well established in various diseases including inflammatory bowel diseases and cancers, evaluation of vitamin D status in patients with FD needs to be actively pursued given its immuno-regulatory attributes[3]. Irene and his coworkers documented a retrospective study on vitamin abnormalities (low vitamin B1, vitamin B6, 25 -OH vitamin D, zinc and total CoEnzyme Q levels) in patients with gastrointestinal motility and functional intestinal disorders[4]. Studies have also revealed that vitamin D deficiency (VDD) is prevalent in irritable bowel syndrome patients[5]. The beneficial roles of vitamin D, particularly in gut and neurological functioning of the body counts in an effective option in treating irritable bowel syndrome[5,6]. The work by Hari and colleagues proposed the potential involvement of hypoxia-inducible factors in the pathophysiological mechanisms underlying FD. This prospective novel hypothesis established correlation between FD eosinophilia, barrier dysfunction and gut dysbiosis[7]. Du *et al.*[8] established the links between micro-inflammation and FD. The pathogenesis of FD is characterised by these micro-inflammation like local immune cell infiltration, specifically the eosinophils and mast cells[8]. Studies established the correlation of low vitamin D levels with gastric adenocarcinoma[9], gastric incomplete intestinal metaplasia[10], irritable bowel syndrome[5,6] and so on, but the interrelation between vitamin D levels with FD is still unknown. In one study,

HIGHLIGHTS

- Close association of vitamin D deficiency, BMI and perceived stress score in functional dyspepsia (FD).
- Higher prevalence of vitamin D deficiency in FD.
- The design of case-control study helped in correlating the key parameters in FD.

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increased vitamin D receptor (VDR) expression is seen in duodenal mucosa and it has been proposed that since vitamin D acts as a ligand of VDR, assessing vitamin D status in such patients remains an area of active research[11].

Interestingly, VDD is found to be strongly related with functional problems in intestinal neuromotility[12] apart from psychiatric disorders like anxiety and depression, severely affecting the quality of life of the patients[13]. With the weak pyloric sphincter, food from the small intestines will tend to flow back into the stomach. The bacteria will then ferment the semi-digested food causing gas formation, thereby pressurising the already weakened lower oesophageal sphincter (LES)[7]. Resultantly, the LES will open backwards causing acidic contents to reflux and subsequently epigastric pain and heartburn—exhibiting a spectrum of FD symptoms[14,15]. The mechanism of action of calcitriol (the active metabolite of vitamin D (1,25(OH)2 vitamin D)) is mediated by the VDR (subfamily of nuclear receptors) which acts as transcription factors in the target cells post formation of a heterodimer with the retinoid X receptor[16,17]. This types of receptors are found in all cell types, including oesophagus, stomach and the pyloric sphincter cells in the digestive system[18].

Also it has also been seen that chronic stress is increasingly recognised as an aetiological factor, part of brain-gut axis, in the causation of FD[19]. Although usefulness of psychoactive agents are reported[20], but results are not uniform. Salivary alpha amylase activity have been studied and shown as a biomarker of chronic stress in previous studies[21]. Therefore, for more definite objective evidence with regard to role of stress in the etiopathogenesis and thereby management of FD, measuring salivary alpha amylase activity will be a key milestone in FD research. Keeping in mind all these issues, this study is proposed to delve into the serum vitamin D concentration, Perceived Stress Score (PSS) and salivary alpha amylase activity in FD patients and their association if any. This study is envisaged to further establish or strengthen the etiopathogenesis of FD and this particular study is one of its kind.

Research hypothesis

We wish to seek whether patients with FD is associated with vitamin D deficiency and increased salivary alpha amylase activity.

Objectives of the study

(1) To estimate Vitamin D (25OH vitamin D) concentration and salivary alpha amylase activity and PSS in patients with FD.
(2) To find out the association between patients of FD with VDD and salivary alpha amylase activity.

Methods

The study had been reported in line with the STROCSS criteria[22]. The registration unique identifying number (UIN) is osf.io/w7fu6[23].

Study design

It was a case-control study with patients attending medicine out patient department of a tertiary care academic hospital in Eastern India over the period from May 2021 to September 2022.

Selection of cases and controls

(1) All consecutive patients presenting with symptoms of dyspepsia were subjected to history taking, physical examination, recent medical record review and those fulfilling the ROME IV criteria of FD were enroled into the study after fulfilling the below mentioned inclusion and exclusion criteria[24]. Other coexisting comorbidities were also noted.
(2) The stress severity score was assessed by PSS[25].

Healthy controls were selected from subjects attending the hospital for routine health checkup or pre-employment checkup or accompanying patient attendants without any history of self-reported chronic illness.

Inclusion criteria

(1) Age equal to or more than 14 years of age.
(2) Patients fulfilling ROME IV criteria of FD[24].

Exclusion criteria

(1) Those having adequate response to antisecretory agents from history.
(2) Those having documented endoscopic evidence of erosions, ulcers, esophagitis.
(3) Patients with comorbidities like Diabetes Mellitus, Chronic Kidney Disease, Chronic Lung Diseases, Chronic liver Disease, Cardiovascular diseases, inflammatory bowel disease any other organic or systemic illness that explains the symptoms.
(4) On chronic non-steroidal anti-inflammatory drugs use, recent vitamin D intake.
(5) Known psychiatric illness undergoing treatment.
(6) Pregnant women.

Measurement of vitamin D and salivary alpha amylase levels

Serum 25—dihydroxyvitamin D was measured by ELISA kit (DIA source Immnunoassay S.A. Belgium). Hypovitaminosis D was taken as 25 (OH)D3 less than 30 ng/ml while moderate to severe deficiency of vitamin D (VDD) taken as 25 (OH)D3 less than 10 ng/ml[26–29]. Salivary alpha amylase levels were measured with ELISA kit (Fine Test alpha amylase 1 kit). The normal level of salivary amylase range from 27 to 1140 U/ml[30].

Statistical plan

Analysis was performed using SPSS version 27.

(1) Categorical variables were summarised as counts and percentages as well as median for ordinal variables. For continuous data mean (SD) were used.
(2) *P* values were calculated with the use of χ^2 test or Fisher's exact tests, when appropriate and Student's *t*-test for continuous variables. For non-normal distribution, Mann–Whitney U test were performed. Normality of the distribution was performed with Kolmogorov–Smirnov test and the Shapiro–Wilk test. Between two groups difference was significant when *P* value less than 0.05.
(3) To find the predictors associated with FD, multivariate logistic regression analysis was performed.

Sample size calculation

Assuming an equal number of cases and controls and from previous studies, prevalence of VDD among adults to be around 60%[27,28], the number of study subjects required to detect an odds ratio (OR) of 2.0 with 0.80 power using a two-sided 0.05 test will be as follows—
Total number of subjects: 304
Number of cases: 152
Number of controls: 152
"citation(\"epiR\")" using R programming language and software[31].

Ethics statement

This study was approved by the Institutional Ethics Committee (IEC) of AIIMS Bhubaneswar vide no. T/IM-F/20-21/17. Written informed consent was collected from all the participants.

Results

A total of 150 cases and 150 controls were included during the study period matched by sex.

Characteristics of FD cases

Post-prandial distress syndrome represented the major type of FD cases (104 cases; 69.3%), followed by epigastric distress syndrome (46 cases, 30.6%). Among the cases, 6.6% had sleep problems, 18.6% had heart burn, 18.6% had bowel disturbances and 13.4% had headache. (Table 1).

Cases and controls comparison

With regards to demographic features, no significant differences were found between controls and cases except for age, place of residence and BMI. Cases have higher mean age than the controls (42.24 ± 12.047 vs. 38.94 ± 13.8, $P = 0.028$). A higher mean BMI was found among the control group (23.2 vs. 21.2, $P < 0.05$) and higher percentage of obese individuals in the control group (42.7% vs. 29.3%, $P = 0.05$). Majority of the cases are from rural background (89.3% vs. 74%, $P < 0.001$). (Table 2).

Comparison of PSS showed that cases had significantly higher grades of PSS than control ($P < 0.001$). Moderate to high stress as assessed by PSS scale was higher among cases (60.1% and 14%, respectively) compared to controls (36.7% and 2.7%) (Table 3). However, there is no significant difference in the number of family members between the groups ($P > 0.05$).

Association of vitamin D and FD

Cases had significantly lower mean vitamin D levels compared to controls (22.92 vs. 27.85 ng/ml; $P < 0.009$). Hypovitaminosis D (< 30 ng/ml) was found significantly more among cases (73.3% vs. 60%; $P < 0.05$) with an OR of 1.833 (CI 95% = 1.126–2.985). Table 3.

VDD (< 10 ng/ml) was found significantly more among cases (23.3% vs. 12.7%; $P < 0.005$). Females in the case group had significantly higher Hypovitaminosis D than those in control group (79.7% vs. 63.3%; $P = 0.048$) with OR of 2.271. However, there is no such significant difference between the males (68.6% vs. 57.8%; $P = 0.161$). Table 4.

Association between salivary alpha amylase and FD

There was no significant difference between the mean levels of salivary alpha amylase between the cases and control. Table 5.

Table 1

Characteristics of functional dyspepsia cases

Types of FD	N = 150), N (%)
PDS	104 (69.3)
EPS	46 (30.6)

EPS, epigastric pain syndrome; FD, functional dyspepsia; PDS, post-prandial distress syndrome.

Table 2

Demographic characteristics comparison among cases and controls

Variables	Cases	Controls	P
Total, *n* (%)	150 (100)	150 (100)	—
Sex, *n* (%)			0.639
Male	86 (57.3)	90 (60)	
Female	64 (42.7)	60 (40)	
Age (years), mean SD	42.2 ± 12.0	38.9 ± 13.8	**0.028**
Male	41.6 ± 12.4	40 ± 14.1	0.410
Female	42.9 ± 11.5	37.3 ± 13.2	**0.012**
Residence, *n* (%)			**0.001**
Rural	134 (89.3)	111 (74)	
Urban	16 (10.7)	39 (26)	
No. family members, mean SD	5.5 ± 3.0	5.3 ± 2.4	0.921
Educational status, *n* (%)			0.119
Illiterate	13 (8.7)	14 (9.3)	
Primary school	63 (42)	46 (30.7)	
Secondary school and above	74 (49.3)	90 (60)	
Employment status, n (%)			1
Unemployed	111 (74)	112 (74.7)	
Employed	39 (26)	38 (25.3)	
Tobacco use, *n* (%)			0.679
No	114 (76)	118 (78.7)	
Yes	36 (24)	32 (21.3)	
Alcohol use, *n* (%)			0.871
No	127 (84.7)	129 (86)	
Yes	23 (15.3)	21 (14)	
Diet pattern, *n* (%)			0.085
Veg	3 (2)	10 (6.7)	
Non-veg	147 (98)	140 (93.3)	
PSS, *n* (%)			**0.000**
High	21 (14)	4 (2.7)	
Low	38 (25.3)	91 (60.7)	
Moderate	91 (60.7)	55 (36.7)	

Statistically significant values are in bold.
PSS, Perceived Stress Score.

Table 3

Showing comparison of vitamin D levels between cases and controls

	Cases	Controls	P	OR
Vitamin D, mean (ng/ml) SD	22.9 ± 18.3	27.8 ± 17.5	**0.009**	
Vitamin D categories, *n* (%)			**0.020**	
Hypovitaminosis D	110 (73.3)	90 (60)		1.833
Normal Vitamin D	40 (26.7)	60 (40)		

Statistically significant values are in bold.
OR, odds ratio.

Table 4

Hypovitaminosis D as per sex among functional dyspepsia and controls

Hypovitaminosis D, *n* (%)	Cases	Controls	*P*	OR
Males	59 (68.6)	52 (57.8)	0.161	
Females	51 (79.7)	38 (63.3)	**0.048**	**2.271**
Vitamin D level (< 10ng/ml), *n* (%)	35 (23.3)	19 (12.7)	**0.005**	
Vitamin D mean (ng/ml) SD				
Males	24.4 ± 18.6	29.2 ± 18.7	0.091	
Females	20.8 ± 17.8	25.7 ± 15.5	0.107	

Statistically significant values are in bold.
OR, odds ratio.

Effect of BMI on serum vitamin D concentration in FD vs. controls

Serum vitamin D was significantly higher in the overweight controls than overweight FD subjects (33.2 vs. 21.2, $P = 0.009$). Serum vitamin D concentration was similar between normal and obese cases and controls ($P > 0.05$) Figure 1.

Predictors of FD

In the regression analysis, age, place of residence, BMI and vitamin D levels have been found to be the predictors of FD. After adjustment of age, place of residence and BMI, vitamin D levels were significantly associated with FD. (Table 6).

Nagelkerke R Square = 11%, $P = 0.023$, OR = 1.016.

Discussion

In our cohort of cases and controls, the primary finding is the significant higher prevalence of hypovitaminosis D or VDD in FD patients relative to that of controls. Although the sedentary lifestyle habits, irregular meal patterns and fast eating rates account for the prevalence of hypovitaminosis D or for that matter VDD in normal population, the self-limited or restricted dietary food choices (non-pharmacological management strategy to relieve unpleasant sensations in gastrointestinal region) in the FD patients might account for the higher prevalence of VDD in cases as compared to the controls. The impact of VDD in FD patients can be understood from the different studies. Dr. Walter Stumpf studied Vitamin D and outlined the impact of VDRs on oesophagus, stomach and the pyloric sphincter cells in the digestive system[32]. As vitamin D is vital for the functioning of muscle cells; the VDD in the body thus can impair the functioning of the muscle cells (including the LES and pyloric sphincter) guarding the lower end of the stomach which opens to the small intestines[32,33]. Studies have also firmly posits the association of lower vitamin D levels with gastric adenocarcinoma[9], gastric incomplete intestinal metaplasia[10] and irritable bowel syndrome[5,6] .

Table 5

Showing mean SAA levels between the cases and control

Levels of SAA, u/ml SD	Cases	Controls	*P*
Mean value	5.032 ± 1.73	6.232 ± 1.79	0.728

SAA, salivary alpha amylase.

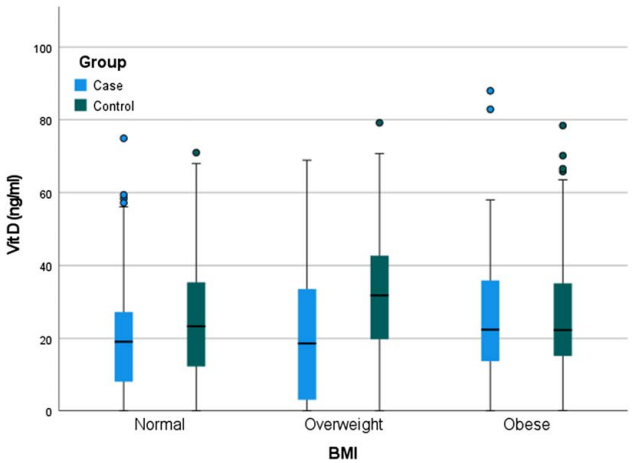

Figure 1. Boxplot showing comparison of vitamin D levels between functional dyspepsia and controls stratified by BMI.

We did not find significant association with regards to consumption of alcohol or tobacco between the cases and control. This might be because of the characteristics of the population in this part of the region as evident by the low percentage of cases as well as controls consuming alcohol or using tobacco thereby giving a too low a sample to find a significant effect.

We also did not find any significant association of salivary amylase between the cases and controls. This might be because of overall decrease in salivary amylase in fasting state[34]. As our population in this part of the region visit the tertiary care centre from far flung areas to make an out patient department visit, they usually prefer to stay fasting overnight till all the necessary investigations are done. Moreover, studies have shown decrease in salivary alpha amylase in the morning hours (circadian rhythm)[35]. Also, salivary amylase may be more increased in acute stress than in chronic stress in addition to the above mentioned possible factors[36].

The BMI was found to be slightly higher in the controls as compared to the cases (FD patients). This may be because of eating disorders of the FD patients or their reluctancy to avoid food as it tends to precipitate the symptoms. Studies reported positive association of functional gastrointestinal disorders, globus and regurgitation with BMI (including obesity) in patients

Table 6

Predictors of FD

Variables	B coefficient	S.E.	Wald	df	Sig	OR
Age (years)	– 0.018	0.009	3.444	1	0.063	
Residence	– 0.939	0.333	7.949	1	0.005	
BMI	0.035	4.630	1	0.031	0.031	
Vitamin D (ng/ml)	0.016	0.007	5.146	1	**0.023**	**1.016**
Model summary						
Step	– 2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square			
	389.824	0.083	0.111			

Statistically significant values are in bold.
FD, functional dyspepsia; OR, odds ratio; Sig, significance.

residing in Europe, Latin American countries and United States[37,38]. However, studies in the Asian population exhibited an inverse relationship between FD and BMI[39–41]. Low BMI may lead to FD via visceral hypersensitivity and delayed gastric emptying due to activation of corticotrophin-releasing factor receptors[41]. The difference in two groups of studies is in line with the BMI differences between the Asian and Caucasian populations[42]. Our study thus is in line with the findings of the above literatures.

For measurement of stress, the PSS is among the psychological scoring instrument widely used[25]. In our study, the FD patients scored higher for PSS as compared to the controls. The study highlighted the significant role (higher PSS score) of stress in the development of FD. This may be attributed to the discomfort or unpleasant sensation of FD which causes stress elevation and in turn high PSS score. Higher PSS score is strongly associated with poor or impaired quality of life of the FD patients as compared to the controls. Equally, the significantly elevated PSS score and VDD in FD patients is in line with other studies[43,44]. The intrinsic role of psychiatric disorders and psychosocial factors, more particularly anxiety and depression has been documented by other research groups in the etiopathogenesis of FD. The association of stress with the activation of the hypothalamus releases corticotrophin-releasing factor, with significant mast cell activation (inflammation), activation of the sympathetic nervous system apart from altered gastric accommodation, gastric dysmotility, and visceral hypersensitivity[45]. Also FD is a common gut-brain interaction disorder. An imbalanced gut microbiota may lead to short chain fatty acid profile and bile acid pool alterations, thus consequently dysregulating cellular stress response pathways in FD (like hypoxia-inducible factor)[46,47]. Further the eating disorders of FD patients are often linked with anxiety neurosis (accounting for high PSS score) and a key factor associated with low BMI[48,49]. In other words, the dietary restrictions owing to persistent manifestation of FD symptoms may have resulted in low BMI and elevated PSS score in FD patients. This fact is corroborated with the cross-sectional study by Beh *et al.*[40]. The authors take the opportunity to caution about the unbalanced, improvised and self-controlled exclusion diets which may enhance anxiety and visceral hyperalgesia.

The findings of the study also presented rural population exhibiting higher FD symptoms as compared to the urban ones. This may be likely because of the preference of the urban population to consult private healthcare and an inclination towards self-medication (purchasing of over-the-counter drugs). This is consistent with other population-based studies[50,51].

The study however reports absence of significant correlation between FD patients and epidemographic factors including age, sex, educational status or occupation. This lack of relationship may be due to the functional nature of FD. These findings are consistent with previous documented studies[52,53]. The study further could not find significant changes in the salivary alpha amylase values between the cases and controls. The inconsistent association of FD with smoking or alcohol intake was also consistent with the findings of Shaib and El-Seraj and Khademolhosseini *et al.*[54,55]. The vegetarian or non-vegetarian diets were found to have no significant effect on FD patients. This fact is further supported by a study on Indian population where FD symptoms were independent of type of diet but the intake of spicy and fried foods consumed from outside the home contributed in insignificantly worsening of the FD symptoms[56].

Strengths and limitations

The strength of this work remains in the designing of the study as case-control study with an objective of probing into the VDD in FD patients, which helped correlating the key parameters in FD cases to comparable parameters in the controls by addressing the potential confounders. Moreover, the study seems to be a beacon in the dark as it has practical applications in the form of therapeutic armamentarium. However, the study has its limitations as well. The variations in salivary alpha amylase stress response, appropriateness of saliva collection and non-assessment of the micronutrient deficiency of the FD patients accounts for major limitations of this study.

Conclusion

In summary, the present work demonstrates a close association of VDD, BMI and PSS score in FD patients for the first time. In this study, a higher prevalence of VDD was found in FD patients as compared to the controls. The findings of this study also showed a difference in rural and urban population exhibiting FD symptoms. To the best of our knowledge, current literature review has shown association of vitamin D with inflammatory bowel disease and but no studies were conducted assessing the association of FD with VDD. Self-restrictive diet accounted for the low BMI of the FD patients, which in turn attenuated the PSS score.

Findings from the study has been able to shed light into the role of vitamin D in FD and the possible need for vitamin D supplementation to further improve the management of such cases, thus opening new avenues for further research. As management of FD is still a conundrum, this research findings of this study is envisaged to find a place in effective management of FD patients. Further in this respect, a randomised double-blinded placebo-controlled trial on the supplementation of vitamin D is planned to support this observational study. The choice of optimum vitamin D supplementation dose and improvement in the quality of life post vitamin D supplementation will also be delved into.

Ethical approval

This study was approved by the Institutional Ethics Committee (IEC) of AIIMS Bhubaneswar vide no. T/IM-F/20-21/17.

Consent

Written informed consent was obtained for all participants for publication and any accompanying images and that copies of the written consent are available on request. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. If any participants were minors, written informed consent was obtained from their parents/legal guardians. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

D.S.D.—study concept and design, data collection, data analysis and interpretation. G.K.S.—sample analysis for vitamin D and alpha amylase estimation. M.K.P.—data collection, critical analysis and review of the manuscript. D.S.—data collection and review of the manuscript. All authors have approved the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

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Dr. Dhriti Sundar Das.

Data availability statement

No dataset is available publicly currently.

Provenance and peer review

Not invited.

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