

# Discriminant Analysis of Factors Distinguishing Patients with Functional Dyspepsia from Patients with Duodenal Ulcer

## Significance of Somatization

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Patients with duodenal ulcer or functional dyspepsia do not differ on dyspeptic symptoms. The aim of the present study was to test the hypothesis that functional dyspepsia and duodenal ulcer are two different diagnostic entities by examining the discriminating power of several anamnestic, biological, and psychosocial variables. Ninety-four patients with duodenal ulcer and 86 patients with functional dyspepsia were included. Anamnestic data, global assessment, *Helicobacter pylori* status, blood group, Lewis<sup>a+</sup> phenotype, and several measures of psychological distress and somatic complaints were registered. Compared to patients with functional dyspepsia, the duodenal ulcer patients were more often infected by *Helicobacter pylori* and had their stomach discomfort more often relieved by eating. Compared to patients with duodenal ulcer, patients with functional dyspepsia had higher scores of depression, trait anxiety, general psychopathology and different somatic complaints (called somatization). They were also less satisfied with the health care system, their disorder had a greater negative impact on their quality of life, and their global assessment of own health was poorer. Discriminant analysis including age, smoking, *Helicobacter pylori* status, global assessment, and somatic complaint classified 86.1% of the patients correctly (77.9% of the patients with functional dyspepsia and 93.6% of the patients with duodenal ulcer). It is concluded that duodenal ulcer and functional dyspepsia are two separate diagnostic entities. Patients with duodenal ulcer are older, smoke more often, and almost all are infected with *Helicobacter pylori*, while patients with functional dyspepsia are characterized by somatization and a negative assessment of their own health.

**KEY WORDS:** functional dyspepsia; duodenal ulcer; erosive prepyloric changes; *Helicobacter pylori*; psychological factors; somatization.

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Several observations suggest that peptic ulcer and nonulcer dyspepsia are two separate entities. The separation is made according to the endoscopic appearance, but there are also differences in clinical findings.

Active peptic ulcer disease has been characterized by the presence of antral gastritis, *Helicobacter pylori* (HP) infection, Lewis<sup>a+</sup> phenotype (nonsecretor status of ABO blood group antigens), and O-blood

group in young men (1). Duodenal ulcer (DU), which is the most common form of peptic ulcer, is also characterized by specific factors such as smoking, stress, and increased acid secretion (2). HP is strongly associated with gastritis (3) and has in recent years been proposed as the main etiological factor in DU (4).

Nonulcer dyspepsia, today mostly called functional dyspepsia (FD), is defined as chronic or recurrent upper abdominal pain or discomfort with no organic explanation. FD is associated with increased state and trait anxiety and neuroticism (5, 6), and symptoms of depression and neuroticism have also been reported (7, 8). There may be several subgroups of patients with FD. One group, which appears to be rather homogenous, is patients with erosive prepyloric changes (EPC) (9, 10). This group of patients is characterized by higher stress scores, lower vagal tone, and wider gastric antrum than healthy controls (11, 12).

In an earlier paper, we described how patients with FD, DU, and normal controls differ in psychological and somatic symptoms (13). Using 15 anamnestic and psychological variables, we could classify 71.5% of the subjects correctly. In the present study biological variables also were included. Our hypothesis was that FD and DU are two different diagnostic entities and that adding biological measures to the anamnestic and psychosocial variables in the discriminant analysis would strengthen the discrimination power.

## MATERIALS AND METHODS

### Patients

One hundred patients with FD and EPC grade 2–3 (14) and 100 patients with DU were included in a clinical trial with a cross-sectional and two longitudinal parts. In the longitudinal parts, described elsewhere (15–17), the effect of cognitive psychotherapy on dyspeptic symptoms and psychological distress in the FD group and the one-year relapse rate in the DU group were examined. The endoscopic finding of EPC is defined as the presence of standing prepyloric folds, with erosions (grade 3), with red spots/streaks (grade 2), or without visible macroscopic lesions on top of the folds (grade 1). The patients had been referred to the gastroenterological department of Haukeland Hospital, where neoplasm and esophagitis were excluded by upper endoscopy. In both groups, age was between 16 and 65 years, and the patients with FD had dyspeptic symptoms of at least three months' duration. In order to avoid selection bias, exclusion criteria were identical in both groups: previous or planned gastric surgery, concomitant serious somatic or psychiatric disease, use of steroids or nonsteroidal antiinflammatory drugs, abuse of drugs or alcohol, disablement, language difficulties, or expected bad compliance.

This study belongs to the cross-sectional part. One hundred twenty-three patients with DU were found eligible for inclusion, but 23 withdrew before actually entering the study. These patients tended to be older than the rest. In the FD group, 143 patients were found eligible for inclusion, but 43 did not want to take part. The reasons for not participating were lack of time, change of mind, or unknown. The majority of DU patients were included within one week after endoscopically verified ulcer, when standard treatment with H<sub>2</sub>-blocker or omeprazole was started, and FD patients one month after endoscopy. Patient inclusions were done from March 1989 to May 1991, and both groups were evaluated at about the same time.

### Follow-up

All the patients were followed up for a year as a part of the longitudinal clinical trials (15–17), including gastroscopy at the 12-month follow-up.

### Biological Measures

**[<sup>14</sup>C]Urea Breath Test.** The presence of HP infection was assessed by the [<sup>14</sup>C]urea breath test and was performed at the one-year follow up in the longitudinal trials. The test is noninvasive and measures urease activity in the stomach/duodenum. We used a cutoff value of 1.47% recovery of <sup>14</sup>C activity within 30 min. This gives the probability of a correct decision of 0.977, described in detail elsewhere (18). The urea breath test is widely accepted for the diagnosis of HP infection and is considered by some to be superior to bacterial culture and histology (19, 20).

**Lewis<sup>a+</sup> Phenotype and ABO Blood Group Antigen.** Lewis<sup>a+</sup> phenotype (nonsecretor of ABO blood group antigen) is common in patients with peptic ulcer, especially in patients with duodenal ulcer (21). The Le<sup>a</sup> phenotype (Le<sup>a+</sup> vs Le<sup>a-</sup>) was determined immunohistochemically as binding of a Le<sup>a+</sup>-specific monoclonal antibody to surface epithelial secretory mucosubstances in antral biopsy specimens (21). Blood group O is another genetically determined factor found to be more common in patients with duodenal ulcer (DU) than in normal controls (22). ABO blood groups were determined by standard agglutination techniques.

### Psychosocial Measures

**Interview.** The initial interview lasted 1–2 hr and included a general history, a semistructured interview consisting of the 28 reported items designed for nonpsychotic disorders from the Comprehensive Psychopathological Rating Scale (CPRS) (23), and the person's global assessment of their health (physical, psychological, and social) on a 10-cm visual analog scale.

**Self-Rating Instruments.** The patients received the following self-rating instruments, which were handed in at the interview: Goldberg's General Health Questionnaire (GHQ-30), often used as screening instrument to find psychiatric morbidity in somatic settings (24); Eysenck Personality Questionnaire (EPQ-10), which measures neuroticism, defined as a general tendency to emotional over-reactiveness or over-responsiveness (25); Beck Depression Inventory (BDI), a scale which contains many cognitive aspects (26); Spielberger State-Trait Anxiety Scale (STAI-1

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TABLE I. CHARACTERISTICS OF PATIENTS AT INCLUSION\*

	Functional dyspepsia (N = 86)	Duodenal ulcer (N = 94)	P
Age, years	40.1 (37.5–42.8)	43.8 (41.5–46.1)	0.037(a)
Sex			
Females/males	50/36	41/53	0.052(b)
% females	58	44	
Duration of disease, months	118.6 (91.2–146.1)	140.9 (115.5–166.2)	NS(a)
Coffee, cups/day	3.5 (2.7–4.2)	4.4 (3.5–5.2)	0.118(a)
Alcohol, liters/year	2.00 (1.39–2.60)	4.02 (2.55–5.50)	0.016(a)
Smoking daily, N (%)	37 (43)	58 (62)	0.012(b)
Sick leave last year, N (%)	55 (64)	41 (44)	0.006(b)
Relationship of pain to eating, N (%)			
Unchanged	28 (33)	11 (12)	
Better	25 (29)	74 (79)	
Worse	32 (38)	9 (10)	<0.000001
<i>Helicobacter pylori</i> -positive, N (%)	30 (35)	90 (96)	<0.000001
Lewis <sup>st</sup> phenotype, N (%)	17 (25)	24 (28)	NS(a)
ABO blood group, N (%)			
O	30 (38)	47 (50)	
A	39 (49)	36 (38)	
B	7 (9)	8 (9)	
AB	3 (4)	3 (3)	NS(a)

\*P values estimated by t-test(a) and cross-tabs (chi-square)(b) 95% confidence interval in parentheses.

and STAI-2)—STAI-1 measures “state,” while STAI-2 measures “trait” of anxiety (27), and Psychosocial Adjustment to Illness Scale (PAIS-SR), which has seven subscales representing health care orientation, vocational environment, domestic environment, sexual relationship, extended family relationships, social environment, and psychological distress (28–30). All persons also filled in a Giessen Subjective Complaints List (31), which has subscores for symptoms of exhaustion, discomfort from muscle–skeleton, heart, and respiratory organs, stomach (six items in each subscore), and a sum score encompassing other body complaints (57 items). The items have five response categories (0–4), varying from “not at all” to “strong.” All the test instruments are available in validated versions in Norwegian translation. For GHQ, the usual 0-0-1-1 scoring method was used. On CPRS, global assessment, and the self-rating questionnaires higher score indicates more discomfort.

**Ethics**

The study was approved by the Ethical Committee of Health Region III in Norway. All procedures were in accordance with Declaration of Helsinki. The patients received written information about the project, and written consent was given by all the patients.

**Statistics**

Discriminant analysis was used to distinguish between the two patient groups. By means of forward stepwise selection, the model was simplified to contain only the variables with highest discriminating power. Significance level was set at 5% in the discriminant analysis. Because of the many tests, the significance level was conservatively set at 0.005 for the *t* tests and chi-square tests used to examine differences between the groups at baseline (Bonferroni correction). Correlations were used to examine the relationship between psychological measures. Statistical analyses were done on IBM-compatible computer with SPSS/PC+ (32).

**RESULTS**

Thirteen patients with FD and three patients with DU did not want to participate in the [<sup>14</sup>C]urea breath test and were excluded from further analysis. One other patient with FD and three other patients with DU were excluded because of missing data on one of the other discriminating variables used in the final model. Consequently 180 patients were included in the analysis, 86 with FD and 94 with DU. Of the patients with FD, 20 (23%) had erosions (EPC grade

TABLE 2. CHARACTERISTICS OF PATIENTS AT INCLUSION\*

	Functional dyspepsia (N = 86)	Duodenal ulcer (N = 94)	P
BDI	8.5 (7.1–10.0)	5.4 (4.4–6.4)	0.0004
EPQ-10	4.2 (3.6–4.8)	3.6 (3.0–4.1)	NS (0.13)
GHQ-30	7.0 (5.3–8.6)	4.9 (3.5–6.2)	NS (0.051)
CPRS	23.4 (20.6–26.2)	13.6 (11.7–15.5)	<0.00001
STAI-1	37.6 (35.7–39.5)	35.2 (33.5–36.9)	NS (0.07)
STAI-2	39.6 (37.7–41.5)	35.9 (34.2–37.7)	0.0049
PAIS-SR Health Care Orientation	5.7 (5.1–6.2)	4.2 (3.7–4.7)	0.0003
PAIS-SR Sum	31.7 (27.8–35.5)	23.5 (20.7–26.3)	0.0007
Global Assessment	39.1 (34.6–43.7)	24.7 (21.3–28.1)	<0.00001
Giessen Sum Score	52.3 (45.8–58.7)	33.8 (29.9–37.7)	<0.00001

\*P values estimated by *t* test; 95% confidence interval in parentheses. BDI, Beck Depression Inventory; EPQ-10, Eysenck Personality Questionnaire; GHQ-30, General Health Questionnaire; CPRS, Comprehensive Psychopathological Rating Scale; STAI1+STAI2, Spielberger State(1)-Trait(2) Anxiety Scale; PAIS-SR, Psychosocial Adjustment to Illness Scale; global assessment, 10-cm visual analog scale.

III) and 66 (77%) prepyloric folds with rubor (EPC grade II). Further patient characteristics are found in Tables 1 and 2.

Improvement of stomach discomfort or pain by eating was reported significantly more often by patients with DU compared to those with FD ( $P < 0.0001$ ). Ninety-six percent of DU patients were infected by HP, which is significantly higher than the 35% positive for HP in the FD group ( $P < 0.0001$ ).

On the other hand, patients with FD were found to have higher mean score on the Beck Depression Inventory ( $P = 0.0004$ ) and Spielberger's Trait Anxiety Scale ( $P < 0.005$ ), as well as a significantly higher score of general psychopathology in the semistructured interview CPRS ( $P < 0.0001$ ). They were also less satisfied with the health care system than the DU patients ( $P = 0.0003$ ), and their disorder had a greater negative impact on their quality of life as measured by PAIS-SR ( $P = 0.0007$ ). When asked to make a global assessment of their health (physical, emotional, and social) the patients with FD reported poorer health ( $P < 0.0001$ ), and they reported higher frequency of somatic complaints from different organ systems ( $P < 0.0001$ ). The different subscores of the Giessen Subjective Complaints List are found in Fig-

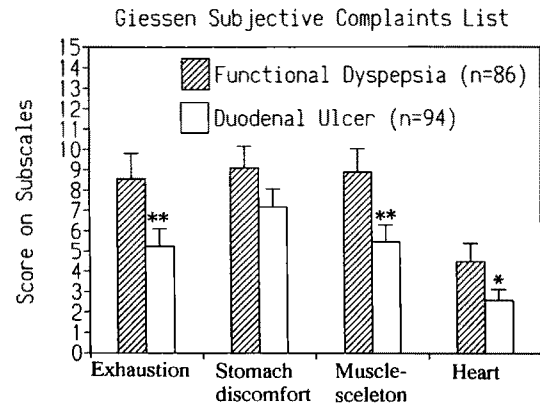


Fig 1. Scores on the subscales of Giessen Subjective Complaints List for patients with functional dyspepsia and duodenal ulcer. P values estimated by *t* tests. \*\* $P < 0.0001$ ; \* $P < 0.0003$ .

ure 1. Patients with FD were more exhausted ( $P < 0.0001$ ) and had higher frequency of symptoms from muscles-skeleton ( $P < 0.0001$ ) than the patients with DU, and they also had more often symptoms like palpitations, chest pain, and breathing difficulties ( $P < 0.0003$ ).

Before the discriminant analysis was done, a correlation coefficient matrix of the psychosocial variables was examined. STAI-1 (state anxiety) was dropped from further analysis because of high correlation to STAI-2 (trait anxiety) (0.68). Likewise GHQ-30 and CPRS were dropped because of high correlations to BDI (0.77 and 0.73, respectively). The correlation coefficients between the subscales and sum score of the Giessen Subjective Complaints List were all high (0.74–0.79), and only the sum score was entered into the discriminant analysis. There were also high correlations between PAIS-SR sum score and most of the subscales, with values from 0.62 to 0.83, and all subscores were dropped except health care orientation (indicates how satisfied the patient is with the health care system), which had a correlation coefficient of 0.37. Correlation between the Giessen sum score and global assessment was low (0.20).

The following variables were entered into the discriminant analysis: age, sex, coffee, sick leave last year, smoking, yearly alcohol consumption, relationship of pain to eating, blood group, Lewis factor, HP status, STAI-2, global assessment, Giessen sum score, BDI, EPQ, PAIS-SR sum score, and health care orientation. This model classified 89.6% of the cases correctly (82.1% with FD and 94.9% with DU). When Lewis phenotype was removed, the percentage correctly classified increased to 90.2% (82.4% with FD and 96.5% with DU). The eigenvalues of this optimal

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TABLE 3. DISCRIMINANT ANALYSIS OF OPTIMAL MODEL, INCLUDING 16 VARIABLES, AND LIMITED MODEL, INCLUDING 5 VARIABLES, TO PREDICT DIAGNOSTIC STATUS FOR FUNCTIONAL DYSPEPSIA AND DUODENAL ULCER\*

Variables	Optimal model function 1	Limited model function 1
<i>Helicobacter pylori</i>	0.75	0.79
Global assessment	-0.32	-0.36
Giessen sum score	-0.30	-0.35
Health Care Orientation	-0.26	
Psychosocial adjustment (sum score)	-0.23	
Beck Depression Inventory	-0.23	
Smoking daily	0.21	0.18
Sick leave last year	-0.20	
Trait anxiety	-0.17	
Alcohol consumption	0.15	
Age	0.11	0.15
Coffee	0.10	
Sex	-0.09	
Blood group	-0.06	
Neuroticism	-0.04	
Pain related to eating	-0.01	

\*Overall discriminating power is expressed by eigenvalues. Pooled within-groups correlations between discriminating variables and canonical discriminant functions.

model are presented in Table 3. When the somatic variables (blood group, Lewis factor, and HP status) were removed, 78% of the cases were correctly classified (74% with FD and 82% with DU).

With forward stepwise inclusion, the following variables were included: smoking, alcohol, pain related to eating, HP status, Lewis factor, global assessment, BDI, and Giessen sum score. Some of the factors had a low discriminating power and were subsequently dropped. Our final limited model included the following variables: age, smoking, HP status, global assessment, and Giessen sum score. Even with this model, 86.1% of the patients were correctly classified, 67 of 86 with FD (77.9%) and 88 of 94 (93.6%) with DU (see Table 3). When HP status was removed from the limited model, 76% of the patients were correctly classified, 75% with FD and 76% with DU.

### Incorrectly Placed Patients

**Duodenal Ulcer.** Six of 94 patients were incorrectly placed by our limited model, including the four HP negative patients. Among those four one turned out to have Crohn's disease and one had lactase deficiency. Blood group was O in two and A in two. None of the HP-negative patients had DU relapse during the one-year follow-up, compared to 92% among the 88 HP-positives who were correctly classified. Of the two HP-positive patients who were misclassified, one

had a DU relapse, and both had high scores on Giessen sum score (44 and 60), GHQ-30 (25 and 13), BDI (21 and 12), and global assessment (73 and 57).

**Functional Dyspepsia.** All 19 patients who were incorrectly classified were HP-positive. None of those developed DU during the one-year follow-up. The patients that were incorrectly classified had lower scores of depression and general psychopathology than the correctly classified patients. They also had significantly better global assessment of their health and fewer complaints from other organ systems.

## DISCUSSION

Our simple model with five variables was capable of classifying 155 of 180 patients with dyspepsia correctly into DU or FD. This strongly supports the notion that we are dealing with two separate clinical entities. DU was characterized by the presence of HP, while a negative evaluation of one's health combined with multiple somatic complaints characterized patients with FD. Variables known to be increased in DU, such as smoking, relief of pain by eating, and genetic factors (eg, blood group O) contributed somewhat, but added little extra compared to the overwhelming contribution of the HP factor.

In our study multiple somatic complaints was the most important factor that characterized patients with FD. This finding is compatible with the report of Nyrèn et al (33) that patients with nonulcer dyspepsia had more nongastrointestinal symptoms than patients with peptic ulcer disease. Somatization is defined by some as the somatic presentation of psychological distress (34). The essential feature of somatization in recent diagnostic manuals (35) is recurrent and multiple somatic complaints, without any speculation about etiology. Loss of perceived control over the environment is assumed to produce a sustained activation of the central nervous system (36). When acting in the presence of genetic and environmental factors, such sustained activation might produce changes in organs that are susceptible to such damage. In patients with FD, low vagal tone has been postulated as a possible mediating mechanism for the association between the psychological factors and motility disturbance (37). A decreased threshold to visceral sensory stimulation has been reported in patients with noncardiac chest pain (38) and irritable bowel syndrome (39). Somatic hypersensitivity, increasing the amount of somatic discomfort experienced by the person, might also be present in patients with FD. We also found increased levels of general

psychopathology, depression, and trait anxiety in the patients with FD compared to DU patients. The symptoms of psychological distress might lower the threshold at which somatic symptoms are perceived, thereby influencing illness behaviour in the direction of seeking health care.

Our initial classification of the patients (the "gold standard") was based on endoscopy. We do not propose that our model will make endoscopy unnecessary. Our objective is to point out that FD and DU have different psychological and biological findings, in spite of similar dyspeptic symptoms. Our final model classified patients with DU better than FD, due to the strong predictive power of HP infection. This is compatible with the finding that presence of HP infection in patients with FD and EPC merely is a consequence of increasing age (40, 41). In the six DU patients who were incorrectly classified as FD by the mathematical model, the possibility of comorbidity (DU and FD in the same patient) cannot be excluded. Of the four HP-negative patients with endoscopically diagnosed DU, but incorrectly classified as FD by the limited model, the one-year follow-up revealed that one had Crohn's disease and one lactase deficiency. The 19 FD patients misclassified as DU were all HP positive and, compared to the HP-positive patients with FD who were correctly classified, they had fewer somatic complaints, better global assessment of own health, lower general psychopathology, and lower depression scores. The duration of their disease tended to be longer than the others (17.7 years compared to nine years), but seemingly had less negative impact in their lives. The possibility that this group of "nonsomatizers" might comprise a subgroup with a common underlying physiological abnormality remains open.

The selection criteria of EPC probably have contributed in making our group of FD patients fairly homogenous. Physical and psychological stress has been found to aggravate EPC (42). In this patient group studies have shown no or negative effect of the most common drugs used to heal peptic ulcer (43, 44). On the background of the multiple somatic complaints experienced by these patients, these findings are not surprising.

DU was for many years considered one of the classical psychosomatic diseases (45). Our study does not support this notion. DU seems mainly to be a somatic disease. However, FD seems to have considerable psychosomatic components. The high level of psychological distress, the multiple somatic complaints, and the negative psychosocial effect of the disorder in the majority of these patients call for a

treatment that does not concentrate on a specific organ or symptom, but rather offers a way to support the patients' coping strategies in order to reduce the hypothesized sustained activation of the CNS (36).

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