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Psychologic Predictors of Duodenal Ulcer Healing

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We investigated psychologic influences on duodenal ulcer by examining the effect of personality, stress, and mood, measured at diagnosis, on subsequent ulcer healing. Stressful life events, psychopathology (assessed using the Minnesota Multiphasic Personality Inventory), anxiety, depression, smoking, alcohol consumption, nonsteroidal antiinflammatory drug use, and serum pepsinogen I levels were determined immediately after endoscopy showed duodenal ulcer craters in 70 patients with recent onset of symptoms. Endoscopy was repeated following 6 weeks of ranitidine therapy. Six ulcers (8.6%) persisted, and the duodenum remained inflamed in an additional five cases, for a total of 16% with incomplete healing. The only baseline characteristic significantly associated with poor healing was anxiety ($p = 0.03$ for ulcer persistence, $p = 0.02$ for incomplete healing). Being in the highest anxiety tertile was associated with a more than fourfold elevation in the risk of incomplete healing ($p = 0.02$). The association between anxiety and poor healing was not changed by modification of the anxiety score to eliminate gastrointestinal symptom items or by adjustment for serum pepsinogen, sex, or cigarette smoking. Anxiety inhibits the healing of duodenal ulcers treated with adequate antisecretory therapy.

Key Words: Psychological influences–Duodenal ulcer–Healing–Peptic ulcer–Stress.

Despite decades of investigation, the question of a relationship between psychologic distress and peptic ulcer remains open (1). Although there has been some evidence relating ulcer formation to adverse life events (2–4), work stress (5–8), family problems (8,9), and other long-term difficulties (10,11), not all studies have shown such results (12–14). With rare exceptions (8,15, 16), the evidence in favor of a connection between ulcer onset and preceding life stressors or subjective distress has been cross-sectional or retrospective. It is therefore of particular interest to examine the relationship between psychological characteristics, ascertained at diagnosis, and the subsequent course of the patient.

Previous studies have suggested that psychosocial factors may have an impact both on healing (17–19) and on recurrence (9,17,19). As part of a prospective study of the role of psychosocial factors in the course of a selected group of patients who had recently developed symptomatic duodenal ulcer for the first time or following a prolonged period of well-being, we tested the hypothesis that psychological distress and a context of severe life stress would tend to hamper endoscopic healing following standardized antisecretory therapy.

METHODS

Consecutive symptomatic patients in whom an active duodenal ulcer was seen endoscopically between November 1987 and December 1992 were invited to participate if symptoms of the present ulcer had been present for $\leq$6 months, preceded by a period of $\geq$1 year with neither symptoms nor specific anti-ulcer therapy. After September 1990, patients with symptomatic relapse within 3 months of suspending H_2-receptor blocker maintenance therapy were also recruited, if they had been asymptomatic on medication for $\geq$1 year.

Smoking, drinking, and any use of nonsteroidal antiinflammatory drugs for $\geq$2 weeks during the 6 months before symptom onset were recorded, and, in a subgroup of subjects, blood was drawn for pepsinogen I levels; serum antibodies against *Helicobacter pylori* were measured only in a subgroup (21 patients) too small to warrant analysis against the present outcomes.

Within 1 week of endoscopy, the psychologist (V.V.) administered the Italian version of Paykel's Interview for Recent Life Events (20), scored as positive for a major life event if any item judged as contextually severe (21) was reported to have occurred within 6 months before symptom onset. Patients then completed the Minnesota Multiphasic Personality Inventory (MMPI) (22) and measures of depression and anxiety (our versions of Zung's Self-Administered Depression Scale [23] and Self-Administered Anxiety Scale [24], produced using translation and back-translation by native speakers, in the first 33 patients and the Center for Epidemiologic Studies Depression Scale [25] and the State-Trait Anxiety Inventory [26], which have been validated in Italy, in the rest).

A uniform 6-week therapeutic program included ranitidine at a dose of 150 mg twice a day, antacids as needed,

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and abstention from alcohol and cigarettes. At the end of 6 weeks, patients were recalled for endoscopy. In all cases the endoscopist recorded whether the ulcer was closed; a subset of the endoscopic reports were adequate to determine in addition whether there had been complete normalization of the duodenal mucosa in patients with healed ulcers or whether, on the contrary, there was any degree of persistent duodenitis. Endoscopists were blinded to psychological findings.

This study was approved by the Ethics Committee of the Nuovo Regina Margherita Hospital, and all patients gave written informed consent.

ANALYSIS AND STATISTICAL METHODS

MMPI scores were scored on the 10 standard scales, three "validation" scales (L, F, and K), and supplemental ego strength and dependency scales (27). Profiles with F scores of ≥85 or L scores of ≥70 were considered to be invalid (27) and were excluded from all analyses. The sum of the scores on all 15 MMPI scales, reversing the scores on scales measuring positive traits (ego strength and K), was used as a global, objective measure of psychopathology. Unified depression and anxiety scores ranging between 0 and 1 were derived as previously described (28).

Statistical analyses were performed using the Statview 4.01 statistical package for Macintosh, comparing healed and unhealed ulcers by the Fisher exact test for dichotomous variables, by chi-square (with continuity correction) for other categorical variables, and by two-tailed *t* tests for continuous variables. Possible confounders or mediators were explored using multiple logistic regression. The level of statistical significance was taken as $p < 0.05$.

RESULTS

Population

A total of 81 eligible patients were identified, and 75 agreed to meet with the psychologist; the subset of 70 of the latter group who had a test-of-cure endoscopy are reported here. In 43 cases the follow-up endoscopy report specifically described the mucosal appearance in addition to the status of the ulcer crater.

Fifty-three study subjects were men, and 17 were women, ranging in age from 17 to 78 years (Table 1). Thirty-one were having their first episode of ulcer, 26 had had episodes in the distant past, and 13 were having a relapse after stopping maintenance therapy. Pepsinogen I levels were >125 μg/L in 11 of the 31 subjects in whom the enzyme was measured. Fifty-two percent smoked, and 56% consumed alcoholic beverages regularly. Twenty-six subjects (37%) reported a severely stressful event within the 6 months before ulcer onset; anxiety and depression scores were available in 66 and 67 subjects, respectively. Sixty-three subjects completed the MMPI, but five MMPI profiles were excluded from analysis on the ground of elevated L or F scales.

Baseline Characteristics in Relation to Ulcer Persistence (Table 2)

Six of the 70 ulcers (8.6%) were still present on endoscopy after 6 weeks of treatment. Persistence of the ulcer crater was not significantly related to any of the physiologic variables examined. Anxiety scores at diagnosis, however, were significantly higher among patients whose ulcers were still open at 6 weeks than among those whose ulcers were closed (0.67 versus 0.40, $p < 0.03$). When the 10 nonsteroidal antiinflammatory drug–exposed patients were excluded from analysis, the results regarding anxiety were identical, and the association also held when analysis was limited to the 55 patients without recent therapy (anxiety level 0.67 in the five with unhealed ulcers and 0.41 in the rest, $p = 0.04$).

TABLE 1. *Baseline characteristics of 70 subjects at the time of endoscopic diagnosis of active duodenal ulcer*

Variables	Number (percent)	Mean (SD)
Categorical variables		
Male sex	53 (76%)	
Ulcer history		
First ulcer	31 (44%)	
Recurrent, no recent therapy	26 (37%)	
Relapse after therapy	13 (19%)	
NSAIDs used before symptom onset	10 (14%)	
Smoker	36 (52%)	
Major life event before symptom onset	26 (37%)	
Continuous variables		
Pepsinogen I, μg/L (n = 31)		119 (82)
Age (years)		41.7 (14.0)
Cigarettes/day		9.4 (11.8)
Alcoholic drinks/day		1.3 (2.5)
Total MMPI score (n = 58)		626 (110)
Anxiety (n = 66)		0.42 (0.27)
Depression (n = 67)		0.44 (0.21)

NSAIDs, nonsteroidal antiinflammatory drugs.

Baseline Characteristics in Relation to Completeness of Healing (Table 3)

In addition to the six patients with unhealed ulcers, another five with closed ulcers were reported to have persistent inflammation of the duodenal bulb (ranging from erythema to erosion) on follow-up endoscopy, for a total of 11 patients known to have incomplete healing (16% of the entire group and 26% of the 43 patients on whom information on mucosal appearance was available). Again, none of the physical variables were associated with healing, though a strong trend linked incomplete healing with high pepsinogen I levels ($p = 0.06$).

With complete normalization of the duodenal mucosa, rather than simply ulcer closure, as the end point, anxiety proved to be still more strongly associated with nonhealing (anxiety scores of 0.60 in nonhealers and 0.39 in healers, $p = 0.02$). This finding was not changed by exclusion of patients exposed to nonsteroidal antiinflammatory drugs (scores 0.60 versus 0.39, $p = 0.03$), by excluding those with posttherapy relapses (scores

TABLE 2. *Baseline characteristics of duodenal ulcer patients according to endoscopic outcome at 6 weeks: persistent versus closed ulcer*

Variables	Ulcer closed (n = 64)	Persistent ulcer (n = 6)	p	Ulcer closed (mean ± SD)	Persistent ulcer (mean ± SD)	p[c]
Categorical variables						
Male sex	78%	50%	>0.30[a]			
Ulcer history			>0.30[b]			
First ulcer	44%	50%				
Recurrent, no recent therapy	36%	50%				
Relapse after therapy	20%	—				
NSAIDs used before symptom onset	16%	0%	>0.30[a]			
Major life event before symptom onset	36%	50%	>0.30[a]			
Continuous variables						
Pepsinogen I, μg/L (n = 31)				110 (0.75)	181 (115)	0.11
Age (years)				42 (15)	44 (6)	>0.30
Cigarettes/day				8.8 (12)	16 (13)	0.16
Alcoholic drinks/day				1.2 (2.3)	2.2 (4.0)	>0.30
Total MMPI score (n = 58)				620 (110)	703 (88)	0.15
Anxiety (n = 66)				0.40 (0.26)	0.67 (0.28)	0.03
Depression (n = 67)				0.43 (0.20)	0.57 (0.25)	0.13

NSAIDs, nonsteroidal antiinflammatory drugs.
[a] Fisher's exact test.
[b] Chi-square test.
[c] Student's *t* test.

0.65 versus 0.40, p = 0.02), or by omitting gastrointestinal symptom items (p = 0.03). There was also a strong trend (p = 0.07) for an association of depression with nonhealing. When patients were divided into tertiles by anxiety score, six of 21 of the patients in the highest tertile still had acute mucosal abnormalities after 6 weeks of therapy, versus only three of 45 of the others, for a risk ratio of 4.4 (p = 0.02).

Possible Confounders or Mediators

The relationship between anxiety and ulcer healing could have been confounded by sex and could have been mediated by cigarette smoking or by pepsinogen levels. Logistic regression models were therefore built between anxiety and persistent ulcer and between anxiety and incomplete healing, adding each of these biologic variables singly and in combination. The associations of

TABLE 3. *Baseline characteristics of duodenal ulcer patients according to endoscopic outcome at 6 weeks: complete normalization of the duodenal mucosa versus persistent ulcer and/or duodenitis*

Variables	Complete healing (n = 59)	Incomplete healing (n = 11)	p	Complete healing (mean ± SD)	Incomplete healing (mean ± SD)	p[c]
Categorical variables						
Male sex	78%	64%	>0.30[a]			
Ulcer history			>0.30[b]			
First ulcer	36%	45%				
Recurrent, no recent therapy	45%	36%				
Relapse after therapy	19%	18%				
NSAIDs used before symptom onset	17%	0%	>0.30[a]			
Major life event before symptom onset	36%	45%	>0.30[a]			
Continuous variables						
Pepsinogen I, μg/L (n = 31)				107 (74)	182 (99)	0.06
Age (years)				41 (12)	43 (12)	>0.30
Cigarettes/day				8.5 (12)	14 (12)	0.15
Alcoholic drinks/day				1.2 (2.4)	1.6 (3.0)	>0.30
Total MMPI score (n = 58)				617 (112)	681 (89)	0.13
Anxiety (n = 66)				0.39 (0.25)	0.60 (0.32)	0.02
Depression (n = 67)				0.42 (0.20)	0.55 (0.22)	0.07

NSAIDs, nonsteroidal antiinflammatory drugs.
[a] Fisher's exact test.
[b] Chi-square test.
[c] Student's *t* test.

anxiety with persistent ulcer (OR of 1.04 per increase of 0.01 in anxiety score, p = 0.04) and with incomplete healing (OR of 1.03, p = 0.03) were not altered substantially by any of these adjustments.

The Zung anxiety scale included an item regarding indigestion. We therefore recalculated the relationship between anxiety and healing after eliminating this item; the associations with persistent ulcer (0.66 versus 0.39, p = 0.03) and incomplete healing (0.60 versus 0.38, p = 0.03) were essentially unchanged.

DISCUSSION

In our study we attempted to elucidate the relationship between psychologic factors and duodenal ulcer by examining the effect of baseline psychologic characteristics on healing rather than by using a nonulcer comparison group, bypassing the problem of recall bias (29) that casts doubts on case-control studies. We recognize that we have addressed only indirectly the contribution of psychologic factors to ulcer etiology.

Our principal finding was a significantly higher level of anxiety at the time of diagnosis among duodenal ulcer patients whose ulcers were destined to remain unhealed after 6 weeks of standard therapy than among those who healed promptly. An even stronger association was found when incomplete normalization of the duodenal mucosa, rather than ulcer healing, was taken as the end point; these associations persisted after consideration of possible biologic confounders, after exclusion of subjects whose ulcers were related to nonsteroidal antiinflammatory drugs or to stopping maintenance therapy, and after elimination of gastrointestinal items from the anxiety score.

Congruent results have been found by others. A Danish group (17) found anxiety to be the only one of several MMPI characteristics to predict a decreased likelihood of endoscopic healing at 2 and 6 weeks. In a South African study, ulcers occurring in the context of life stress were less likely to heal (18), as in an American study reported in abstract form (30) and a large Swiss study using physician assessments of stress (19). All these groups, however, enrolled unselected ulcer patients and are therefore subject to confounding by disease severity: a refractory ulcer, resistant to healing, could cause anxiety by giving chronic symptoms. Our recruitment protocol, which enrolled only patients with recent-onset symptoms after at least a year symptom-free, diminishes the likelihood of such confounding.

The Danish patients were untreated, and the South African study did not specify the therapy used, so that it might be thought that the minor prognostic disadvantage conferred by psychological characteristics could be wiped out by potent antisecretory therapy, as some have reported for smoking (31). Our data demonstrate that this is not the case, since our patients were uniformly treated according to currently accepted standards for antisecretory therapy.

Although an influence of psychological states on the onset and course of peptic ulcers has been a recurrent theme for the past half century (32) and has penetrated so deeply into the public consciousness as to become a cliché, it has never been established convincingly to physicians. The discovery of a bacterial component to ulcer etiology (33–35) has seemed to many to put the stress hypothesis to rest. Yet most individuals encounter *Helicobacter pylori* without developing ulcer (36), while others form ulcers despite lack of exposure to either *H. pylori* or nonsteroidal antiinflammatory drugs (37). Treatment aimed at eradicating this pathogen, while greatly decreasing the chances of relapse (38), adds little to the high rate of short-term healing achieved using antisecretory therapy alone (91% in the present study).

In the attempt to identify possible confounders of associations between psychologic factors and ulcer healing, we examined characteristics that have been reported to have an adverse prognostic effect in peptic disease. Like some others (39), we did not confirm earlier reports (40) of an association between nonhealing and alcohol use, while previous ulcer history (39,40) and male sex (31) tended to promote, rather than inhibit, healing; they could be excluded by multivariate techniques as confounders of the effect of anxiety. With a very small number of patients, we did confirm an association between high pepsinogen I levels and nonhealing (30,41).

Two possible pathways for the inhibitory effect of anxiety on ulcer healing are behavioral (cigarette smoking) and neuroendocrine (gastric acid hypersecretion). We examined and ruled out smoking as a mediator between anxiety and poor healing, using multivariate analyses; the modestly adverse univariate effect of cigarette smoking corresponds to the mixed reports in the literature, both for healing (31,39,40) and for recurrence (42–45).

Gastric acid secretion has generally been found to rise in states of psychologic distress (46,47), especially in ulcer patients (48), though negative studies also exist (49), and associations have been reported between psychological characteristics and serum pepsinogen levels (50,51). It is not implausible that anxiety could push acid production to levels high enough to overcome H_2-receptor blockade, given that 10- and even 20-fold increases in basal acid output have been observed in individuals undergoing severe real-life stress (52,53). We attempted to use pepsinogen levels to assess a possible mediating role of gastric acid hypersecretion, but the small number of patients makes firm conclusions impossible.

Our study has several limitations beyond its size. First, *Helicobacter pylori* was not studied. Second, we did not assess compliance, which might have been a source of confounding if anxious patients were either more or less likely than others to take their medications—though compliance is likely to have been high overall with a regimen that was simple, free of charge, non-experimental, and unlikely to cause side effects. Finally, we examined the effects of several independent variables to test the study hypothesis, only one of which had significant prognostic impact, indicating some caution in interpreting the results.

Our data show that duodenal ulcers heal relatively poorly in anxious patients despite adequate antisecretory therapy: a person in the most anxious third of the ulcer population has a more than fourfold increased chance of still having an abnormal duodenum after 6 weeks of H_2-receptor blocker treatment. Hospitalization and sedation were mainstays of ulcer treatment in the past but have lost favor with the advent of effective drug therapy (54). While we would stop short of the "absolute rest in bed" that was Osler's first therapeutic precept (55), the current findings suggest that soothing the anxious ulcer patient may be indicated on the grounds of medical efficacy as well as compassion. Even though such practical implications may prove to be dwarfed by the effectiveness of currently evolving medical therapy, the pathogenetic significance of our results remains: if psychological distress can impair the healing of ulcers, it may well have a role in causing them, after all.

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