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BRIEF ARTICLE

Anxiety and depression in adult patients with celiac disease on a gluten-free diet

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Abstract

AIM: To compare anxiety and depression levels in adult patients with celiac disease (CD) on a gluten-free diet (GFD) with controls.

METHODS: The levels of anxiety, depression and of a probable anxiety or depressive disorder were assessed by the Hospital Anxiety and Depression Scale in 441 adult patients with CD recruited by the German Celiac Society, in 235 age- and sex-matched patients with inflammatory bowel disease (IBD) in remission or with slight disease activity, and in 441 adult persons of a representative German general population sample (GP). Potential demographic (age, sex, social class, family status) and disease-related (latency to diagnosis, duration of GFD, compliance with GFD, thyroid disease) predictors of anxiety and depression in CD were tested for by regression analyses.

RESULTS: The level of anxiety in CD patients was predicted (R^2 = 0.07) by female gender (P = 0.01). Female sex (OR = 3.6, 95% CI: 1.3-9.4, P = 0.01) was associated with a probable anxiety disorder. Living alone (OR = 0.5, 95% CI: 0.2-0.9, P = 0.05) was associated with a reduced risk of an anxiety disorder. The level of depression and a probable depressive disorder were not predicted by any of the demographic and medical variables tested for. The levels of anxiety in patients with CD (6.6 ± 3.4) and with IBD (6.9 ± 3.7) were higher than those of persons in the GP (4.6 ± 3.3) (both P < 0.001). The levels of depression in persons with CD (4.2 ± 3.4), IBD (4.6 ± 3.4) and of the GP (4.2 ± 3.8) did not differ (P = 0.3). The prevalence of a probable anxiety disorder in persons with CD (16.8%) and IBD (14.0%) was higher than that of the GP (5.7%) (P < 0.001). The prevalence of a probable depressive disorder did not differ significantly between the three groups (P = 0.1).

CONCLUSION: Anxiety in adult German female celiacs on a GFD is higher than in persons of the GP. Female celiacs on a GFD should be screened for anxiety.

Key words: Celiac disease; Anxiety; Depression; Gender

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INTRODUCTION

Celiac disease (CD) is an autoimmune disorder which is precipitated, in genetically predisposed persons, by the ingestion of gluten, the major storage protein of wheat and similar grains. Originally considered a rare malabsorption syndrome of childhood, CD is now recognized as a common condition that may be diagnosed at any age and that affects many organ systems. In most affected people, CD remains undiagnosed, although the rate of diagnosis is increasing. CD occurs in adults and children at rates approaching 1% of the population. The disease is recognized not only throughout Europe and in countries populated by persons of European ancestry but also in the Middle East, Asia, South America and North Africa[1]. The highest CD prevalence in the world is found in a North African population originally living in the Western Sahara with a figure of 5.6%[2]. Among adults, two to three times as many women have the disease as men, for unknown reasons. The therapy for the disease is a gluten-free diet (GFD); however, the response to therapy is poor in up to 30% of patients mainly because of non-adherence to the GFD[1].

Along with the many gastrointestinal, nutritional and metabolic consequences of CD, there have been significant concerns about increased rates of psychological symptoms and mental disorders in celiacs (CDs)[3]. Most studies have been on depression[4-17]. Case series in Gastroenterological departments[4] and case control studies in primary care demonstrated that depression can be a symptom of undiagnosed CD[5]. Whether the levels of depression in CDs under a GFD are comparable to those of controls [general population (GP), other chronic somatic diseases] is under debate. Some studies found more depression in CDs compared to controls of the GP[6-11,13,15,17], others did not[12,14,16]. A few studies also explored anxiety. Some studies reported more anxiety in CDs compared to controls[8,13], some did not[7,16]. The majority of studies were performed in Italy[6-11,13,17] and Scandinavia[12,15,16]. No study has been performed in Germany until now. Only two studies included more than 200 CDs[14,15].

The data regarding potential disease-related determinants of anxiety and depression in CDs on a GFD are also contradictory: one Italian study found no correlation between duration of, and compliance with, GFD and depressed mood[10], whereas another reported increasingly depressed mood with the duration of GFD[13]. An elevated risk of depression in CD patients with type 1 diabetes mellitus and autoimmune thyroiditis has been reported by one study for each of these diseases[14,9]. The influence of demographic factors which are associated with depression in the GP, such as marital status or social class index[18], were only controlled for in a minority of studies[7,8,13]. Moreover, gender aspects in anxiety/depression in CD have been considered only by a few studies, although Scandinavian studies found that female CDs reported more anxiety and depression than male patients[16]. These open questions on anxiety and depression in CDs on a GFD provided us with the aims of our study which were: (1) to explore the potential impact of disease-related, demographic and gender variables on anxiety/depression in CDs; and (2) to compare the levels of anxiety/depression and the frequency of anxiety and depressive disorder in CDs with a sample of the GP and with patients having another chronic somatic disease, with adequate large sample sizes, in a central European country (Germany).

MATERIALS AND METHODS

Ethics

The surveys were approved by the ethics committees of the University of Tübingen and Leipzig and of the board of physicians of the Saarland.

Patients

CD: Within the German Celiac Health Survey of the German Celiac Society DZG, a set of questionnaires was sent out in May 2005 by the DZG to 1000/18 355 of their members ≥ 18 years old, self-reporting a diagnosis of CD according to the membership directory of the DZG, following consecutive postal codes 0-9. To ensure a geographically representative sample every 18th member of the list was contacted by a letter signed by the board of directors of the DZG in which the aims of the study were explained. The letter included a set of questionnaires with a stamped self-addressed envelope enclosed. The patients were asked to give their written informed consent and to fill out and send back the questionnaires within four weeks. Patients < 18 years were not included in the study. There were no other primary exclusion criteria. All patients gave their voluntary informed consent after full written explanation of the aims of the study, including considerations regarding ethics and data protection and the anonymous deposition of the questionnaires[19].

Inflammatory bowel diseases: We selected inflammatory bowel diseases (IBDs) (patients with IBD) for comparison because both diseases have similar gastrointestinal (abdominal pain, diarrhea) and general (fatigue) symptoms and disease-associated disorders (e.g. bone, skin, liver).

Consecutive adult patients (≥ 18 years) with diagnosis of Crohn's disease or ulcerative colitis confirmed

by endoscopy and histology, attending three tertiary care centers for evaluation and/or therapy and members of the German's Crohn's Disease/Ulcerative Colitis Foundation (DCCV), were invited to participate in a study on health-related quality of life (HRQOL)[20]. Patients unable to speak German or with suspicious diagnosis and indeterminate colitis were excluded. Based on the hospital registry and medical documentation, a total of 730 adults were identified who had been attending the specialized outpatient clinic of the Tübingen University Hospital at least once in the last three years with confirmed diagnosis of either Crohn's disease or ulcerative colitis. Every one of these patients received a set of questionnaires by mail and was asked to return it once completed. One reminder was sent out three weeks after initial postal contact. Forty-five consecutive IBD patients of the coloproctological outpatient department of the Department of General and Abdominal Surgery of the University of the Saarland and 23 consecutive IBD inpatients of the Department of Internal Medicine I of the Klinikum Saarbrücken were asked to participate in the study during regular outpatient visits or during a hospital stay after admission for any acute complications of their disease. Physicians were trained to offer instruction and help if persons did not understand the meaning of questions when needed, to collect the questionnaires and to record clinical data using standardized forms. The study took place between January and June, 2000. In edition 4 (2000) of the journal of the German Crohn's disease/Ulcerative Colitis Foundation (DCCV) "Bauchredner", the main topic was "Health-related quality of life and life satisfaction in IBD" and all readers suffering from IBD were invited to participate in our study. The DCCV is the largest patient association for IBD in Germany with around 15 000 members (patients, relatives, physicians). Seventy-six patients indicated their interest to the DCCV and received the set of questionnaires by mail and were asked to return the completed set to the study center in Saarbrücken.

Disease activity was measured by the German Inflammatory Bowel Disease activity Index (GIBDI$_{\text{Crohn's disease}}$ resp. GIBDI$_{\text{Ulcerative colitis}}$). The GIBDI had been validated for the assessment of disease activity in surveys within the German Competence Network Inflammatory Bowel Diseases[21].

General German population: A representative sample of the German GP was selected with the assistance of a demographic consulting company (USUMA, Berlin, Germany). The random selection was based on multistage sampling with three stages (according to the typical random selection procedure in national surveys in Germany). First, 258 sample point regions were randomly drawn from the last political election register, covering rural and urban areas from all regions in Germany. The second stage was a random selection of households using the random route procedure (based on a starting address). The third stage was a random selection of household respondents with the Kish selection grid. The sample aimed to be representative in terms of age, gender, and education for the general German population. The inclusion criteria for the study were age at or above 14 and the ability to read and understand the German language. All subjects were visited by a study assistant informed about the investigation. Self-rating questionnaires were presented. The assistant waited until participants answered all questionnaires, and offered help if persons did not understand the meaning of questions. Data collection took place in 1998[22].

Questionnaires

Medical questionnaires: In both patient surveys a self-developed medical questionnaire assessing the history of the disease and therapy, current symptoms necessary to calculate activity scores, disease-related comorbidities and current medication was included. CDs were asked about comorbid dermatitis herpetiformis, diabetes mellitus type 1, autoimmune thyroiditis, autoimmune liver-biliary tract disease, recurrent aphtae, anemia, Addison's disease, osteoporosis and duodenal carcinoma or lymphoma. Latency of diagnosis was calculated by the reported difference of the time between first medical assessment because of CD-associated symptoms and final diagnosis.

The demographic questionnaire of the German Competence Network "Inflammatory Bowel Diseases"[21] was included in both patient surveys. By questions on education, the occupational status and the available income were used to calculate a social index. Data of this social index can be compared to a representative sample of the general German population[23].

The Hospital Anxiety and Depression Scale (HADS) was specifically designed for the assessment of anxiety and depression in patients with physical illness. With 7 items each on a 4-point Likert scale ranging from 0 to 3, subscale scores for anxiety and depression can be calculated. Scores $\geqslant$ 11 on the anxiety scale are indicative of a probable anxiety disorder (mainly general anxiety disorder). Scores $\geqslant$ 11 on the depression scale are indicative for a probable depressive disorder[24,25]. The HADS is a reliable and valid psychological screening tool for anxiety and depressive disorder in physically ill persons[25] with a validated German version available[26].

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, Release 17.0, Chicago 2008). One missing item of each subscale of the HADS was substituted by the individual median. If more items were missing the patient was excluded from analysis.

Data derived from descriptive statistical analysis are presented in the form of percentages for categorical variables and of the mean and the standard deviation (SD) for continuous data. Categorical data were compared using the χ^2-test and continuous data by *t*-tests or analysis of variance with post-hoc Bonferroni adjusted pairwise comparisons. In addition, anxiety and depres-

sion scores were compared between CDs and IBDs using analysis of covariance adjusting social class index.

Because we were interested in assessing the possible impact of demographic and medical factors on anxiety and depression, the anxiety and depression scores of the HADS served as dependent variables for a multiple regression analysis. Present age, family status, gender, social class index, latency of diagnosis, duration of and compliance with GFD and CD-associated thyroid disease were included as independent variables in a direct multiple regression analysis.

In order to estimate the risk for a possible anxiety and depressive disorder (coded 1 = no, 2 = yes), a logistic regression (all independent variables were included within a single step; no automated stepwise selection procedures were used) was performed with the same variables. The variables were coded as follows for the regression analyses: (1) Demographic variables: sex (1 = male, 2 = female), present age (continuous), living in a family or partnership (1 = yes; 2 = no) and social class index (1 = low, 2 = middle, 3 = high); and (2) CD-associated variables: reported latency between first medical assessments because of CD-associated symptoms and final CD diagnosis (continuous), reported duration of GFD (continuous), reported adherence to GFD (1 = rarely; 2 = sometimes; 3 = most of the time; 4 = all of the time), thyroid disease (1 = no, 2 = yes), DM type 1 (1 = no, 2 = yes).

The internal validity of the model of the logistic regression analysis was tested by the omnibus test of the model coefficient and the Hosmer-Lemeshow-test.

A prevalence of mental disorders of 10% estimated by the HADS in the general German population[23] given a sample size of 219 for each group was calculated to provide 80% power to assess a 10% difference between CD and controls.

Due to multiple comparisons the level of significance was set to $P = 0.01$ for group comparisons.

RESULTS

Return rates

CD: Almost half of the total questionnaires (52.2%, 522 of 1000) were returned. Since six questionnaires were excluded due to missing data, a total of 516 questionnaires were usable for further analyses. Of these, 213 (41.3%) of the respondents indicated that the CD diagnosis was made by duodenal biopsy, 37 (7.2%) by serological tests (CD-specific antibodies), 34 (6.6%) by stool tests (transglutaminase antibodies), and 232 (45.0%) by duodenal biopsy plus serological tests. The 445 patients reporting a biopsy-proven CD were included for further analysis. HADS data were available from 441 patients. Patients who took part in the survey did not differ from those who did not send back the questionnaires in terms of age, sex and geographical region of Germany.

IBD: The total response rate was 63.4% (550/868). Of the 550 returned questionnaires, 128 were excluded from analysis due to colo- or ileostoma ($n = 59$), uncertain diagnosis ($n = 16$), impossibility of calculation of GIBDI because of missing data ($n = 51$), missing HADS data ($n = 6$) or missing declaration of consent ($n = 2$). Patients with moderate ($n = 40$) and severe ($n = 10$) disease activity were excluded from comparison. The IBD group thus consisted of 366 patients; 50% were females. To ensure a sex-matched comparison with CDs, 131 randomly selected male patients were excluded from analysis. Of the 235 included for comparison, 138 (56.3%) patients were in remission, 107 (43.7%) patients had a slight disease activity.

To check for a possible selection bias, the data of responders were compared to the known structural data on all outpatients of the Tübingen outpatient clinic (place of residence, diagnosis, gender, age, duration of disease, age at disease onset, number of consultations in 2000). No indication of systematic selection effect was found in respondents *vs* non-respondents. Likewise, there was no difference in terms of gender and age in patients from the departments of the Saarland University Clinics who did and did not participate. There were no significant differences in the demographic variables and HADS scores of the patients included in and excluded from comparison.

GP: The initial sample consisted of 2952 subjects of whom 2037 (69.0%, $n = 1142$ women) fully participated. Forty-five subjects < 18 years were excluded. Thus the GP sample consisted of 1992 adult persons. Of these, 441 GPs (persons of GP) (346 women, 95 men) were randomly selected for comparison. There were no significant differences in the demographic variables and HADS scores of the persons included in and excluded from comparison.

Medical and demographic data of the celiac sample

The sample consisted of 78.5% women. The most frequently self-reported CD-associated diseases were dermatitis herpetiformis Duhring ($n = 45$, 9.3%) and autoimmune thyroiditis ($n = 25$, 5.6%). Type 1 diabetes mellitus was reported by 2 patients (0.5%). There were no gender differences in the demographic and medical variables assessed. The level of anxiety ($P = 0.0002$) and the frequency of a probable anxiety disorder ($P = 0.01$) were higher in female than in male CDs (Table 1).

Predictors of anxiety and depression in CD

Anxiety was significantly predicted only by female gender ($R^2 = 0.07$, $P = 0.01$). Depression was not significantly predicted by any of the medical and sociodemographic variables tested.

Predictors of a probable anxiety and depressive disorder

Because only in 2/8 patients with CD and diabetes mellitus type 1 an anxiety or depressive disorder was diagnosed, this variable was not entered into the regression analysis.

Anxiety disorder: The model correctly classified 84.8%

Table 1 Demographic data of the celiac disease sample with gender comparison

Variable	Total sample	Females	Males	Test-value *P*-value
Sex (*n*, %)	441 (100)	346 (78.5)	95 (21.5)	
Age, mean (SD)	46.3 (15.1)	45.7 (15.0)	48.5 (15.0)	Not significant
Living in partnership (*n*, %)	334 (76.1)	253 (73.8)	80 (84.2)	Not significant
Social class index (*n*, %)				Not significant
Lower class	26 (6.3)	18 (5.6)	7 (7.5)	
Middle class	271 (65.3)	220 (68.8)	50 (53.8)	
Upper class	118 (28.4)	82 (25.6)	36 (38.7)	
Number of CD-associated diseases (*n*, %)				Not significant
None	240 (55.2)	175 (51.3)	65 (69.9)	
One	118 (27.1)	100 (29.3)	17 (18.3)	
Two	48 (11.0)	40 (11.7)	8 (8.6)	
> Two	29 (6.7)	26 (7.7)	3 (3.2)	
Latency to diagnosis, yr, mean (SD)	5.6 (10.0)	5.9 (9.8)	4.9 (10.7)	Not significant
Years since start of GFD, mean (SD)	8.5 (7.7)	8.5 (7.7)	8.7 (7.7)	Not significant
Compliance with GFD				Not significant
Rarely		20 (5.8)	2 (2.1)	
Sometimes		9 (2.9)	0	
Most of the time		86 (25.0)	30 (32.3)	
All of the time		229 (66.6)	61 (65.6)	
Anxiety, mean (SD)	6.7 (4.09)	7.1 (4.1)	5.3 (3.5)	t = -3.7, P < 0.001
Depression, mean (SD)	4.1 (3.6)	4.3 (3.8)	3.2 (3.9)	t = -2.5, P = 0.01
Probable anxiety disorder (*n*, %)	68 (15.4)	63 (18.2)	5 (5.2)	χ^2 = 9.6, P = 0.001
Probable depressive disorder (*n*, %)	25 (5.7)	24 (6.9)	1 (1.0)	Not significant

Some discrepancies between total number of patients and absolute numbers of some variables are due to missing data. CD: Celiac disease; GFD: Gluten-free diet.

of the patients. Only female sex (OR = 3.6, 95% CI: 1.3-9.4, P = 0.001) was associated with a probable anxiety disorder. Living alone (OR = 0.45, 95% CI: 0.20-0.99, P = 0.05) was associated with a reduced risk of a probable anxiety disorder. The omnibus test of the model coefficient was significant (χ^2 = 20.2, P = 0.009). The level of significance in the Hosmer Lemeshow test was P = 0.5 (χ^2 = 6.9) above the predefined P-value of 0.05, thus confirming the adequacy of the model.

Depressive disorder: None of the variables tested was significantly associated with a probable depressive disorder. The omnibus test of the model coefficient was not significant (χ^2 = 13.5, P = 0.10).

Comparison with GP and patients with chronic IBD

In the CD sample, there were more patients of a higher social class than in the IBD sample (χ^2 = 14.0, P = 0.006). There were no differences between the samples in the other variables tested (Table 2).

The level of anxiety in CDs (6.7 ± 4.0) and IBDs (6.9 ± 3.7) was higher than that seen in GPs (4.6 ± 3.6) (all P < 0.001). After adjusting for social class there was no significant difference in the anxiety level between CDs and IBDs (F = 1.3, P = 0.3).

The level of depression in CDs (4.1 ± 3.6), IBDs (4.6 ± 3.4) and GPs (4.2 ± 3.8) did not differ (P = 0.3). After adjusting social class index, IBDs reported higher depression than CDs (F = 3.9, P = 0.02).

The frequency of a probable anxiety disorder was higher in CDs (15.4%) and IBDs (14.0%) than in GPs (5.7%) (all P < 0.001). There was no difference in the frequency of a probable depressive disorder between the three groups (P = 0.1).

DISCUSSION

We assessed medical and demographic predictors of anxiety and depression in adult patients with CD and compared their levels of anxiety and depression and the frequency of an anxiety or depressive disorder with age- and sex-matched patients with IBD in remission or slight disease activity, and with a representative German population sample. Only female sex, but not medical variables such as duration of and compliance with GFD, predicted anxiety. Depression was not predicted by any of the medical and demographic variables. Anxiety, but not depression, was higher in CDs and IBDs than in GPs.

Comparisons of the results with other studies

Factors associated with anxiety and depression in CD: Two Italian studies found no gender differences in anxiety and depression[10,27] whereas two Scandinavian studies reported lower levels of psychological well-being in female CD patients[16,28]. The higher levels of anxiety in German and Scandinavian women might be explained by general gender differences and/or CD-specific factors. Higher levels of anxiety and frequency of anxiety disorder in women have also been found in the general German population[22]. A higher psychosocial burden on female CDs because of buying and preparing food for the family can be presumed[28,29].

Table 2 Comparisons of patients with celiac disease with patients with inflammatory bowel disease in remission or having slight disease activity and with subjects of the general population

Variable	Celiac disease *n* = 441 (1)	Inflammatory bowel disease *n* = 235 (2)	General population *n* = 441 (3)	Overall comparison	Comparison subgroups
Sex (female) (*n*, %)	346 (78.5)	183 (77.9)	346 (78.5)	Not significant	
Age (mean, SD)	46.3 (15.1)	44.9 (12.4)	49.9 (16.8)	Not significant	
Social class index (*n*, %)			No comparable data available	Not possible	$\chi^2 = 14.5$
Lower	26 (6.3)	28 (11.9)			$P < 0.01$
Middle	271 (65.3)	167 (71.1)			
Upper	118 (28.4)	40 (17.0)			
Living in partnership or with family (*n*, %)	334 (76.1)	187 (80.3)	No comparable data available	Not significant	
Anxiety				$F = 45.9$	1, 2 > 3
Total, mean (SD)	6.7 (4.0)	6.9 (3.7)	4.6 (3.3)	$P < 0.001$	
Depression				Not significant	
Total, mean (SD)	4.1 (3.6)	4.6 (3.4)	4.2 (3.8)		
Probable anxiety disorder				$\chi^2 = 23.2$	1, 2 > 3
Total (*n*, %)	68 (15.4)	33 (14.0)	25 (5.7)	$P < 0.001$	
Probable depressive disorder				Not significant	
Total (*n*, %)	25 (5.7)	12 (5.1)	38 (8.6)		

In contrast to findings in the GP[18,30], low social class index was not associated with anxiety and depression in CDs. In contrast to the GP[18,30], living in a family was associated in CDs with the risk of an anxiety disorder. We speculate that the problems of buying and preparing food in a family with CDs and non-CDs might lead to financial and interpersonal problems which can contribute to an anxiety disorder.

In line with one Italian longitudinal study[7] and one Italian cross-sectional study[10], we found no association between depressed mood and the duration of GFD. We also found no association between anxiety and the duration of GFD. This finding is not contradictory to the results of longitudinal studies which reported a decrease of anxiety (state) after starting a GFD[7,12]: a GFD may reduce psychological symptoms due to malabsorption of tryptophan, but may also increase psychological distress associated with the financial and social restrictions of GFD and disease-related worries[6,31].

We confirm the results of two Italian studies which found no association between non-compliance with GFD and anxiety/depression[10,13].

The limited number of CDs with diabetes mellitus type 1 prohibited a comparison with an American study which reported a higher prevalence of depression in CD patients with type 1 diabetes mellitus (5.8% of the sample) compared to celiacs without type 1 diabetes mellitus[14]. We could not confirm a higher prevalence of depressive disorders in CDs with autoimmune thyroiditis[9].

Anxiety/depression in CDs compared to controls: The different instruments used to assess anxiety and depression do not allow a comparison of prevalence rates in studies on anxiety/depression in CD. Moreover, the studies differed in the ways of recruiting patients and in the type of controls used. Some studies used healthy subjects[6-10,13,14,17], GP[15,16] or patients with diabetes[13], IBD[6], irritable bowel syndrome[14] and chronic hepatitis[10] for controls. Despite these limitations, we can state that our finding that CDs are not more depressed than controls is in line with the results of one American[14] and two Scandinavian[11,16] studies and in contrast to the findings of the Italian studies[6-11,13,17]. Our finding of more anxiety in CDs compared to GP controls is in line with that of Italian studies[7-9] and in contrast to Scandinavian studies[11,16].

Limitations of the study

Some limitations of the study have to be considered. First, the study population consisted of adult CDs recruited among members of the German Celiac Society which may have induced a selection bias. A large hospital-based register of CD patients is not available in Germany. Furthermore, to our knowledge, most CDs attending tertiary care outpatient departments in Germany are associated with the German Celiac Society. Additionally, we cannot exclude a response bias of CDs sending back the questionnaires. Nevertheless, the CD sample of our study is the best available one in Germany. Second, we cannot exclude a response bias of CD and IBD patients sending back the questionnaires. Third, another potential bias of the study is the different approach to completing and returning the questionnaires. In the subsamples of the GP and the IBD patients of the departments of Homburg/Saar and Saarbrücken, help was offered if persons did not understand the meaning of questions and the questionnaires were recollected by research assistants or physicians. The questionnaires of the celiac and IBD sample of the department of Tübingen were completed without potential external support and returned by mail. Fourth, all data on the history and type of diagnosis, CD-associated diseases and on adherence to regimen relied solely on the participants' self report. Due to data protection in this type of survey, information from clinical records, interviews or serological/radiological tests was not available. Fifth, due to the type of study (postal survey) we were unable to use standardized psychiatric interviews for the confirmation of a probable

mental disorder when the critical cut-off scores of the HADS were surpassed. Furthermore, the items on anxiety of the HADS cover general anxiety but not phobic symptoms. Therefore, our data cannot comment on the high frequency of social phobia seen in Italian patients[8]. However, the HADS is one of the best screening tools available for anxiety and depressive disorders in patients with somatic diseases[25]. Finally, because of the cross-sectional nature of the study the results show only associations between factors and do not allow for conclusions for causality.

In conclusion, German patients with CD on a GFD do not differ from the GP in levels of depression, but there is a subgroup of mainly female CDs with a probable anxiety disorder. Mental disorders increase the risk of a reduced health-related quality of life[31] and of irritable bowel-like symptoms in CDs[32]. A screening for comorbid anxiety disorders in female patients with CD on a GFD by general practitioners and gastroenterologists is therefore recommended, and screening is possible by using the ultra-brief screening scale for anxiety and depression, PHQ-4[33]. The two questions on anxiety in the PHQ-4 can be directly asked: "Over the last two weeks, have you often been bothered by feeling nervous, anxious, or on edge? Over the last two weeks, have you often not been able to stop or control worrying?"

COMMENTS

Background

Previous studies have yielded conflicting results regarding the presence of an association of celiac disease (CD) in patients on a gluten-free diet (GFD) and anxiety/depression.

Research frontiers

Anxiety and depression are common symptoms in the general population (GP) as well as in other chronic somatic diseases and are associated with demographic factors such as age, gender and social class. Most studies on anxiety/depression in CD were not adequately powered to detect differences in anxiety and depression between CD and controls. In this study with adequately powered sample sizes, the authors demonstrate that anxiety in CD patients on a GFD is higher than in the GP and comparable to that of patients with inflammatory bowel disease who are in remission and have slight disease activity.

Innovation and breakthroughs

Recent reports have highlighted the importance of female gender and other autoimmune disorders associated with CD as predictors of depression in CD. This is the first study to report an association between anxiety disorder and female gender in CD. The study did not confirm findings that autoimmune thyroid disorder is a risk factor for depressive disorder in CD.

Applications

The study substantiated the necessity of exploring not only somatic but also anxiety symptoms in female CD patients on a GFD.

Peer review

This paper is worthy of publication as the first comprehensive study of anxiety and depression in German adult CD. It needs to be substantially revised, reduced in size, particularly in the Discussion and number of tables, and be less speculative.

REFERENCES

1 **Green PH**, Cellier C. Celiac disease. *N Engl J Med* 2007; **357**: 1731-1743

2 **Catassi C**, Rätsch IM, Gandolfi L, Pratesi R, Fabiani E, El Asmar R, Frijia M, Bearzi I, Vizzoni L. Why is coeliac disease endemic in the people of the Sahara? *Lancet* 1999; **354**: 647-648

3 **Addolorato G**, Leggio L, D'Angelo C, Mirijello A, Ferrulli A, Cardone S, Vonghia L, Abenavoli L, Leso V, Nesci A, Piano S, Capristo E, Gasbarrini G. Affective and psychiatric disorders in celiac disease. *Dig Dis* 2008; **26**: 140-148

4 **Hallert C**, Derefeldt T. Psychic disturbances in adult coeliac disease. I. Clinical observations. *Scand J Gastroenterol* 1982; **17**: 17-19

5 **Cannings-John R**, Butler CC, Prout H, Owen D, Williams D, Hood K, Crimmins R, Swift G. A case-control study of presentations in general practice before diagnosis of coeliac disease. *Br J Gen Pract* 2007; **57**: 636-642

6 **Addolorato G**, Stefanini GF, Capristo E, Caputo F, Gasbarrini A, Gasbarrini G. Anxiety and depression in adult untreated celiac subjects and in patients affected by inflammatory bowel disease: a personality "trait" or a reactive illness? *Hepatogastroenterology* 1996; **43**: 1513-1517

7 **Addolorato G**, Capristo E, Ghittoni G, Valeri C, Mascianà R, Ancona C, Gasbarrini G. Anxiety but not depression decreases in coeliac patients after one-year gluten-free diet: a longitudinal study. *Scand J Gastroenterol* 2001; **36**: 502-506

8 **Addolorato G**, Mirijello A, D'Angelo C, Leggio L, Ferrulli A, Vonghia L, Cardone S, Leso V, Miceli A, Gasbarrini G. Social phobia in coeliac disease. *Scand J Gastroenterol* 2008; **43**: 410-415

9 **Carta MG**, Hardoy MC, Boi MF, Mariotti S, Carpiniello B, Usai P. Association between panic disorder, major depressive disorder and celiac disease: a possible role of thyroid autoimmunity. *J Psychosom Res* 2002; **53**: 789-793

10 **Ciacci C**, Iavarone A, Mazzacca G, De Rosa A. Depressive symptoms in adult coeliac disease. *Scand J Gastroenterol* 1998; **33**: 247-250

11 **Cicarelli G**, Della Rocca G, Amboni M, Ciacci C, Mazzacca G, Filla A, Barone P. Clinical and neurological abnormalities in adult celiac disease. *Neurol Sci* 2003; **24**: 311-317

12 **Collin P**, Kaukinen K, Mattila AK, Joukamaa M. Psychoneurotic symptoms and alexithymia in coeliac disease. *Scand J Gastroenterol* 2008; **43**: 1329-1333

13 **Fera T**, Cascio B, Angelini G, Martini S, Guidetti CS. Affective disorders and quality of life in adult coeliac disease patients on a gluten-free diet. *Eur J Gastroenterol Hepatol* 2003; **15**: 1287-1292

14 **Garud S**, Leffler D, Dennis M, Edwards-George J, Saryan D, Sheth S, Schuppan D, Jamma S, Kelly CP. Interaction between psychiatric and autoimmune disorders in coeliac disease patients in the Northeastern United States. *Aliment Pharmacol Ther* 2009; **29**: 898-905

15 **Ludvigsson JF**, Reutfors J, Osby U, Ekbom A, Montgomery SM. Coeliac disease and risk of mood disorders--a general population-based cohort study. *J Affect Disord* 2007; **99**: 117-126

16 **Roos S**, Kärner A, Hallert C. Psychological well-being of adult coeliac patients treated for 10 years. *Dig Liver Dis* 2006; **38**: 177-180

17 **Siniscalchi M**, Iovino P, Tortora R, Forestiero S, Somma A, Capuano L, Franzese MD, Sabbatini F, Ciacci C. Fatigue in adult coeliac disease. *Aliment Pharmacol Ther* 2005; **22**: 489-494

18 **Akhtar-Danesh N**, Landeen J. Relation between depression and sociodemographic factors. *Int J Ment Health Syst* 2007; **1**: 4

19 **Häuser W**, Gold J, Stein J, Caspary WF, Stallmach A. Health-related quality of life in adult coeliac disease in Germany: results of a national survey. *Eur J Gastroenterol Hepatol* 2006; **18**: 747-754

20 **Janke KH**, Klump B, Gregor M, Meisner C, Haeuser W. Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11**: 272-286

21 **Janke KH**, Raible A, Bauer M, Clemens P, Meisner C, Häuser W, Steder-Neukamm U, Henrich G, Herschbach P, Gregor M, Klump B. Questions on life satisfaction (FLZM) in inflammatory bowel disease. *Int J Colorectal Dis* 2004; **19**: 343-353

22 **Hinz A**, Schwarz R. [Anxiety and depression in the general

population: normal values in the Hospital Anxiety and Depression Scale] *Psychother Psychosom Med Psychol* 2001; **51**: 193-200
23 **Deck R**, Röckelein E. Assessment of sociodemographic and socialmedical indicators within cooperatives of research in rehabilitation medicine. *DRV Schriften* 1999; **16**: 85-96
24 **Zigmond AS**, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361-370
25 **Bjelland I**, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**: 69-77
26 **Herrmann C**, Buss U, Snaith RP. HADS-D: Hospital Anxiety and Depression Scale - German Version. Bern: Hans Huber, 1995
27 **Ciacci C**, D'Agate C, De Rosa A, Franzese C, Errichiello S, Gasperi V, Pardi A, Quagliata D, Visentini S, Greco L. Self-rated quality of life in celiac disease. *Dig Dis Sci* 2003; **48**: 2216-2220
28 **Hallert C**, Sandlund O, Broqvist M. Perceptions of health-related quality of life of men and women living with coeliac disease. *Scand J Caring Sci* 2003; **17**: 301-307
29 **Sverker A**, Ostlund G, Hallert C, Hensing G. 'I lose all these hours...'--exploring gender and consequences of dilemmas experienced in everyday life with coeliac disease. *Scand J Caring Sci* 2009; **23**: 342-352
30 **Jacobi F**, Wittchen HU, Holting C, Höfler M, Pfister H, Müller N, Lieb R. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). *Psychol Med* 2004; **34**: 597-611
31 **Häuser W**, Stallmach A, Caspary WF, Stein J. Predictors of reduced health-related quality of life in adults with coeliac disease. *Aliment Pharmacol Ther* 2007; **25**: 569-578
32 **Häuser W**, Musial F, Caspary WF, Stein J, Stallmach A. Predictors of irritable bowel-type symptoms and healthcare-seeking behavior among adults with celiac disease. *Psychosom Med* 2007; **69**: 370-376
33 **Kroenke K**, Spitzer RL, Williams JB, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics* 2009; **50**: 613-621

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