Impact of gluten-free diet on quality of life in celiac patients.

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Abstract

Background and study aims : **Celiac disease (CD) is a common gluten-related disorder, whose only treatment is a gluten-free diet (GFD). Since a unique view on psychological consequences of a GFD still lacks, our aim was to assess the quality of life (QoL) and the depression state in symptomatic CD patients after GFD. Socio-demographic features were considered.**

Patients and methods : **210 adult CD patients were recruited and divided into 3 groups : 70 newly diagnosed patients (Group A),70 patients who have been on GFD for 6-12 months (Group B), and 70 patients who have been on GFD for more than 12 months (Group C). We recruited 210 healthy controls (Group D). Psychological General Well-Being Index (PGWBI) and Beck Depression Inventory (BDI) questionnaires were administered. Each group was evaluated according to age, gender and school ranking.**

Results : **Groups A and B showed lower PGWBI scores compared with both Group C and D ($p < 0.001$ for each comparison). Moreover, Groups A and B showed higher BDI scores compared with both Group C and D ($p < 0.001$ for each comparison). Women, the elderly and the poorly educated seemed to suffer more psychological stress.**

Conclusions : **GFD induces an improvement of well-being and a decrease of depression state after 12 months of strict GFD. Negative psychological implications were observed only in specific risk categories.** (Acta gastroenterol. belg., **2016**, 79, **447-453**).

Key words : celiac disease, gluten-free diet, well-being, depression, PGWBI, BDI.

Introduction

Celiac disease (CD) is a complex autoimmune enteropathy caused by dietary gluten in genetically susceptible individuals (1). With a prevalence close to 1-3%, it may be considered one of the most common food-related gastroenterological diseases (2,3). CD is characterized by duodenal mucosa alterations consisting in villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis (4). Nowadays CD diagnosis is based on histology, albeit supported by specific HLA haplotypes (DQ2 and DQ8) and serological tests: IgA and IgG anti endomysium (EMA), as well as IgA and IgG anti-transglutaminase (anti-tTG) antibodies are among the most sensitive and specific tests (5). This specific CD antibody detection can be performed also in cultural supernatants of duodenal mucosa biopsies (6). The only known treatment for CD to date is a lifelong and strict GFD with complete avoidance of any food containing gluten, thus making habit changes inevitable (7).

Since the main target organ of CD is the small bowel, the most common detectable signs and symptoms are diarrhea, bloating, abdominal pain and iron deficiency anemia (8,9). CD extra-intestinal manifestations are well-known too, such as dermatitis herpetiformis, arthritis and neurologic disorders, peripheral neuropathy and ataxia (10). Moreover, health care professionals should be aware of the psychological burden of CD (11-13). In particular, anxiety and depression are common complaints in untreated patients and contribute to lower their quality of life (QoL). This may be secondary to reduced well-being itself (14), malabsorption of micronutrients (15) or specific comorbidities (such as autoimmune (16), chronic (17) or functional disorders (18). Despite the fact that some of these conditions may improve rapidly, some CD patients may continue to suffer from significant psychological morbidity (19) even after a GFD. Probably, lifelong habit change, dietary restrictions and alimentary alternatives may have a negative impact on their psychological equilibrium, leading to a reduced QoL (20).

Although CD patients have been extensively studied, a definitive and unique view on this issue has not been reached yet (21). Some authors reported a positive effect of the GFD both in symptomatic and in asymptomatic patients (22), while others described an increased QoL only in symptomatic patients (23-25). Conversely, other authors even found no significant differences in QoL between healthy and celiac population at short- and long-term GFD (26, 27).

To go further into detail, a systematic review by Hall et al. (28) tried to evaluate the influence of different socio-cultural factors on the adherence to GFD and consequent QoL, without univocal results. After a first rapid recovery, CD patients – especially women – seem to do less well in the course of treatment, but data on the long-term outcome in these subjects are scarce (29).

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As anticipated above, a real debate on the psychological consequences of a GFD in CD patients is still open and the aim of our work was to assess the well-being and depression state of symptom-detected CD patients before and after a strict GFD. We also wanted to investigate any demographic or cultural influence in the psychological response to GFD, considering criteria such as such as sex, age and education.

Materials And Methods

Patients

A total of 210 subjects referring to our Gastrointestinal Unit and 210 blood donors were enrolled from September 2013 to March 2015 : the first 210 were enrolled as symptom-detected CD outpatients and the other 210 as healthy controls. All subjects were enrolled consecutively until the predetermined fixed sample size was reached in the above mentioned span of time.

The 210 symptom-detected CD patients (40M/170F, median age 36, range 18-60 years) were divided in 3 groups:

- 70 newly diagnosed CD patients (**Group A**) : all these patients still presented positive serological IgA EMA and IgA anti-tTG antibodies, as well as typical duodenal mucosa abnormalities according to Marsh-Oberhuber classification (class III A, B or C).
- 70 CD patients who have been on GFD for 6-12 months (**Group B**) : these patients showed negative results for serum IgA EMA and IgA anti-tTG antibodies, as well as duodenal histological picture <III A according to Marsh-Oberhuber classification.
- 70 CD patients who have been on GFD for more than 12 months (**Group C**) : these patients showed negative results for serum IgA EMA and IgA anti-tTG antibodies, as well as histological picture <III A according to Marsh-Oberhuber classification. Twelve months of GFD was established as enough to reach actual serological and histological remission (30, 31). Dietetic assessment by an expert dietician, based on an interview and food diary was also regularly guaranteed as objective non-invasive method of measuring adherence to GFD (32).

The 210 healthy controls (90M/120F ; median age 35 ; range 18-60 years) (**Group D**) were asymptomatic and showed negative CD antibodies on gluten-containing diet.

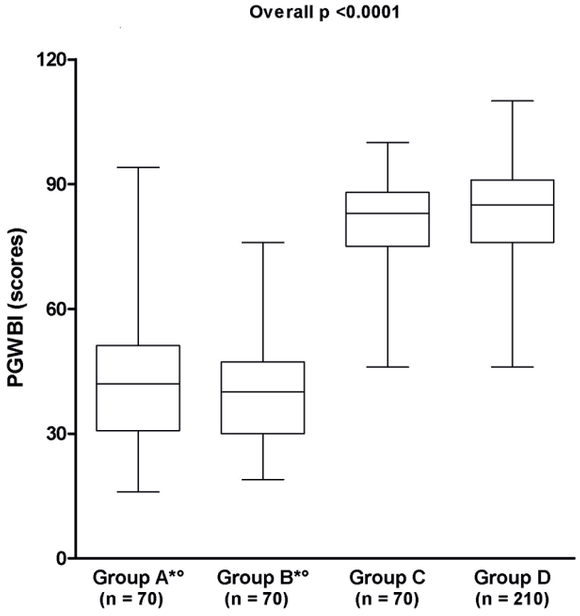

Fig. 1. — PGWBI scores calculated in all study participants PGWBI scores computed in the Groups A, B, C and D are plotted in the graph as median values, quartile cutpoints (first and third quartile) and range (maximum and minimum value). The overall p refers to Kruskal-Wallis test applied among the four groups, while the symbols refer to Dunn multiple comparison applied as posttest between each groups' pair (* p <0.001 vs. Group C,° p <0.001 vs. Group D).
GFD, gluten-free diet ; Group A, untreated CD patients ; Group B, CD patients on GFD from 6-12 months ; Group C, CD patients on GFD from >12 months ; Group D, healthy controls;

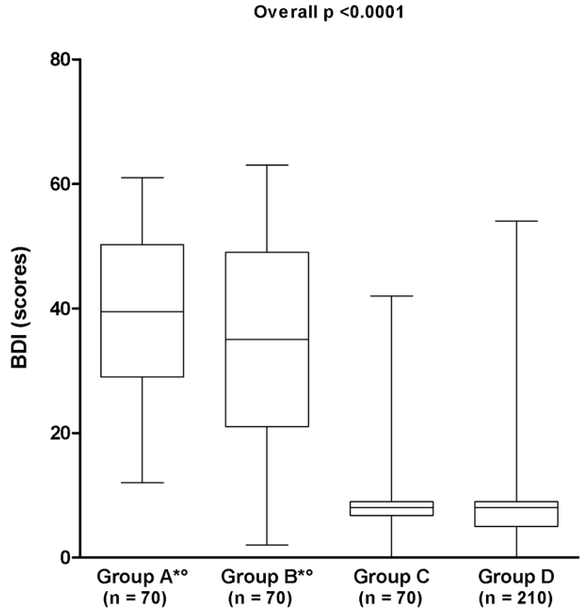

Fig. 2. — BDI scores calculated in all study participants BDI scores computed in the Groups A, B, C and D are plotted in the graph as median values, quartile cut-points (first and third quartile) and range (maximum and minimum value). The overall p refers to Kruskal-Wallis test applied among the four groups, while the symbols refer to Dunn multiple comparison applied as post-test between each groups' pair (* p <0.001 vs. Group C,° p <0.001 vs. Group D).
BDI,beck depression inventory; GFD,gluten-free diet ; Group A, untreated CD patients;
Group B, CD patients on GFD from 6-12 months; Group C, CD patients on GFD from >12 months ; Group D, healthy controls.

Table 1. — Results of the six HRQoL domains included in PGWBI calculation

	HRQoL domain scores					
	Anxiety	**Depression**	**Positivity**	**Self control**	**Health**	**Vitality**
***Group A* (n = 70)**	5 (4-9)*°	5 (1.5-9)*°	6 (5-10)*°	7 (5-10)*°	9 (6-10)*°	9 (6-11)*°
***Group B* (n = 70)**	5 (4-8)*°	5.5 (3.75-9)*°	8 (5.75-10)*°	7 (4-9)*°	7.5 (5-10)*°	6.5 (4-9)*°
***Group C* (n = 70)**	16 (11-19)	13 (10-15)	15 (12-18)	12 (10-14)	12.5 (10-14.25)	15 (10.75-19)
***Group D* (n = 210)**	16 (12-20)	14 (11-15)	15 (12-18)	13 (10-14)	12 (10-15)	15 (12-18)

HRQoL domain scores calculated in the ***Groups A***, ***B***, ***C***and ***D*** are reported in the table as median values and quartile cut-points (first and third quartile). The symbols refer to Dunn multiple comparison applied as Kruskal-Wallis post-test between each groups' pair (* p <0.001 vs. ***Group C***, ° p <0.001 vs. ***Group D***).
Group A, untreated CD patients ; ***Group B***, CD patients on GFD from 6-12 months ; ***Group C***, CD patients on GFD from >12 months ; ***Group D***, healthy volunteers ; ***HRQoL***, healt-related quality of life ; ***PGWBI***, psychological general well-being index.

Each group (***Group A-D***) was divided into 3 further sub-groups : age (18-29, 30-44, 45-60 years), gender (male, female) and school ranking (high and low school ranking, where low school ranking included subjects who have fulfilled only the compulsory schooling or less). For more details about sample size of each subgroup see Figures 3-5.

Exclusion criteria were: age <18 and age> 65 ; screen-detected asymptomatic CD.

Psychological Questionnaires

Two questionnaires were administered to each patient studied: Psychological General Well-Being Index (PGWBI) and Beck Depression Inventory (BDI).

Psychological general well-being index

The Psychological general well-being index (PGWBI) was administered to each patient studied in order to assess the psychological well-being state. This questionnaire consists of 22 self-administered items, rated on a 6-point scale, which assess psychological and general well-being of respondents in six health-related quality of life (HRQoL) domains : anxiety, depressed mood, positive well-being, self-control, general health and vitality (33). The scores for all domains can be summarized to provide a summary score, which reaches a maximum of 110 points, representing the best achievable "well-being".

Beck depression inventory

The Beck Depression Inventory (BDI) is a 21-item questionnaire that assesses cognitive, behavioral, affective and somatic components of depression (34, 35). Responses are made on a 4-point scale from 0 to 3. The severity of the symptoms is rated numerically by total score : 0-9 normal ; 10-15 mild depression ; 16-19 mild to moderate depression ; 20-29 moderate to severe depression ; and 30-63 severe depression.

Statistical Analysis

Data achieved in this study were firstly analyzed by the D'Agostino-Pearson omnibus test to verify the normal distribution hypothesis within each statistical sample. Given that some resulting p values were significant (p <0.05), it is reasonable to assume that not all data obtained from every group of participants fall into Gaussian distributions and therefore, were calculated as median values, quartile cut-points (first and third quartile) and range (maximum and minimum value). For the same reason, data were processed by means of non-parametric tests.

Comparisons between the parameters calculated in two different groups or subgroups of participants were performed by using the Mann-Whitney test. Differences among the parameters computed in more than two different groups or subgroups of participants were assessed by the Kruskal-Wallis test where, for overall p values <0.05, the Dunn multiple comparison was used as post test.

In all tests applied, the p values <0.05 were considered significant. The statistical evaluations were carried out by using the GraphPad Prism package version 5.2 (GraphPad Software Inc., San Diego, CA).

All procedures followed in this study were in accordance with the ethical standards of the institutional committee responsible for human experimentation. Furthermore, a written informed consent was obtained from each patient being studied.

Results

In CD patients belonging to ***Groups A*** and ***B***, PGWBI scores were significantly lower than those calculated in ***Groups C*** and ***D*** (p <0.001 for each comparison), showing a reduced QoL. CD patients belonging to ***Group C*** showed a good QoL, similar to healthy controls from ***Group D*** (Figure 1). Also the HRQoL domain scores, including anxiety, depression, positivity, self control, health and vitality, were significantly lower in the study participants belonging to ***Groups A*** and ***B*** than in those from the ***Groups C*** and ***D*** (p <0.001 for each comparison) (Table 1).

In CD patients belonging to ***Groups A*** and ***B***, BDI scores were significantly higher than those calculated for ***Groups C*** and ***D*** (p <0.001 for each comparison),

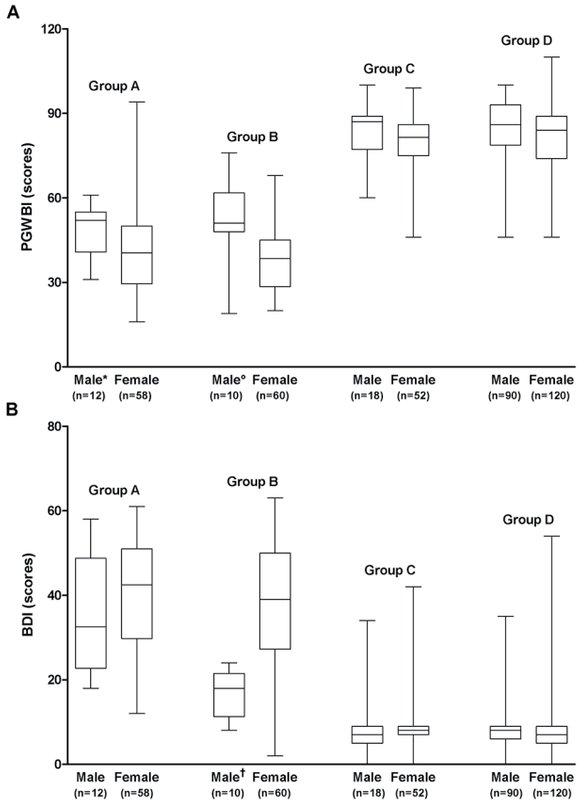

Fig. 3A and 3B. — PGWBI and BDI scores in the study groups subdivided according to gender

PGWBI [A] and BDI [B] scores are plotted in the graphs as median values, quartile cut-points (first and third quartile) and range (maximum and minimum value). The symbols refer to Mann-Whitney test applied between each subgroups' pair (* p = 0.0185 vs. female subgroup, ° p = 0.0017 vs. female subgroup, †p <0.0001 vs. female subgroup).

BDI, beck depression inventory ; GFD, gluten-free diet ; Group A, untreated CD patients ;

Group B, CD patients on GFD from 6-12 months ; Group C, CD patients on GFD from >12 months ; Group D, healthy controls ; PGWBI, psychological general well-being index.

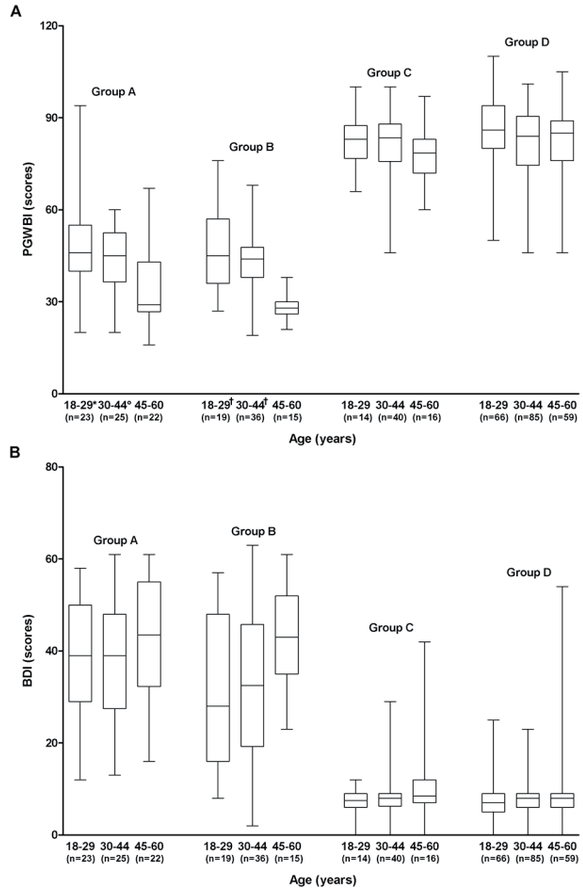

Fig. 4A and 4B. — PGWBI and BDI scores in the study groups subdivided according to age

PGWBI [A] and BDI [B] scores are plotted in the graphs as median values, quartile cut-points (first and third quartile) and range (maximum and minimum value). The symbols refer to Dunn multiple comparison applied as Kruskal-Wallis post-test between each subgroups' pair (* p < 0.01 vs. 45-60 year subgroup, ° p < 0.05 vs. 45-60 year subgroup, † p <0.001 vs. 45-60 year subgroup).

BDI, beck depression inventory ; GFD, gluten-free diet ; Group A, untreated CD patients ; Group B, CD patients on GFD from 6-12 months ; Group C, CD patients on GFD from >12 months ; Group D, healthy controls ; PGWBI, psychological general well-being index.

showing an increased depressive state. CD patients belonging to ***Group C*** showed no depression, similarly to healthy controls from the ***Group D*** (Figure 2). PGWBI scores were significantly higher in males belonging to ***Groups A*** and ***B*** than in females from the same groups (p = 0.0185 and p = 0.0017, respectively) (Figure 3A). Moreover, BDI scores were significantly lower in males belonging to ***Group B*** than in females from the same group (p <0.0001) (Figure 3B).

In the ***Group A***, PGWBI scores were significantly higher in patients aged 18-29 and 30-44 years than in those 45-60 year old (p <0.01 and p <0.05, respectively). Also in the ***Group B***, PGWBI scores were significantly higher in patients ranging 18-29 and 30-44 years than in those 45-60 year old (p <0.001 for both comparisons) (Figure 4A). In both ***Groups A*** and ***B***,BDI scores tended to be lower in patients aged 18-29 and 30-44 years than in those aged 45-60, although statistical significance was not reached (Figure 4B).

PGWBI scores were significantly lower in the poorly educated patients (I degree) from

Groups B,***C*** and ***D,*** compared with more educated patients (II degree) from the same groups (p = 0.0090, p = 0.0004 and p <0.0001, respectively) (Figure 5A). No significant difference in BDI scores was found according to school degree (Figure 5B).

Discussion

CD, a chronic immune-mediated disease of the intestinal tract, also has extra-intestinal implications,

including psychological ones. It affects genetically susceptible individuals, it is triggered by gluten ingestion (36) and its only treatment is a life-long GFD.

A real debate on the psychological consequences of GFD in CD patients is still open. Some authors describe a persistently low (29) or even a progressively worsening (37) QoL of long-term strictly treated CD patients, regardless of symptoms.

Another school of thought affirms that GFD induces a rapid and significant psychological improvement in symptomatic patients (25)**.**In particular, Nachman et al. assessed that after one year of treatment, BDI improved and was comparable to healthy controls, irrespective of the clinical severity at diagnosis (38), as well as Martínez Cerezo et al. demonstrated that symptoms and PGWBI improve after a GFD (12).

Our work intends to support and integrate the last view point, confirming that a strict GFD is able to induce not only clinical remission, but also a general psychological improvement. Our study may result limited since asymptomatic CD patients have been excluded, but according to our experience and previous literature (22), symptomatic patients can provide a clearer and more objective clinical presentation, more suitable for this kind of follow-up.

According to our data, well-being was low in CD patients at diagnosis and at the beginning of GFD (***Groups A*** and ***B***)and seemed to improve on prolonged GFD (***Group C***),even reaching results comparable with the healthy controls (***Group D***).The same improvement was also observed for the depression state.

These data suggest that the achievement of psychological well-being could depend on the ***long lasting*** and ***correct*** GFD, properly supported by serological and histological disease remission, as well as dietetic assessment by an expert dietician (32).

In regard to socio-demographic factors, our data clearly confirm that female CD patients at diagnosis and at the beginning of GFD suffer more psychological stress compared to men. Moreover, the older CD patients (aged over 45) at diagnosis or on early GFD were found to be more affected by poor QoL than younger patients. Finally, a significantly worse QoL was found in low-educated CD patients, maybe conditioned by the fact that following a GFD is also more expensive: lower educated individuals may have less economic flexibility to purchase gluten-free products or substitutes.

It is conceivable that the initial depression and the poor well-being of CD patients may be due to the disease itself and its symptoms, rather than the harsh restrictions of GFD. However, negative psychological implications related to GFD were observed in specific categories (women, elderly and poor-educated), in which the individuals were probably more reluctant to accept radical changes to eating habits. Psycho-sociological and economic issues could be important, particularly in Italy, where the major source of carbohydrates are pasta, bread or pizza and food derived from wheat which are inexpensive, easily available and considered healthier. This is evident especially for women, who still carry the main responsibility to provide food for themselves and their family and feel the weight of this burden especially when shopping for food, cooking and when feeding their family (39). Going deeper into the problem, negative psychological implications related to GFD in poor-educated patients could be much more likely due to social and socialization issues, rather than economic ones. it is surely no coincidence that the Italian law number 123 (July 4, 2005) recognizes CD as "social disease" and even a financial support is guaranteed to CD patients to buy gluten-free food. We should also not underestimate the wide spread and consumption of pasta, bread and pizza (especially

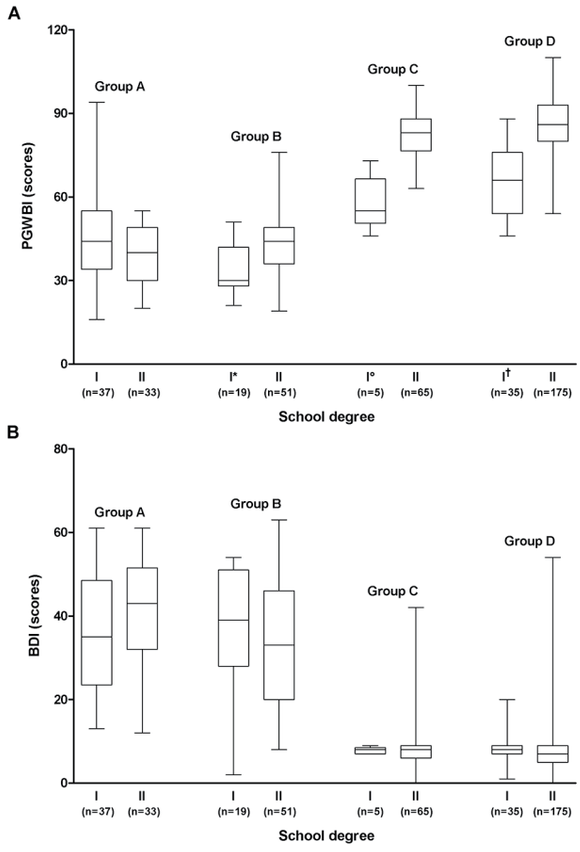

Fig. 5. — PGWBI and BDI scores in the study groups subdivided according to school degree

PGWBI [A] and BDI [B] scores are plotted in the graphs as median values, quartile cut-points (first and third quartile) and range (maximum and minimum value). The symbols refer to Mann-Whitney test applied between each subgroups' pair (* $p = 0.0090$ vs. II degree subgroup, ° $p = 0.0004$ vs. II degree subgroup, $^{\dagger}p < 0.0001$ vs. II degree subgroup).

BDI, beck depression inventory; GFD,gluten-free diet; Group A,untreated CD patients;

Group B,CD patients on GFD from 6-12 months; Group C,CD patients on GFD from >12 months; Group D,healthy controls; PGWBI,psychological general well-being index.

in Italy), which prevent restaurants and food service establishments from following procedures to maintain a gluten-free environment and, consequently, being certified as gluten-free places. All these anthropological and economic considerations surely deserve further investigations.

To conclude, a ***strict*** GFD is mandatory in order to induce the resolution of both organic disorders and psychological imbalances in CD patients. It is equally clear that certain socio-economical groups also need psychological support and a proper education, together with clinical follow-up.

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Authors contribution:R. Borghini and A. Picarelli have contributed in the conception, design, performing experiments, data interpretation and writing of the work; M. Di Tola and M. Marino have contributed in data interpretation and statistical analysis; E. Salvi has contributed in the conception, design, performing experiments and data interpretation of the work; C. Isonne and M. Puzzono have contributed in data interpretation and writing of the work; G. Donato performed endoscopic diagnostic procedures.

All authors approved the final version of the article, including the authorship list.

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References

1. ABADIE V., SOLLID L.M., BARREIRO L.B., JABRI B. Integration of genetic and immunological insights into a model of celiac disease pathogenesis. *Annu. Rev. Immunol*., 2011, **29** : 493-525.
2. PICARELLI A., BORGHINI R., ISONNE C., DI TOLA M. Reactivity to dietary gluten: new insights into differential diagnosis among gluten-related gastrointestinal disorders. *Pol. Arch. Med. Wewn*., 2013, **123(12)** : 708-12.
3. MYLÉUS A., IVARSSON A., WEBB C., DANIELSSON L., HERNELL O., HÖGBERG L. *et al*. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. *J. Pediatr. Gastroenterol. Nutr*., 2009 Aug, **49(2)** : 170-6.
4. DATTA GUPTA S. Pathology of celiac disease : a brief review. *Trop. Gastroenterol*., 2013 Oct-Dec, **34(4)** : 207-26.
5. MOONEY P.D., HADJIVASSILIOU M., SANDERS D.S. Coeliac disease. *BMJ*, 2014 Mar 3, **348** : g1561.
6. PICARELLI A., DI TOLA M., MARINO M., LIBANORI V., BORGHINI R., SALVI E. *et al*. Usefulness of the organ culture system when villous height/crypt depth ratio, intraepithelial lymphocyte count, or serum antibody tests are not diagnostic for celiac disease. *Transl. Res*., 2013 Mar, **161(3)** : 172-80.
7. LUDVIGSSON J.F., BAI J.C., BIAGI F., CARD T.R., CIACCI C., CICLITIRA P.J. *et al*. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut*., 2014 Aug, **63(8)** : 1210-28.
8. DUGGAN J.M. Coeliac disease : the great imitator. *Med. J. Aust*., 2004 May, 17, **180(10)** : 524-526.
9. REILLY N.R., FASANO A., GREEN P.H. Presentation of celiac disease. *Gastrointest. Endosc. Clin. N. Am*., 2012 Oct, **22(4)** : 613-21.
10. HERNANDEZ L., GREEN P.H. Extraintestinal manifestations of celiac disease. *Curr. Gastroenterol. Rep*., 2006 Oct, **8(5)** : 383-9.
11. URBAN-KOWALCZYK M., OEMIGIELSKI J., GMITROWICZ A. Neuropsychiatric symptoms and celiac disease. *Neuropsychiatr. Dis. Treat*., 2014 Oct, **10** : 1961-4.
12. MARTÍNEZ CEREZO F.J., CASTILLEJO G., GUILLEN N., MORENTE V., SIMÓ J.M., TENA F.J. *et al*. Psychological alterations in patients with adult celiac disease. *Gastroenterol. Hepatol*., 2014 Apr, **37(4)** : 240-5.
13. CIACCI C., IAVARONE A., SINISCALCHI M., ROMANO R., DE ROSA A. Psychological dimensions of celiac disease: toward an integrated approach. *Dig. Dis. Sci*., 2002 Sep, **47(9)** : 2082-7.
14. KURPPA K., COLLIN P., MÄKI M., KAUKINEN K. Celiac disease and health-related quality of life. *Expert Rev. Gastroenterol. Hepatol*., 2011 Feb, **5(1)** : 83-90.
15. HALLERT C., SVENSSON M., THOLSTRUP J., HULTBERG B. Clinical trial: B vitamins improve health in patients with coeliac disease living on a gluten-free diet. *Aliment. Pharmacol. Ther*., 2009 Apr 15, **29(8)** : 811-6.
16. CARTA M.G., HARDOY M.C., BOI M.F., 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.
17. CIACCI C., IAVARONE A., MAZZACCA G., DE ROSA. Depressive symptoms in adult coeliac disease. *Scand. J. Gastroenterol*., 1998, **33** : 247-250.
18. SAINSBURY A., SANDERS D.S., FORD A.C. Prevalence of irritable bowel syndrome-type symptoms in patients with celiac disease: A meta-analysis. *Clin. Gastroenterol. Hepatol*., 2013, **11** : 359-365.
19. ZINGONE F., SWIFT G.L., CARD T.R., SANDERS D.S., LUDVIGSSON J.F., BAI J.C. Psychological morbidity of celiac disease: A review of the literature. *United European Gastroenterol. J*., 2015 Apr., **3(2)** : 136-45.
20. LEE A., NG D., DIAMOND B., CIACCIO E.J., GREEN P.H. Living with coeliac disease: Survey results from the USA. *J. Hum. Nutr. Diet*., 2012, **25** : 233-238.
21. NORDYKE K., ROSÉN A., EMMELIN M., IVARSSON A. Internalizing the threat of risk-a qualitative study about adolescents' experience living with screening-detected celiac disease 5 years after diagnosis. *Health Qual. Life Outcomes*, 2014 Jun. 11, **12** : 91.
22. MUSTALAHTI K., LOHINIEMI S., COLLIN P., VUOLTEENAHO N., LAIPPALA P., MÄKI M. Gluten-free diet and quality of life in patients with screen-detected celiac disease. *Eff. Clin. Pract*., 2002, **5** : 105-113.
23. JOHNSTON S.D., RODGERS C., WATSON R.G.P. Quality of life in screen-detected and typical coeliac disease and the effect of excluding dietary gluten. *Eur. J. Gastroenterol. Hepatol*., 2004, **16** : 1281.
24. VILPPULA A., KAUKINEN K., LUOSTARINEN L., KREKELÄ I., PATRIKAINEN H., VALVE R., LUOSTARINEN M., LAURILA K., MÄKI M., COLLIN P. Clinical benefit of gluten-free diet in screen-detected older celiac disease patients. *BMC Gastroenterol*., 2011 Dec. 16, **11** : 136.
25. UKKOLA A., MÄKI M., KURPPA K., COLLIN P., HUHTALA H., KEKKONEN L., KAUKINEN K. Diet improves perception of health and well-being in symptomatic, but not asymptomatic, patients with celiac disease. *Clin. Gastroenterol. Hepatol*., 2011, **9** : 118-123.
26. VILJAMAA M., COLLIN P., HUHTALA H., SIEVÄNEN H., MÄKI M., KAUKINEN K. Is coeliac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. *Aliment. Pharmacol. Ther*., 2005, **22** : 317-24.
27. ROOS S., KÄRNER A., HALLERT C. Psychological well-being of adult coeliac patients treated for 10 years. *Dig. Liver Dis*. ,2006 Mar., **38(3)** : 177-80. Epub 2006 Feb 7.
28. HALL N.J., RUBIN G., CHARNOCK A. Systematic review : adherence to a gluten-free diet in adult patients with coeliac disease. *Aliment. Pharmacol. Ther*., 2009 Aug. 15, **30(4)** : 315-30.
29. PAAVOLA A., KURPPA K., UKKOLA A., COLLIN P., LÄHDEAHO M.L., HUHTALA H., MÄKI M., KAUKINEN K. Gastrointestinal symptoms and quality of life in screen-detected celiac disease. *Dig. Liver Dis*., 2012 Oct., **44(10)** : 814-8.
30. Akobeng A.K., Thomas A.G. Systematic review: tolerable amount of gluten for people with coeliac disease. *Aliment. Pharmacol. Ther*., 2008 June 1, **27(11)** : 1044-52.
31. PERÄAHO M., KAUKINEN K., PAASIKIVI K., SIEVÄNEN H., LOHINIEMI S., MÄKI M. *et al*. Wheat-starch-based gluten-free products in the treatment of newly detected coeliac disease : prospective and randomized study. *Aliment. Pharmacol. Ther*., 2003 Feb. 15, **17(4)** : 587-94.
32. SEE J.A., KAUKINEN K., MAKHARIA G.K., GIBSON P.R., MURRAY J.A. Practical insights into gluten-free diets. *Nat. Rev. Gastroenterol. Hepatol*., 2015 Oct., **12(10)** : 580-91.

33. GROSSI E., MOSCONI P., GROTH N., NIERO M., APOLONE G. Questionario Psychological General Well-being Index. Versione Italiana. Istituto Ricerche Farmacologiche "Mario Negri" Milano, May 2002.
34. BECK A.T., WARD C.H., MENDELSON M., MOCK J., ERBAUGH J. An inventory for measuring depression. *Arch. Gen. Psychiatry*, 1961 June, **4** : 561-71.
35. AARON T. BECK, ROBERT A. STEER, GREGORY K. BROWN. BDI-II, Beck depression inventory -AI: manual. Adattamento italiano a cura di Ghisi M, Flebus GB, Montano A, Sanavio E, Sica C. GIUNTI O.S. 2006.
36. GUANDALINI S., ASSIRI A. Celiac disease : a review. *JAMA Pediatr*., 2014, **168** : 272-8.
37. PAARLAHTI P., KURPPA K., UKKOLA A., COLLIN P., HUHTALA H., MÄKI M., KAUKINEN K. Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients : a large cross-sectional study. *BMC Gastroenterol*., 2013 Apr. 30, **13** : 75.
38. NACHMAN F., MAURIÑO E., VÁZQUEZ H., SFOGGIA C., GONZALEZ A., GONZALEZ V. *et al*. Quality of life in celiac disease patients : prospective analysis on the importance of clinical severity at diagnosis and the impact of treatment. *Dig. Liver Dis*., 2009 Jan., **41(1)** : 15-25.
39. CIACCI C. The happy Scandinavian celiac world. *Dig. Liver Dis*., 2006 Mar., **38(3)** : 181-2. Epub 2006 Jan 24.