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LONGITUDINAL EVALUATION OF QUALITY OF LIFE IN PEDIATRIC COELIAC DISEASE PATIENTS: A MULTICENTER STUDY

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ABSTRACT

Background: This study evaluates Health-Related Quality of Life (HRQoL) in a longitudinal cohort of pediatric coeliac patients, using both disease-specific and generic questionnaires.

Methods: Data were collected from multiple Italian Centers, using standardized questionnaires to ensure uniformity. The study employed multivariate analysis to identify factors impacting on HRQoL.

Results: Significant variations in HRQoL were observed based on demographic characteristics and diagnostic methods ($p<0.05$). The main factors related to worse HRQoL are poor compliance to GFD, female sex, living in Northern Italy, low parents' education level and non-biopsy diagnosis. Further investigation is needed to understand the influence of cultural and social factors.

Discussion: Comparing current data with that collected five years earlier reveals a trend towards HRQoL stability, despite a deterioration of "Emotional functioning" over time. Continuous monitoring of these patients is essential to prevent the disease-related psychological distress.

Conclusion: The study highlights the importance of considering various demographic and clinical aspects in managing pediatric coeliac disease to enhance interventions and support better quality of life outcomes. Continuous monitoring is crucial for a deeper understanding of long-term health implications.

1. INTRODUCTION

1.1 Definition

Coeliac disease (CD) is a chronic immune-mediated disease, triggered by gluten consumption, in genetically predisposed individuals[1].

It affects approximately 1.5% of the population, with a female:male ratio of approximately 2:1[2].

Gluten-free diet (GFD) is the only available therapy, but the life change imposed by strict adherence to GFD and the social repercussions for all the family may increase distress and experience of stigma[3].

CD can be asymptomatic or characterized by gastrointestinal or extra-intestinal manifestations[4].

In adult population, diagnosis still requires a duodenal biopsy[5], while in children it is possible to avoid an invasive approach, if certain serological criteria are met[6].

1.2 Epidemiology

In a recent systematic review and meta-analysis, performed by Singh et al. in 2017, the global CD seroprevalence was 1.4% (95% C.I., 1.1-1.7%), while the prevalence of biopsy-confirmed CD was 0.7% (95% C.I., 0.5-0.9%). The prevalence was higher in female *vs* male individuals (0.7% vs 0.3%, p< .001) and in children *vs* adults (0.9% vs 0.5%, p< .001)[7].

The increased prevalence over the last decades is due to better diagnostic methods, such as proactive screening, especially when CD prevalence is kown to be higher than general population: first-degree relatives (15%-20%), IgA deficiency (10%), Down syndrome (10%), idiopathic short stature (10%), dermatitis herpetiformis (10%), dental enamel defects and recurrent aftous stomatitis (8%), type 1 diabetes mellitus (6%), hypertransaminesemia (5%), Turner syndrome (4%), Wilson syndrome (4%), autoimmune hepatitis (3%), autoimmune thyroid disease (3%), iron deficiency anemia (3%), irritable bowel syndrome (3%), osteopenia/osteoporosis (2%), infertility (2%)[8].

As highlighted in a 2020 systematic review and meta-analysis realized by King et al., the incidence of CD has increased by 7.5% (95% CI: 5.8, 9.3) (I = 79.6%) per year over the past several decades[9].

This increased incidence can also be explained by modern flour processing techniques and antibiotics-mediated dysbiosis, with greater intestinal susceptibility to gluten damage[10].

The epidemiological situation in Italy is described in the Annual Report to the Parliament on Coeliac Disease, produced by the Ministry of Health: the latest edition, published in 2024 and referring to 2022, reports a total of 251.939 coeliac subjects (70% females and 30% males), with a CD prevalence of 0.43%, less than expected, based on global prevalence data. It is estimated that at least 300.000 Italian people have not yet received the diagnosis[11].

In order to reduce the submerged portion of the "coeliac iceberg", universal screening for CD is increasingly supported by many experts. As several scientific works demonstrate, CD diagnosis is frequently delayed or missed by limiting screening only to symptomatic patients. Most individuals with screening-identified CD have previously unrecognized symptoms and signs of impaired nutrition, growth, bone health and quality of life, which improve with GFD. Anyway, more data are needed to determine the cost-effectiveness of different mass screening approaches[12].

1.3 Pathogenesis

Gluten is a complex of proteins, which provides elasticity and cohesion to the dough. Given the high content of proline and glutamine, a sequence of 19 aminoacids contained in alpha-gliadin (an alcohol-soluble gluten fraction) is the most immunogenic peptide, with a leading role in CD pathogenesis[13].

After transglutaminase-mediated deamidation (conversion of glutamine into glutamic acid), this peptide gains affinity for HLA receptors on the antigen-presenting cells (APC)[13].

The APC-mediated exposition to Th1 CD4+ lymphocytes leads to their activation, secretion of pro-inflammatory cytokines, immune-mediated mucosal damage and B lymphocytes production of anti-tissue transglutaminase (TTG), anti-endomysial (EMA) and anti-gliadin deamidated peptite (DGP) antibodies[13].

Genetic susceptibility is necessary, but not sufficient, for CD pathogenesis. In fact, approximately 30% of the population carries at least one of the predisposing HLA haplotypes (HLA-DQ2 and/or HLA-DQ8), but only 1 in 30 actually develops CD[14].

Genetic variants involving signal transduction and cytokines production (IL-2, IL -21, IL-18RAP, IL-12A, CCR3, RGS1, SH2B3, TAGAP)[15], but also enviromentale factors - such as early gastrointestinal infections causing tight junctions damage or molecular mimicry phenomena between viral/bacterial epitopes and self-antigens - can play a role in CD developing[10].

1.4 Clinical presentation

Traditionally, CD has been considered a childhood disease, with typical malabsorptive presentation (diarrhea, abdominal distention, failure to thrive, dystrophic appearance, irritability) during the first years of life[16], sometimes to the point of developing a "celiac crisis" (rapidly progressive diarrhea, dehydration, hypokalemia, metabolic acidosis, hypoalbuminemia), a potentially life-threathing condition[17].

However, this concept has been changed in recent years, as it became increasingly evident that CD can affect individuals of any age and patients may present symptoms that in the past were considered highly unusual[18].

Among children, these non-classical forms include silent cases, atypical gastrointestinal findings (abdominal pain, vomiting, constipation), as well as a number of extraintestinal problems, like iron deficiency anemia, altered bone metabolism, short stature and unexplained transaminase elevation: in the last 30 years, the classical CD presentation is absent in almost half of newly diagnosed pediatric CD cases[18].

In adults, the above mentioned non classical forms affect up to 70% of patients. The extreme variability of this "clinical chameleon" requires high awareness levels in order to avoid potential misdiagnosis[19].

Specific CD issues in adult population include infertility[20], neurological manifestations (cerebellar ataxia, peripheral neuropathy and cognitive impairment)[21] and long term complications, such as refractory CD, characterized by negative serology, persistent malabsoption symptoms and villous atrophy despite GFD, with high risk of progression toward T-cell lymphoma[22].

1.5 Diagnosis

According to 2020 ESPGHAN Guidelines, a common algorithm and a unique screening test (total IgA and anti-transglutaminase IgA antibodies) can be used for CD diagnosis in children, regardless of symptoms and age[6].

HLA haplotype determination is no longer necessary, but is useful in risk categories (first degree relatives, IgA deficiency, autoimmune diseases, syndromic conditions) to establish the need for periodic monitoring of serum antibodies[6].

If the IgA value is within the normal range and the titer of the anti-transglutaminase IgA antibodies is at least 10 times higher than the reference value, the positivity of the anti-endomysial IgA antibodies on a second sample allows CD diagnosis without biopsy[6].

If the titer of anti-transglutaminase IgA antibodies is less than 10 times the reference value or the anti-endomysial IgA antibodies are negative on a second sample, biopsy is mandatory[6].

If the anti-transglutaminase IgA antibodies are negative, it is necessary to rule out IgA deficiency, low gluten intake or immunosuppressive drugs

consumption. If doubts persist, the HLA haplotype can be determined[6].

If IgA deficiency is found, the corresponding IgG class antibodies must be measured (anti-transglutaminase IgG and anti-endomysial IgG antibodies on two different samples). In case of positive results, a biopsy confirmation is required[6].

The esophagogastroduodenoscopy must be performed under sedation, obtaining at least 4 biopsies from the descending duodenum at least one biopsy from the duodenal bulb. In fact, mucosal injury in CD can be patchy and up to 12% of patients can have mucosal changes limited to the duodenal bulb[23].

The Marsh-Oberhuber classification of histologic findings includes the following categories[24]:

- 0 (pre-infiltrative): normal villus-crypt ratio (3:1) and less than 25 intra-epithelial lymphocytes (IEL)/100 enterocytes (EC).

- 1 (infiltrative): normal villus-crypt ratio and more than 25 IEL/100 EC.

- 2 (infiltrative-hyperplastic): reduces villous-crypt ratio, with slighthly enlongated crypts, hyperplasia of glandular elements and more than 25 IEL/100 EC.

- 3 (destructive): progressively deeper cripts and shortened villi (3a: mild -> 3b: moderate -> 3c: severe villous atrophy), with more than 25 IEL/100 EC.

Histological confirmation is obtained in cases 2 and 3, while in cases 0 and 1 a potential CD can be diagnosed: in this latter category, symptomatic subjects can make a GFD trial, although clinical improvement is not always achieved, while in asymptomatic patients on a free diet an annual clinical and serological follow-up is recommended and bioptic re-evaluation must be done in case of symptoms or increase in antibody titers[25].

In adult patients with positive serology, a biopsy is recommended to confirm CD diagnosis and to allow differentiation from other conditions (inflammatory bowel diseases, cancer, infections). HLA determination is necessary only to exclude first degree relatives from the serological follow-up, if not genetically at risk[5].

1.6 Follow-up

In children and adolescents, the follow-up visits after the diagnosis must be done every 6 months until TTG negativization and then every 12-18 months. Additional visits may be necessary in case of poor GFD adherence, nutrirional imbalances, abnormal laboratory values or persistent symptoms despite a correct diet[26].

At every check-up, it is mandatory to evaluate anti-transglutaminase antibodies levels, sign and symptoms, growth trend, GFD compliance and quality of life[25].

Blood exams - including complete blood count, liver function, ferritin, vitamin B12, folate, vitamin D and thyroid function - must be done in every new patient. The re-check timing is left to the discretion of the clinician, obviously taking into account abnormal values and their response to GFD and supplementation therapy[25].

Routine determination of bone mineral density (BMD) is not recommended in pediatric population[25], while a DEXA is recommended in adult patients with malabsorption symptoms at the time of the diagnosis and in any case by the age of thirthy. DEXA must be repeated

every 2-3 years in case of low BMD, poor GFD adherence or persistent villous atrophy, otherwise every 5 years[5].

The transition from pediatric to adult setting for CD patients is important to prevent gaps in care and requires a well-defined organization, possibly using a formal document with essential informations about diagnosis, follow-up, comorbidities and level of GFD adherence[27].

CD patients who received regular visits and specialized dietary counselling during childhood are more likely to maintain a good GFD compliance and to attend follow-up as adults[27].

1.7 Therapy

GFD currently represents the only available therapy for CD management, in terms of symptoms regression and prevention of long-term complications[28].

The GFD principles are easily summarized by the Italian Celiac Association (AIC) in the "Celiac ABC", a simple classification, in which foods are divided in three classes, according to the risk of gluten presence.

- The red face refers to prohibited foods (they contain gluten): wheat, barley, rye, spelt, kamut, einkorn, spelt and triticale.

- The yellow face indicates risky foods (they may contain gluten): before consumption, it is necessary to check the presence of the "gluten-free" label, which indicates that gluten presence is less than 20 ppm and that no contamination occurred during the production phase.

- The green face refers to permitted foods (they are naturally gluten-free): rice, corn, sorghum, teff, millet, buckwheat, amaranth, quinoa, oats, potatoes, fruit, nuts, vegetables, legumes, eggs, milk , cheeses, meat, fish, molluscs, crustaceans.

  GFD, if not adequately monitored, can lead to nutritional imbalances. In fact, an excessive consumption of substitute foods instead of naturally gluten-free foods (fruit, vegetables, legumes, meat, fish) can cause high

intake of lipids, carbohydrates and salts, with poor levels of proteins, vitamins, minerals and fibers[29].

Since the catch-up growth, after starting GFD, first affects weight (maximum weight gain at 12 months) and only later height (maximum height recovery at 24 months), coeliac children may present an initial increase in BMI. However, a balanced GFD, respectful of the Mediterranean diet principles (by obtaining daily calories 55% from carbohydrates, 30% from lipids, 15% from proteins and by choosing fresh, seasonal and local foods) can promote, over time, the ideal BMI recovery[30].

One of the aims of clinical follow up is to achieve a good quality of life, reducing psychological distress associated to GFD.

According to the World Health Organization (WHO), health is defined as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”[33], while Quality of life (QoL) is described as "a subjective perception of reality, considering someone's goals, culture and value system"[34].

The most widely accepted definition of Health-related Quality of Life

(HRQoL), provided by the Food and Drug Administration (FDA), is “the patient’s general perception of the effects that the illness and the related treatments have on physical, emotional, social and cognitive aspects of life”[35].

HRQoL is a multidimensional concepts, which aims to consider both objective experiences and subjective attitudes, in order to evaluate how health status influences patient’s perception of his own wellbeing over time, in terms of physical functioning (self-care, ability to move independently), emotional functioning (feelings and expectations about his conditions), social functioning (possibility of satisfying interaction with family and friends) and role functioning (cognitive ability to study or work efficiently)[35].

HRQoL, which explores the connection between health and QoL, is not only an individual concern, but also a public health issue, commonly used as a valid indicator of service need and intervention efficacy, in order to assess the cost-utility of specific healthcare interventions[35].

HRQoL assessment in CD is specifically recommended by the 2022 ESPGHAN Position Paper on Management and Follow-up of Children and Adolescents with Coeliac Disease[26].

2. AIMS OF THE STUDY

The study aimed to assess HRQoL and further characterise the socio-demographic and clinical factors associated with reduced HRQoL in a large multicenter paediatric cohort with CD living in Italy[36].

Moreover, we wanted to evaluate the long-term HRQoL in a group of children and their parents 5 years after the first HRQoL assessment at Gaslini Children's Hospital in Genoa[37] (10 years after the CD diagnosis)[38].

3. MATERIALS AND METHODS

3.1 Study design

Inclusion criteria were age 8-18 years and histological or non-biopsy diagnosis according to 2020 ESPGHAN Guidelines, while exclusion criteria were psychiatric disorders, cancer or poor knowledge of Italian language[36,37,38].

All parents signed an informed consent for inclusion in these studies, that were conducted in accordance with the Declaration of Helsinki[36,37,38].

The protocols were approved by the Regional Ethics Committee with regard to the monocentric studies (132/19; 131/18)[37,38] and by the Ethics Committees of all partecipating centers relatively to the multicenter study (PC 131/18; 2019/22)[36].

3.2 Quality of life questionnaires

Two different questionnaires were administered both to children and their parents: a version of the Coeliac Disease Dutch Questionnaire (CDDUX), a disease-specific questionnaire for children with CD[39] - translated and adapted to Italian coeliac families[37] - and an already available Italian version of the Paediatric Quality of Life Inventory (PedsQL), a generic questionnaire which can be used to assess quality of life both in healthy children and in those with acute or chronic health conditions[40].

The questionnaires were self-completed independently by coeliac patients and their parents, at the end of the clinical visit, after a brief explanation[36,37,38].

The Coeliac Disease Dutch Questionnaire (CDDUX) includes 12 items and

explores 3 health domains: "Having CD" (3 items), "Communication" (3 items) and "Diet" (6 items), providing informations about how the patient feels regarding the disease itself, the need to communicate this condition to others and the GFD restrictions, respectively. Each answer has a five-point Likert face scale, composed of different emojis (very happy, happy, neutral, unhappy, very unhappy). The items were categorised in number from 1 (the worst score) to 100 (the best score) by transforming the 5-point Likert scale and the global scores in the following HRQoL categories: very bad (score 1–20), bad (score 20–40), neutral (score 40–60), good (score 60–80) and very good (score 80–100)[39].

The Paediatric Quality of Life Inventory (PedsQL) includes 23 questions, divided into 4 subscales, which evaluate physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). Each question has one of five possibile answers, regarding how frequently the disease impacts on everyday activities: almost always (score 1-20), often (score 20-40), sometimes (score 40-60), almost never (score 60-80) and never (score 80-100). The sum of the answers gives a final score, on a scale of 1 to 100. The higher scores

indicate better HRQoL (1 to 20: very bad; 20 to 40: bad; 40 to 60: neutral; 60 to 80: good; 80 to 100: very good)[40].

Both questionnaires have a version for children (age 8–18 years) and a corresponding version for parents, with the same structure. In the case of the caregiver, the questions are interpreted as the caregiver's appreciation of how the child feels in each of the addressed situations[39,40].

3.3 Statystical analysis

Demographic and clinical data were expressed as mean and standard deviation (SD) for continuous variables and as proportions for categorical variables. Distribution frequencies were estimated for qualitative variables and scores for the different scales are reported as mean with their SD[36,37,38].

Bivariate correlation analysis was used to demonstrate the coherence in the score of child/parent pairs by subclass indexes of CDDUX[36,37,38].

The psychometric properties of the CDDUX questionnaire were analysed by using Cronbach's α coefficient for intra-questionnaire reliability and

intraclass correlation coefficient with 95% confidence intervals (CI) for inter-children/parents reliability. The Cronbach's α coefficient showed an overall high internal consistency for the CDDUX tool, while the intraclass correlation coefficient revealed a significant degree of inter-children/parents reliability for all CDDUX subdomains[36,37,38].

The different frequency or mean of overall scores and subclasses of the CCDUX and PedsQL questionnaires - according to different strata of demographic and clinical variables - was tested with the unpaired Student's *t*-test and with the paired Student's *t*-test when patients' scores were compared with parents' scores. The ANOVA test and the Bonferroni post-hoc analysis were performed for categorical variables. Significant differences found with univariate analysis for demographic and clinical parameters were re-evaluated with multivariate analysis (a binary logistic regression model)[36,37,38].

All data were analysed with the software SPSS for Windows (IBM Corporation). Overall, $p<0.05$ was accepted as a statistically significant result[36,37,38].

4. RESULTS

4.1 Study population

The first monocenter study (5 years follow-up) enrolled 223 child/parent pairs from the only Paediatric Regional Center for Coeliac Disease at Gaslini Children's Hospital in Genova. Most of the partecipants were females (64.1%). The mean age at diagnosis was 12.6 years (SD ± 3.0, range 8–18). The age at interview was 8-11 years in 32.2%, 12-15 years in 39.7% and 16-18 years in 28.1%. The time since diagnosis was < 4 years in 24,6%, 5–8 years in 46,7% and > 9 years in 28,7%. At the time of enrolment, 78 children (39.6%) reported a family history for CD and 23 patients (11,1%) showed a recent high value of anti-tissue transglutaminase antibodies (TTG). Coeliac disease was associated in 44 children (21.9%) to other chronic diseases[37].

The second monocenter study (10 years follow-up) re-evaluated 80 child/parent pairs, from January 2021 to August 2022, 5 years after the previous work. Most of the partecipants were females (70%). The mean age was 10.9 ± 1.6 years at 5 years follow-up and 15.8 ± 1.7 years at 10 years follow-up. The mean time since diagnosis was 4.8 ± 3.0 years at the 5 years follow-up and 9.7 ± 3.1 years at the 10 years follow-up.

During the follow-up, the prevalence of TTG positivity and the positive family history for CD were almost stable (from 11.1% to 10.5% and from 31.1% to 33.7%, respectively). The associated comorbidities increased from 30.3% to 43.8%[38].

The sensitivity analysis comparing the characteristics of the 223 original patients with the 80 subgroup members ruled out the possibility of a selection bias[38].

In the multicenter Italian study, 11 Pediatric Centers, included Gaslini Children's Hospital, recruited 871 families, 540 (62%) from Northern regions (5 centers) and 331 (38%) from Central-Southern regions (6 centers), from January 2021 to December 2022. The mean age at diagnosis was 7.0 ± 3.7 years, while the mean age at interview was 12.9 ± 2.9 years. Most of the participants were females (66.4%). Histological diagnosis was performed in 66% of patients, while 34% had serological diagnosis. At the time of enrolment, 193 children (23.3%) reported a positive family history for CD and 240 patients (27.8%) had associated comorbidities[36].

4.2 HRQoL assessment and correlation with demographic and clinical characteristics

4.2.1 First monocenter study (5 years follow-up)

The CDDUX questionnaire was completed by 223 children and 219 parents, while the PedsQL questionnaire was completed by 216 children and parents[37].

Mean CDDUX total score was 52.6 ± 17.2 in children and 49.5 ± 17.9 in parents, indicating a neutral evaluation of HRQoL. Only the "Communication" subdomain showed significantly different values between the two groups: telling other people about CD was apparently much easier for children (62.4 $\pm$ 22.0 *vs* 57.3 $\pm$ 22.2, $p < 0.05$)[37].

Mean PedsQL total score was 81.2 ± 11.1 in children and 80.3 ± 12.9 in parents, indicating a good-very good evaluation of HRQoL. In the "Social functioning" subdomain, children showed a significantly easier approach to their problems (89.2 $\pm$ 14.4 *vs* 84.3 $\pm$ 18.3, $p < 0.01$)[37].

By associating demographic and clinical variables with the CCDUX (overall and subclasses) and the PedsQL (overall), the only parameter which appeared to significantly affect quality of life, according to

patients, was age, with children aged 8–11 years reporting a lower mean in "Having CD" score (36.5 ± 19.5, $p < 0.05$) and in overall PedsQL score (77.1 ± 12.3, $p < 0.05$)[37].

Parents reported more conditions negatively affecting "Having CD" score: younger age, i.e. 8–11 years (34.6 ± 19.3, $p < 0.01$), positive TTG (32.1 ± 17.6, $p < 0.05$) and recent diagnosis, i.e. 1–4 years (33.1 ± 19.1, $p < 0.01$)[37].

4.2.2 Second monocenter study (10 years follow-up)

The CDDUX and PedsQL questionnaires were completed by all parents and by 98.8% and 97.5% of children, respectively[38].

Total CDDUX scores showed a non-significant reduction in both groups, when compared with the results of the previous study (for children, 47.7 ± 18.8 *vs* 50.6 ± 17.6, - 2.8 ± 24.5; for parents, 45.4 ± 18.0 *vs* 47.9 ±19.4, - 2.5 ± 22.8). "Having CD" showed an increase of +2 points (although not statistically significant) in children and remained stable in parents, while "Communication" and "Diet" showed a non-significant decline over time. All the values ranged between 40 and 60, indicating a

neutral evaluation of HRQoL[38].

Total PedsQL scores were lower than the previous study, although not statistically significant (for children, 78.1 ± 13.5 *vs* 80.3±11.4, - 2.3± 14.5; for parents, 76.2 ± 15.7 *vs* 79.5 ± 13.1, - 3.4 ± 16.2). Regarding the PedsQL subdomains, “Emotional functioning” showed a marked decrease in children compared to parents (65.9 ± 21.6 *vs* 73.6 ± 17.0, - 9.0 ± 22.7, $p < 0.01$), "Social functioning" was reported to be significantly worse by parents (80.8 ± 19.2 *vs* 85.1 ± 17.5,- 4.3 ±23.0, $p< 0.05$), "School functioning" showed a mild reduction in both groups and "Physical functioning" remained stable in children, while parents reported a slight decline, without statistical significance. All the values ranged between 60 and 90 points, reflecting a good-very good HRQoL[38].

Regarding the influence of demographic and clinical characteristics on CDDUX and PedsQL scores in children, although the small number prevented reaching statistical significance for most differences, some evident discrepancies were observed in specific subdomains[38].

Patients adherent to GFD showed significant higher scores in "Diet" (46.4 ± 21.4 vs 38.7 ± 26.4, $p<0.05$), while patients who admitted eating gluten had significant lower scores in the same area (32.9 ± 22.8 *vs* 47.4 ± 20.3,

$p<0.05$)[38].

PedsQL items revealed a statistically significant difference for "Emotional functioning" according to the child's sex (male 73.1 ± 18.0 *vs* female 61.9 ± 22.2, $p < 0.05$). Patients with negative TTG had better scores in "Physical functioning" (84.0 ± 14.1 vs 71.9 ± 15.7, $p<0.05$) as well as children without associated diseases (85.7 ± 12.1 vs 78.0±16.3, $p<0.05$)[38].

Results of CDDUX and PedsQL questionnaires administered to parents showed that fathers have a more positive view than mothers, especially in CDDUX "Diet" (55.3±22.7 *vs* 41.6±19.7, $p<0.05$) and in PedsQL "Emotional functioning" (81.8 ± 16.8 *vs* 64.7±21.2, $p<0.05$)[38].

In order to evaluate the presence of demographic or clinical characteristics that might predict non-adherence to GFD, 17 non-adherent children, defined by TTG positivity (8 children) and/or voluntary admission of eating gluten (11 children) were compared to 62 GFD-compliant children: non-adherent CD patients were not significantly younger (15 *vs* 16 years, $p<0.05$), more often female (94.1%) and with a shorter time from diagnosis (8.5 *vs* 10 years, $p=0.06$)[38].

4.2.3 Multicenter Italian study

The CDDUX and PedsQL questionnaires were completed by 861 child/parent pairs[36].

Children's CDDUX total score was slightly, yet significantly, higher compared to their parents (47.1 ± 18.8 *vs* 45.1 ± 18.6, p=0.025). In the "Communication" subdomain, children scored much better than parents (60.9 ± 23.3 *vs* 54.9 + 22.2, p<0.01). Almost all mean values fell within the 40-60 range, indicating a neutral assessment of HRQoL, excepted for “Having CD”, where both groups showed a bad HRQoL, ranging from 20 to 40 points[36].

Children's PedsQL total score was slightly, yet significantly, higher compared to their parents (81.4 ± 12.6 *vs* 79.9 ± 14.5, p=0.025). A marked difference was detected in the "Social Functioning" subdomain, where children reported fewer limitations (89.7 ± 13.9 *vs* 85.5±16.9, p < 0.001). All mean values ranged between 70 and 90 points, indicating a good-very good HRQoL[36].

Regarding the influence of demographic and clinical characteristics on

CDDUX-assessed HRQoL, histological diagnosis was associated with better CD-related quality of life, with significantly higher scores in total CDDUX (48.0 ± 19.3 *vs* 45.0 ± 17.7, p<0.05), “Having CD” (40.5 ± 20.3 *vs* 36.4 ± 19.7, p<0.005) and “Diet" (45.4 ± 22.6 vs 41.6 ± 20.9, p<0.05). The same results were also confirmed by parental reports (total CCDUX 46.1 ± 18.8 *vs* 43.0 ± 17.6, p<0.05; “Having CD” 39.5 ± 19.5 *vs* 36.0 + 19.8, p<0.05; "Diet" 44.8 ± 21.6 *vs* 41.0 ± 20.0, p<0.05)[36].

Patients aged 14-18 years reported higher scores than patients aged 8-13 years regarding "Having CD" (43.2 ± 19.4 *vs* 36.4 ± 20.2, p<0.005). This divergence was also corroborated by parental reports (40.5 + 18.9 *vs* 36.9 ± 19.8, p<0.05)[36].

Parents of patients with a longer time since diagnosis (>12 years) reported higher scores in total CDDUX (51.5 ± 16.4 *vs* 44.5 + 19.7, p<0.05), “Having CD” (45.6 ± 17.9 vs 37.3 ± 19.6, p<0.005) and “Diet” (51.5 ± 19.1 *vs* 42.8 ± 21.4, p<0.005)[36].

Patients residing in the Northern Regions of Italy had better scores in “Diet” subdomain (45.4 ± 21.9 *vs* 42.0 ± 21.3, p<0.05)[36], as well as parents of male patients (45.7 ± 20.3 *vs* 42.4 ± 21.5, p<0.05)[36].

The presence of another family member affected by CD was associated with lower scores in “Communication” subdomain, as reported by parents (52.0 ± 20.2 *vs* 56.0 ± 22.3, p<0.05)[36].

Regarding the influence of demographic and clinical characteristics on PedsQL-assessed HRQoL, female sex was associated with significative lower scores, not only in total PedsQL (80.3 ± 12.3 *vs* 83.3 ± 12.9 p<0.005), but also in "Physical functioning" (83.2 ± 14.3 *vs* 87.0 ± 12.7, p<0.005) and "Emotional functioning" (69.0 ± 20.0 *vs* 76.1 ± 19.2, p<0.005). These data were also confirmed by parental reports (total PedsQL 79.3 ± 14.3 *vs* 81.8 ± 13.0, p<0.05; "Physical functioning" 82.5 ± 17.8 *vs* 85.8 ± 15.1, p<0.05; "Emotional functioning" 68.6 ± 20.2 *vs* 74.8 ± 17.5, p<0.005)[36].

Younger age (8-13 years *vs* 14-18 years) was associated with better "Emotional functioning" in both children (72.9 ± 19.3 *vs* 68.8 ± 20.8, p<0.005) and parents (72.2 ± 18.5 *vs* 68.1 ± 20.6, p<0.05) and with higher PedsQL total score according to the parents (81 ± 13.3 *vs* 78.5 ± 14.6, p<0.05)[36].

Children whose parents had higher educational levels reported better scores in total PedsQL (82.1 ± 12.1 *vs* 78.1 ± 13.3, p<0.05), as well as in

"Physical functioning" (86.0 ± 12.4 *vs* 80.8 ± 16.3, p<0.005) and "School functioning" (79.2 ± 16.6 *vs* 72.5 ± 19.9, p<0.005). These data were also confirmed in the by parental reports (total PedsQL 81.0 ± 13.7 *vs* 76.5 ± 15.2, p <0.005; "Physical functioning" 84.6 ± 16.2 *vs*79.5 ± 18.8 p< 0.005; "School functioning" 80.65 ± 17.1 *vs* 70.1 + 20.6 p<0.005)[36].

Living in Southern-Central Italy was associated with higher total PedsQL scores in both children (82.7 ± 13.2 *vs* 80.7 ± 12.2, p<0.05) and parents (81.5 ± 13.9 *vs* 79.3 ± 13.9, p<0.05), with significant differences in "Emotional functioning" (73.3 ± 20.2 *vs* 70.4 + 19.9, p<0.05) and "School functioning" (81.3 ± 16.8 *vs* 76.8 + 17.0, p<0.005) for children and in "Social functioning" (87.8 ± 15.2 *vs* 84.3 ± 17.1, p<0.005) for parents[36].

Having a family member with CD was associated with better "Emotional functioning" in children (98.7 ± 20.6 *vs* 72.1 + 19.5, p<0.05)[36].

Multivariate analysis showed that patients aged 8-10 years and their parents had better total PedsQL scores (p<0.05). Children's total PedsQL score was negatively influenced by female sex (p<0.05). Histological diagnosis was an independent predictor of higher total CDDUX scores in both groups (p<0.05). Compliance to GFD was associated with better total CDDUX and total PedsQL scores in patients and caregivers

($p<0.05$)[36].

5. DISCUSSION

In the last decades, the universally recognized importance of HRQoL assessment in CD patients has produced an increasing body of scientific works, mostly perform on adult population, showing that CD burden may lead to HRQoL impairment[41].

The number of studies on HRQoL in children and adolescents with CD is more limited and there are even fewer works that also take into consideration the parents' point of view[42].

5.1 HRQoL assessment

Both the 10 years follow-up analysis at Gaslini Children's Hospital[37,38] and the Italian Multicenter Study[36] reports a neutral HRQoL by using CDDUX and a good-very good HRQoL by using PedsQL.

This discrepancy confirms what is already validated by the scientific literature on this topic: a disease-specific questionnaire shows, with

greater accuracy, what children and parents think and feel about CD[39], while a generic tool may fail to detect the specific discomfort due to their condition, but is able to provide a broader view on HRQoL, allowing comparisons across different populations and health conditions[40].

Regarding CDDUX subdomains, “Having CD” is associated with a neutral HRQoL in the monocenter study[37,38] and with a bad HRQoL in the multicenter study[36], while "Diet" and "Communication" obtain a neutral score in both works[36,37,38], with children significantly more skilled than parents in talking with other people about CD[36,37,38].

All PedsQL subdomains indicate a good-very good HRQoL, with significantly higher scores for children in "Social Functioning"[36,37,38].

The scientific literature on this topic does not always reach the same conclusions: in a recent CDDUX evaluation of HRQoL by Rojas and colleagues, more than 50% of caregiver-child dyads reports a good/very good score in "Having CD" and "Diet", while "Communication" is described as "bad/very bad"[43].

About PedsQL assessment of HRQoL, most studies are focused on coeliac children *versus* healthy controls, so a comparison with our data is

difficult. In these works both patients and controls seem to have a good-very good HRQoL, although appropriate analytical methods can elicite specific factors contributing to a lower HRQoL in coeliac children, such as comorbidities and difficulties with GFD adherence[44].

Our results indicate that parents tend to underestimate their children's ability to cope with CD[36,37,38]. Other works on HRQoL have previously shown that CD has a worse impact on parents and this discrepancy highlights the importance of letting the children themselves be heard about their perceived quality of life[45].

5.2 HRQoL trend over time

The consistently stable HRQoL perception among coeliac patients and caregivers during the 10 years follow-up study highlights their long-term resilience in coping with this chronic condition[37,38].

However, a slight deterioration is evident for all the CDDUX subdomains, except "Having CD", which improves in older patients, probably because CD, like every chronic illness[46], is characterized by a gain in terms of management skills over time[37,38].

The parallel evaluation of HRQoL by using PedsQL shows a statistically significative lowering in “Emotional functioning” and "Social functioning" subdomains, respectively in children and parents: in fact, teenagers have a growing awareness about CD limitations[45], especially in terms of social interactions during meals, so their psychological burden tends to increase and it is perceived as social withdrawal by parents[37,38].

In a previous study, carried out at Garrahan Children Hospital in Argentina, the CDDUX total score recorded in first follow-up visit, 9 months after the diagnosis, was significantly higher both in coeliac children and their parents: this pioneering study reflects the HRQoL improvement derived from CD acceptance in the short term[47], but the 10 years analysis performed at Gaslini Children's Hospital - one of the longest follow-up on CD pediatric patients - demonstrates that, over time, the emotional impact of CD on children is real and a treatement should be performed before HRQoL deterioration[37,38].

A strength of our study is the prospective long-term and simultaneous administration of disease-specific and generic questionnaires, which allow a broader evaluation of overall well-being and functioning from different perspectives[37,38].

However, the absence of a healthy control group, the lack of data on the socio-economic status and the potential information bias due to children and parents filling the questionnaires at the same time, should be considered as weak points, so more data will be necessary before our results could be generalized[37,38].

5.3 Influence of demographic and clinical characteristics on HRQoL

Regarding CDDUX, in the monocenter study older patients report higher scores compare to younger patients in "Having CD", while patients who admit gluten consumption, regardless of age, have lower scores in "Diet"[37,38]. Younger age, recent diagnosis and positive TTG are associated with worse scores in "Having CD", according to parents' opinion[37,38].

In the multicenter study, older patients and their parents report higher scores in "Having CD", while caregivers indicate a longer time since diagnosis as a positive predictor on “Having CD” and “Diet”. Histological diagnosis is associated with higher scores in total CDDUX, “Having CD” and “Diet" both in patients and caregivers, while the PedsQL-assessed HRQoL is not impaired by serological diagnosis. The limited use of

disease-specific questionnaires and biopsy-proven CD, as inclusion criteria in other works, explain why this data was not already reported. A biopsy-sparing approach might not ensure the same long-term benefits in disease management, potentially due to a different perception of CD "real presence", so the diagnostic strategy must be discussed upstream with the family and, based on the level of maturity achieved, with the patient himself[36].

Regarding PedsQL, in the monocenter study, younger age correlates with lower PedsQL total score, "Emotional functioning" is significantly better in male patients and "Physical functioning" is worse in children with positive TTG and associated diseases[37,38].

In the multicenter study, the negative impact of female sex on "Emotional functioning" is confirmed[36], according to the increased psychosocial distress of coeliac women, which tend to develop anxiety, depression and eating disorders more often than males[48]. Also total PedsQL and "Physical functioning" are impaired and the same results are obtained in by-proxy parental reports[36].

Younger age is associated with better "Emotional functioning" in both children and parents[36], according to the 10 years follow-up study's

results[37,38].

Higher educational levels are associated with better scores in total PedsQL, "Physical functioning" and "School functioning" in both children and caregivers[36], probably as an indirect result of better GFD adherence, which is enhanced by a good socio-economic and cultural background[49].

Living in Southern-Central Italy determines higher total PedsQL for both children and parents, with better "Emotional functioning" and "School functioning" in children and greater "Social functioning" in parents, probably due to deeper cohesion not only within the family, but also among the entire community[36].

The good PedsQL level in our multicenter cohort could downsize the fear of compromising HRQoL by a population screening for CD in children[36], as already demonstrated by Iorfida and colleagues in 2021: comparing 37 CD patients diagnosed during childhood by screening programs and 38 controls, in which CD was discoverd at the same age by active-case finding due to symptoms, there were no significant differences in GFD adherence and HRQoL, so the diagnostic strategy does not seem to impact on these aspects[50]. In a long-term follow-up study, designed by Van Koppern and colleagues, after 10 years the HRQoL was similar in

coeliac patients diagnosed with mass screening and in children of the same age with biopsy-detected CD[51].

In the multicenter study, multivariate analysis shows a positive association between GFD adherence and better HRQoL[36], as already demonstrated in a systematic review performed by Myléus and colleagues, in which the major factors related to GFD compliance in children were also reported: costs, availability and palatability of gluten-free foods, parents' knowledge about CD nutritional management and membership in a CD patient society[52].

The transition from adolescence to young adulthood is considered a high-risk period for intentional gluten intake, due to the fear of being different in social situations like eating out and travelling with peers[53].

Determination of TTG level and self-reported gluten consumption can be useful to evaluate GFD adherence, but they may underestimate poor compliance: in fact, the first is not able to detect occasional gluten ingestion and the second is completely dependent on patient's self-report[4]. Despite these limitations, they are both widely accepted in the assessment of GFD adherence, but scientific evidence also recommends the use of validated questionnaires[54].

Therefore, a future goal is to make HRQoL assessment in CD patients a systematic practice in every Pediatric Center, with the contemporary evaluation of GFD adherence, by using validated questionnaires.

6. CONCLUSION

The impact of CD on HRQoL, even many years after the diagnosis, is a real concern, due to limitations in social interactions, preception of being different and need to follow a restrictive and life-long diet[36, 37,38].

Assessing socio-demographic and clinical factors associated with lower HRQoL may be helpful in early identification of high-risk patients, preventing their withdrawal from a regular follow-up[36,37,38].

Following a GFD can be challenging both in terms of practical and psychological aspects, so a multidisciplinary care, with strict medical follow-up and specific nutritional program, is required to promote patient's self-efficacy and continous education[55].

A global approach to CD should be performed not only from a clinical perspective, focused on the control of dietary adherence and

symptomatology, but also from a social and psychological point of view, in order to avoid social isolation, discrimination and psychological distress[55].

Therefore, HRQoL assessment in children with CD should be considered a primary aim in any follow-up program and a critical end-point in every clinical trial[55].