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# Screening for celiac disease among children with overweight and obesity: toward exploring celiac iceberg

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**Abstract**

**Objectives:** The coexistence of celiac disease (CD) and obesity/overweight is not unusual. We investigate the prevalence and clinical presentation of CD, detected by screening, among children with excessive weight gain.
**Methods:** We enrolled 200 children referred for overweight/obesity to our outpatient clinic. Medical history during pregnancy and childhood and lifestyle variables were recorded. Patients were screened for CD with total immunoglobulin A (IgA), IgA anti-transglutaminase (tTG-IgA) and IgA anti-endomysial antibodies (EMA-IgA). In subjects with positive autoantibodies, esophagogastroduodenoscopy (EGDS) was performed and genetic testing for HLA DQ2 and/or DQ8 haplotypes was tested.
**Results:** CD positive antibodies (tTg-IgA and EMA-IgA) were detected in eight patients (4%); in all subjects CD diagnosis was confirmed by HLA-DQ2 and/or DQ8 compatibility and EGDS. No association between CD and medical history during pregnancy and childhood or lifestyle variables was noted; however, a dietary difference was identified with those testing positive for CD also reporting a lower weekly consumption of fruits and vegetables (p=0.04). Headache was reported more frequently in patients with than without CD (p=0.04). Familiar positivity for autoimmune diseases was revealed in CD patients (p=0.01).
**Conclusion:** CD should be considered in children with excessive weight gain. Familial predisposition to other autoimmune diseases may represent a risk factor for development of CD. Even though the relationship between headache and CD is not well defined, the patients with headache of unknown origin should be screened for CD.

**Keywords:** celiac disease; children; excessive weight gain; obesity.

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## Introduction

Celiac disease (CD) is a systemic, lifelong immune mediated disease characterized by small intestinal enteropathy triggered by exposure to dietary gluten, that may occur in individuals with a genetic susceptibility [1–5]. Its global prevalence is estimated at approximately 1%, with regional differences and studies suggest it is increasing [3, 4]. In Italian school children, the most recent literature suggests that prevalence has nearly doubled in the past 25 years from 0.88 to 1.58% [5].

The clinical presentation of CD has changed. In the last two decades, diarrhea, poor growth, and malabsorption have progressively decreased as presenting symptoms of CD among adults and children, whereas symptoms such as fatigue, constipation, headache, nausea, iron deficiency anemia, and joint pain have increased [3, 5, 6]. As reported by Nenna R et al. [7], a modified clinical spectrum was also noted and referred to a large study on school-age children screened for CD, showing a silent, typical, atypical, and potential CD respectively in 64, 28, 7, and 1% of cases. In addition to these changes in presentation, several studies have shown that CD is common in patients who are normal weight, overweight, or affected by obesity and not limited to those who have developed under-nutrition; previous work analyzing weight at CD presentation found that 8.8–20.8% of patients might be overweight and 0–6% of patients might be classified as obese at CD onset [7–17]. The link between CD and excessive weight gain is unknown; however, this co-presence suggests that CD may be more widespread than previously suspected, generating a need for further research to define an appropriate assessment and monitoring according to an overall healthcare plan.

The aim of this study was to investigate the prevalence and clinical presentation of CD, detected by screening children with excessive weight gain in order to explore a new potential part of the celiac iceberg.

# Patients and methods

## Patients

We enrolled 200 Caucasian children and adolescents, aged 10.9 ± 2.65 years (99 females and 101 males), referred to the outpatient clinic of the Pediatric Endocrinology Unit at Fondazione IRCCS Policlinico San Matteo, for excessive body weight, by their general practitioner or primary care pediatrician between May 2018 and October 2018.

According to the World Health Organization criteria [18], the subjects were divided into:

- subjects with obesity (n=106): BMI ≥97th percentile for the age and sex,
- overweight subjects (n=94): BMI ≥85th and <97th percentile.

Exclusion criteria were: previous diagnosis of CD, positive familiar history for CD in which screening excluded CD, specific intestinal symptoms and other intestinal diseases, known secondary obesity conditions.

All patients were screened for CD with total immunoglobulin A (IgA), IgA anti-transglutaminase (tTG-IgA) and IgA anti-endomysial antibodies (EMA-IgA). The study protocol was approved by the Ethic Committee of Fondazione IRCCS Policlinico San Matteo, Pavia, and it was run in accordance with the Helsinki Declaration of 1975, as revised in 2008. All participants or their responsible guardians were asked for and gave their written consent after being informed about the nature of the study.

## Physical examination

The physical examination of the participants included anthropometric evaluation as height, weight, waist circumference, BMI calculation, pubertal stage determination according to Marshall and Tanner (pre-pubertal characteristics corresponding to Tanner stage 1) [19, 20] and blood pressure (BP) measurement.

Height, weight, and waist circumference measurement, were performed as previously reported [21]. BMI was calculated as body weight (kilograms) divided by height (meters squared) and waist-to-height ratio (WHtR) was also considered as central adiposity index.

Pubertal development was classified as: stage 1=Tanner 1; stage 2=Tanner 2–3; and stage 3=Tanner 4–5.

Systolic (SBP) and diastolic (DBP) blood pressure were measured twice with the patient sitting quiet. The second BP measurement was used for analysis. Elevated SBP or DBP was defined with values exceeding the 95th percentile for age and sex [22].

## Biochemical parameters

Metabolic blood assays included glucose, insulin cholesterol, LDL, HDL, TGL, homocysteine, AST, ALT, GGT, ferritin, iron, Vit D-25 OH, Vit B12, folate. Insulin resistance was calculated with the homeostasis model assessment for insulin resistance (HOMA-IR) formula.

Abnormalities in lipid fasting levels were considered for TC and TG values exceeding the 95th percentile and HDL cholesterol values below the 5th percentile for age and sex [23]. Elevated fasting blood glucose (FBG) was defined with values exceeding 100 mg/dL and impaired insulin sensitivity (ISI) with HOMA-IR exceeding the 97.5th percentile for age and sex [24].

Plasma glucose, total, and HDL cholesterol, TGL, insulin levels, AST, ALT, and GGT were measured as previously described [21].

Serum iron was determined by ferrozine colorimetric method, using ADVIA XPT system (Siemens Healthcare Diagnostics).

Serum 25(OH)-vitamin D levels were analyzed on Liaison XL (Diasorin, Italy), an automated immunochemistry analyzer, according to the manufacturing instruction. Vitamin B12 and folate were measured by competitive binding protein methods, on Advia Centaur with chemiluminescence detection (Siemens Healthcare Diagnostics, USA). Ferritin was measured by a homogenous, Sandwich, chemiluminescence immunoassay based on LOCI technology (Dimension Vista, Siemens Healthcare Diagnostics, USA)

## Screening for celiac disease

To assess CD, the patients were checked for total immunoglobulin A (IgA), IgA anti-transglutaminase antibodies (tTG-IgA) and IgA anti-endomysial antibodies (EMA-IgA) together with anti-transglutaminase antibodies (tTg-IgG).

IgA level was measured by a nephelometric method, where the intensity of the scattered light is proportional to the concentration of the

respective protein in the sample. The result is evaluated by comparison with a standard of known concentration (Dimension Vista, Siemens Healthcare Diagnostics, USA). Serum anti-tTG IgA and IgG levels were measured with a commercially available enzyme-immunosorbent assay (ELISA) kit (Eu-tTG IgA and IgG, Eurospital, Trieste, Italy). Using sections from the distal portion of monkey esophagus as an antigenic substrate, EMA were detected by indirect immunofluorescence with a commercially available assay kit (GmbH Labordiagnostik, München).
CD diagnosis was based on a positive tTG-IgA and/or EMA-IgA. Patients with tTG-IgA and/or EMA-IgA positivity underwent genetic testing for HLA DQ2 and/or DQ8 haplotypes were determined. Patients with compatible HLA haplotypes and tTG-IgA 10 times the upper cut off and EMA-IgA positivity were diagnosed with CD without biopsy. If tTG-IgA was 10 times lower than the upper limit of normal, the patient was referred for esophagogastroduodenoscopy gastroscopic procedure (EGD) with multiple specimens to confirm the diagnosis. Biopsies were read by an experienced pathologist blinded to any of the patients' endoscopic or clinical information. The degree of mucosal damage was assessed according to the Marsh Grading [25] with patients who had biopsies consistent with Marsh 3 reported to have confirmed CD.
In order to evaluate the presence of celiac-susceptible DQ heterodimers, the patients were typed for HLA class II polymorphisms by PCR-SSP at high resolution level. DNA was extracted by a salting out procedure [26]. Polymorphism within the exons two of HLA-DQA1 and DQB1 genes was defined using a polymerase chain reaction with sequence specific primers (PCR-SSP) [27].

### Personal history

In all patients, data collection focused on breastfeeding, weaning, timing of solid food and gluten introduction, present or past diseases, medications (past/present) were recorded. Maternal data during pregnancy, such as weight gain, medications or supplements intake, smoking habits or alcohol consumption, were also registered.
In all children and adolescents, intestinal discomfort, abdominal pain/swelling/bloating, meteorism, diarrhea, constipation and extraintestinal symptoms such as weight loss or insufficient weight increase, unintentional weight gain, dermatitis herpetiformis, weakness, arthralgia, concentration disorders, headache, neurological symptoms, alopecia, alterations of tooth enamel were also investigated.
A questionnaire investigating familiar history for other autoimmune pathologies and/or allergies was also distributed.

### Lifestyle variables assessment

Trained dietitians assessed lifestyle variables by means of a structured interview. Due to the absence of follow-up examinations in the study's design, sleep quality was investigated through a self-reported experience of poor sleep quality and a cut-off of 7 h without awakenings like previously published studies [28].
The dietary habits section was designed to investigate the food habits such as starch-rich food, meat, legumes, fruit, vegetables, soft drinks, and water consumption.
Concerning physical activity, questions were structured to quantify the time spent weekly in physical activity and to quantify the hours spent daily on sedentary activities.
Moreover, considering the potential health impact of human–animal interaction, we investigated the presence of pets in the household.

### Statistical analysis

Data were analyzed using Stata 15 (StataCorp, College Station, TX, USA). A 2-sided p-value <0.05 was considered statistically significant. The prevalence of CD in obese patients (primary endpoint) is computed as the ratio of patients with CD to the total number of patients enrolled, together with its binomial exact 95% confidence interval (95% CI). Continuous variables are presented as mean and standard deviation (SD) or median and quartiles, categorical variables as counts and percent (secondary endpoints). They are compared between CD/non CD with the Mann–Whitney U test and the Fisher exact test, respectively. The sample size of 200 patients had been defined based on the primary endpoint of prevalence of CD, assuming the current prevalence to be three times the prevalence in the general population of 1.5%, while retaining a type I error of 5% and a power of 80%. The precision attainable around the prevalence estimate (computed as half the 95% CI) would be 3.1%.

## Results

CD was detected in 8 patients (4%), mean age 9.43 ± 4.68 years, five female and three males. Both tTG-IgA and EMA-IgA autoantibodies were positive in all subjects with CD; no patient showed tTG-IgA 10 times higher than the upper cutoff. CD diagnosis was confirmed by EGDS (Marsh stage 3b in seven patients and stage 3c in one subject). HLA-DQ2 and/or DQ8 haplotypes positivity was reported in all subjects with CD.
Clinical features and biochemical parameters of the patients are reported in Tables 1 and 2. Personal history and lifestyle variables are showed in Tables 3 and 4.

## Clinical and biochemical data

No significant difference in age (p=0.13), gender (p=0.49), pubertal stages (p=0.26), BMI (p=0.21), W/HtR (p=0.3) was noted between subjects with CD and without CD (Table 1). As reported in Table 2, higher vitamin B12 (p=0.02) and iron (p=0.05) levels and triglycerides concentration (p=0.02) were observed in patients with CD compared to subjects without CD, though the number of subjects with pathological values of vitamin B12, iron, and triglycerides did not differ between groups (p>0.1). No other significant difference in biochemical parameters was noted. Hepatic function (p=0.8) and blood pressure (systolic pressure p=0.51; diastolic pressure p=0.6) were similar in both groups.

## Symptoms

As reported in Table 1, headache was reported more frequently in patients with CD compared to patients without CD (p=0.04). No other significant clinical signs were referred.

**Table 1:** Clinical data and recorded symptoms according to presence of absence of the celiac disease.

| Parameters | All (n=200) | Patients with CD (n=8) | Patients without CD (n=192) | p-Value* |
|---|---|---|---|---|
| Age (years) | 10.9 ± 2.65 | 9.43 ± 4.68 | 11.0 ± 2.5 | 0.13 |
| Gender (M/F) | 101/99 | 3/5 | 98/94 | 0.49 |
| Pubertal stages | | | | |
| Tanner I | 73 (36.5%) | 5 (62.5%) | 68 (35.4%) | 0.26 |
| Tanner II–III | 66 (33%) | 1 (12.5%) | 65 (33.9%) | |
| Tanner IV–V | 61 (30.5%) | 2 (25%) | 59 (30.7%) | |
| BMI (kg/m$^2$) | 25.0 ± 4.3 | 23.1 ± 1.7 | 25.1 ± 4.4 | 0.18 |
| BMI >85° percentile | 108 (54%) | 6 (75%) | 102 (53.1%) | 0.29 |
| BMI >97° percentile | 92 (46%) | 2 (25%) | 90 (46.9%) | |
| W/HtR | 0.8 ± 0.2 | 0.7 ± 0.05 | 0.8 ± 0.06 | 0.30 |
| W/HtR >0.5 | 200 (100%) | 8 (100%) | 192 (100%) | |
| Intestinal symptoms | | | | |
| Abdominal pain | 53 (26.5%) | 2 (25%) | 51 (26.5%) | 0.42 |
| Abdominal swelling | 44 (22%) | 3 (37.5%) | 41 (21.3) | 0.07 |
| Protruding abdomen | 24 (12%) | 1 (12.5%) | 23 (11.9%) | 0.48 |
| Meteoerism | 36 (18%) | 2 (25%) | 34 (17.7%) | 0.23 |
| Diarrhea | 8 (4%) | 0 (0%) | 8 (4.1%) | 0.80 |
| Stipsis | 35 (17.5%) | 2 (25%) | 33 (17.2%) | 0.22 |
| Extra-intestinal symptoms | | | | |
| Weight loss/lack of weight increase | 7 (3.5%) | 0 (0%) | 7 (3.6%) | 0.83 |
| Weakness | 20 (1%) | 0 (0%) | 20 (10.4%) | 0.57 |
| Dermatitis herpetiformis | 2 (1%) | 0 (0%) | 2 (1.1%) | 0.94 |
| Arthralgia | 27 (13.5%) | 0 (0%) | 27 (14%) | 0.47 |
| Headache | 67 (33.5%) | 4 (50%) | 63 (32.8%) | 0.04 |
| Concentration disorders | 8 (4%) | 0 (0%) | 8 (4.1%) | 0.80 |
| Neurological symptoms | 9 (4.5%) | 0 (0%) | 9 (4.7%) | 0.78 |
| Alopecia | 1 (0.5%) | 0 (0%) | 1 (0.5%) | 0.97 |

*Patients with CD vs. patients without CD.

### Anamnestic data

As reported in Table 2, birthweight (p=0.3), type of delivery (p=1), breastfeeding duration (p=0.52), weaning timing (p=0.41) as well as timing of gluten introduction (p=0.07) were not associated to CD diagnosis.

Maternal lifestyle habits during pregnancy, including smoking habit, alcohol consumption, dietary supplementation, medications, and gain weight did not differ in offspring with or without CD (p>0.05), Table 3.

A significant familiar positivity for autoimmune diseases was revealed in patients with CD (p=0.01), Table 3.

### Lifestyle variables

Quality of the sleep (p=0.31) and activity levels (p=0.22) did not differ in subjects with or without CD (p=0.25). Use of antibiotics (p=0.25), steroids (p=0.76) and/or antihistaminic (p=0.94) were also similar, Table 4.

As reported in Table 3, limited consumption of fruits and vegetables was noted in subjects with CD compared to those without CD (p=0.04). No other significant differences in dietary habits were detected.

## Discussion

We found the prevalence of CD in overweight and patients with obesity referred to our outpatient clinic of the Pediatric Endocrinology Unit to be 4% which is higher than previously reported in similar cohorts. In addition we found that these patients found to have CD upon screening were more likely to consume less fruits and vegetables weekly. Additionally, these patients were more likely to report headache as a symptom which is consistent with work by Hom et al. which found that one-third of children and adolescents with CD have recurrent headaches at the time of diagnosis [29]. We reported that the familiar positivity for other autoimmune diseases was revealed in six of eight patients who screened positive in our study for CD. These diseases included one rheumatoid arthritis and five autoimmune thyroiditis (AT) confirming the close relationship between CD and AT disease, as already reported

**Table 2:** Metabolic parameters according to presence of absence of the celiac disease.

| Parameters | All (n=200) | Patients with CD (n=8) | Patients without CD (n=192) | p-Value* |
|---|---|---|---|---|
| Fasting glucose (mg/dL) | 74.3 ± 9.2 | 69.7 ± 15.1 | 74.5 ± 8.9 | 0.33 |
| Fasting glycemia >100 mg/dL | 0 (100%) | 0 (100%) | 0 (100%) | |
| Triglycerides (mg/dL) | 70.8 ± 29.9 | 48.0 ± 13.9 | 71.5 ± 30.0 | 0.04 |
| Triglycerides >95° percentile | 14 (7%) | 0 (0%) | 14 (7.2%) | 0.55 |
| HDL-cholesterol (mg/dL) | 50.0 ± 11.4 | 51.8 ± 7.2 | 49.9 ± 11.5 | 0.44 |
| HDL-cholesterol <5° percentile | 7 (3.5%) | 0 (0%) | 7 (3.6%) | 0.74 |
| Total cholesterol (mg/dL) | 155.1 ± 26.2 | 147.0 ± 14.8 | 155.3 ± 26.4 | 0.50 |
| Total cholesterol >95° percentile | 16 (8%) | 0 (0%) | 16 (8.3%) | 0.51 |
| Hb (nv 13.0–17.3 g/dL) | 13.4 ± 0.9 | 13.2 ± 0.8 | 13.4 ± 0.8 | 0.59 |
| Pathological | 77 (38.5%) | 3 (37.5%) | 74 (38.5%) | 0.34 |
| Iron (nv 53–119 mg/dL) | 79.5 ± 29.8 | 104.8 ± 26.2 | 78.79 ± 29.6 | 0.05 |
| Pathological | 5 (2.5%) | 0 (0%) | 5 (2.6%) | 0.36 |
| Vitamin B12 (150–900 pg/mL) | 499.5 ± 184.0 | 691.0 ± 133.8 | 495.2 ± 183.1 | 0.02 |
| Pathological | (0%) | 0 (0%) | 0 (0%) | - |
| Ferritin (nv 8–398 ng/mL) | 38.5 ± 20.6 | 29.2 ± 8.6 | 38.8 ± 20.83 | 0.33 |
| Pathological | 5 (2.5%) | 0 (0%) | 5 (2.6%) | 0.96 |
| Folate (nv 2–9 ng/mL) | 6.6 ± 2.9 | 6.9 ± 2.4 | 6.6 ± 2.9 | 0.67 |
| Pathological | 4 (2%) | 0 (0%) | 4 (2%) | 0.97 |
| Vitamin D (nv 30–100 ng/mL) | 23.1 ± 10.3 | 25.4 ± 12.0 | 22.9 ± 9.9 | 0.52 |
| Pathological | 125 (62.5%) | 5 (62%) | 120 (62.5%) | 0.9 |
| Homocysteine (5–13.9 mmol/L) | 13.3 ± 8.4 | 10.7 ± 3.4 | 13.3 ± 8.5 | 0.21 |
| Pathological | 20 (10%) | 1 (12.5%) | 19 (9.8%) | 0.56 |

*Patients with CD vs. patients without CD.

**Table 3:** Anamnestic data according to presence of absence of the celiac disease.

| Parameters | All (n=200) | Patients with CD (n=8) | Patients without CD (n=192) | p-Value* |
|---|---|---|---|---|
| Birth weight (gr) | 3260.3 ± 615.6 | 3497.1 ± 258.2 | 3251.5 ± 623.5 | 0.13 |
| Type of delivery | | | | |
| Vaginal | 106 (53%) | 3 (37.5%) | 103 (54.2) | 1.0 |
| Cesarean section | 94 (47%) | 2 (25%) | 92 (47.9%) | |
| Breastfeeding duration (months) | 7.1 ± 8.8 | 6.44 ± 4.4 | 7.1 ± 8.9 | 0.52 |
| Timing of the weaning (months) | 5.5 ± 1.4 | 6.0 ± 1.2 | 5.5 ± 1.4 | 0.41 |
| Timing of the gluten introduction (months) | 6.9 ± 2.3 | 9.6 ± 3.3 | 6.8 ± 2.3 | 0.07 |
| Maternal weight gain during pregnancy (kg) | 14.6 ± 9.0 | 18.5 ± 6.6 | 14.5 ± 9.0 | 0.16 |
| Maternal use/consumption during pregnancy of | | | | |
| Alcohol | 4 (2%) | 1 (12.5%) | 3 (1.5%) | 0.1 |
| Tobacco | 21 (10.5%) | 0 (0%) | 21 (10.9%) | 0.56 |
| Medications/supplements | 105 (52.5%) | 3 (37.5%) | 102 (53.1%) | 0.58 |
| Familiar positivity for autoimmune diseases | 60 (17.5%) | 6 (75%) | 54 (28.1%) | 0.01 |
| Familiar positivity for allergy | 74 (37.0%) | 2 (25%) | 72 (37.5%) | 0.70 |

*Patients with CD vs. patients without CD.

by other authors partly and due to a common genetic predisposition [30]. We did not find significant associations between sex, ponderal status, or other lifestyle variables and CD in our sample.

Celiac disease prevalence has increased over recent decades [4, 5] and our findings support previous work suggesting that CD is prevalent in patients with overweigh and obesity. While traditionally CD is thought of as causing malabsorption, and thus researchers and clinicians have focused on weight loss and poor growth, recent studies have found that patients who were normal weight, overweight, and affected by obesity are common [6–17]. Nenna et al. [31] evaluated retrospectively CD prevalence in a large series of overweight/obese children and adolescents and reported that 1.11% of patients were positive for serology and showed villous atrophy; in this population some patients with CD showed gastrointestinal symptoms, though they had not been complaining

**Table 4:** Lifestyle variables of the patients according to presence of absence of the celiac disease.

| Parameters | All (n=200) | Patients with CD (n=8) | Patients without CD (n=192) | p-Value* |
|---|---|---|---|---|
| Quality of the sleep | | | | |
| Good (>7 h without awakenings) | 179 (89.5%) | 7 (87.5%) | 175 (91.1%) | 0.31 |
| Physical activity (>3 h/week) | 139 (69.5%) | 5 (62.5%) | 134 (69.7%) | 0.22 |
| Habitual use of | | | | |
| Antibiotics (>4 times/years) | 88 (44%) | 3 (37.5%) | 85(44.3%) | 0.25 |
| Steroids (>3 times/years) | 10 (5%) | 0 (0%) | 10 (5.2%) | 0.76 |
| Antihistaminic (>3 times/years) | 2 (1%) | 0 (0%) | 2 (1%) | 0.94 |
| Allergy | 84 (42%) | 4 (50%) | 80 (41.6%) | 0.9 |
| Animals at home | 102 (51%) | 4 (50%) | 99 (51.5%) | 0.15 |
| Bread, "pasta", rice, potatoes (>4 times per week) | 165 (82.5%) | 6 (75%) | 159 (82%) | 0.46 |
| Meat/Fish (at least 2 times per week) | 187 (93.5%) | 6 (75%) | 162 (95.3%) | 1 |
| Legumes (>4 times per week) | 16 (8%) | 0 (0%) | 16 (8.3%) | 0.72 |
| Fruit and vegetables (<2 times per week) | 21 (10.5%) | 2 (25%) | 19 (9.8%) | 0.04 |
| Ready meals (>4 times per week) | 7 (3.5%) | 0 (0%) | 7 (3.6%) | 1 |
| Water consumption during meals | 156 (78%) | 5 (50%) | 151 (79%) | 0.28 |
| Passive smoking | 98 (49%) | 3 (37.5%) | 95 (47.5%) | 0.49 |

*Patients with CD vs. patients without CD.

about them, and attended the outpatient visit for the nutritional disorder. Here, we reported a remarkable CD prevalence (4%) in an Italian pediatric population referred to an auxological outpatients' clinic for overweight/obesity. Our overall prevalence is likely even higher than reported here, given that we excluded patients with gastrointestinal symptoms, with previous diagnosis of CD and or family history of CD. Our observation confirms the importance of screening also when excessive weight gain exists [6].

The pathogenetic basis of CD coexistence in subjects with excessive weight gain remains unclear; according to the "compensatory" hypothesis, the duodenum—jejunum atrophy in CD patients could be balanced by an increased distal intestinal absorption [32]. This adaptation is due to structural modifications that cause an increased enteral absorption; so unbalanced diets may lead children to gain weight [33]. Even though no significant difference in age was noted between subjects with and without CD, the age of those affected is young (9.43 ± 4.68) suggesting that intestinal adjustments occur overtime [34–36]. Moreover it can be expected that the youngest children diagnosed with CD show acute and classic symptomatology, while older children present a more nuanced or atypical symptomatology [34–36].

While 75% of patients identified as having CD had a family history of autoimmune disease, we did not find any significant differences in medical history or lifestyle variables in patients with or without CD. These results reinforce the knowledge that an individual's genetic predisposition plays a crucial role in the development of CD. As reported, autoimmune diseases, including CD, result from an interaction between environmental factors and genetic predisposition. More than one autoimmune disease frequently develops and clusters in the same individual and family members, supporting the hypothesis that there are likely to be common chromosomal gene regions conferring susceptibility to more than one disease [37].

Regarding symptoms, our data confirmed that prevalence of idiopathic headache at diagnosis was higher in children with excessive weight gain [38–40]. The pathogenetic mechanism underlying the relationship between CD and headache remains unclear; however, this symptom should be considered as a neurological manifestation among children with CD [38–40]. Headaches associated to CD are predominantly migraines [41] and multiple nutritional, immunological and inflammatory factors could be involved in triggering migraine attacks [41].

Lifestyle including diet plays an important role in health improvement in CD in which the only treatment includes nutritional therapy [1, 2, 42]. Studies to date have focused on timing of gluten introduction and amount of gluten ingested as it relates to celiac disease onset [43]. However, we are unaware of studies evaluating other dietary habits in children prior to CD diagnosis.

The limited weekly consumption of fruits and vegetables noted in our sample with CD could hide an early onset of gastrointestinal symptoms that have driven to such poor plant food intake; however, evidence suggests that western diet, high in sugar and fat and low in vegetables and fruit, a can cause dysbiosis, an alteration in the composition of the microbiota, which could lead to aberrant immune responses. Low intake of fiber alters intestinal microbiota in humans resulting in decreased short chain fatty acid

production by microbes which increase the intestinal pH [44]. Thus, it is plausible that low fruit and vegetable consumption promote the growth of microbes that could have detrimental effects on their host [44] besides being a risk factor for chronic diseases [45].

The emerging role of epigenetic mechanisms and the potential mechanisms of action of the intestinal microbiota and specific components that impact CD pathogenesis [46] may play a key role in CD and obesity coexistence. Additionally, the increase prevalence rate of overweight and obesity in children may also explain excessive weight coexistence in children affected by CD [6]. Finally, the unconfirmed but nonetheless interesting hypothesis that overnutrition is due to a compensatory high energetic yield secondary to slow functional adaptation of the atrophic mucosa could not be excluded [40].

Study limitations should be acknowledged starting from the choice the authors made to exclude patients with family history of CD and intestinal symptoms since in these patients screening is routinely performed and the authors instead wanted to investigate the asymptomatic ones. There is no control group since the prevalence in the general population is already well known also in pediatrics. No weight-loss follow-ups are reported, since this was not the aim of this study, although BMI improvements were detected. Further studies focusing on the relationship between CD and obesity are recommended.

Clinical observational studies with large number of pediatric patients with excessive weight gain are mandatory to confirm the observed results. Further research in this field is needed to achieve a better understanding of the networks involved in CD pathogenesis.

In conclusion, CD should be considered in pediatric patients with excessive weight gain, besides familial predisposition to other autoimmune diseases representing a well-known risk factor for CD development. Additionally, even though the relationship between headache and CD is not well defined, patients with idiopathic headache should be screened for CD. Professionals should be aware of the broad spectrum of this disease, in order to perform an early screening and to prevent the organic complications of untreated CD.

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