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Can Celiac Disease Present Along With Childhood Obesity?

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Abstract Celiac disease is an autoimmune, gluten-induced enteropathy with a prevalence of 1-1.5% in Western populations. It may present with classical gastrointestinal symptoms, non-gastrointestinal symptoms or as an asymptomatic disease. Cases of childhood obesity in gluten sensitive enteropathy have been recently reported. The study aimed to retrospectively evaluate the rate of overweight and obesity prevalence in a large sample of celiac children in comparison to non-celiac group, and to investigate the weight dynamics following gluten-free diet. Among 390 patients, 68 (17.4%) (29 boys) were overweight or obese at diagnosis. Gluten-free diet did not shown a beneficial effect on weight. The study demonstrates comparable rates of overweight and obesity in celiac versus non-celiac population.

Keywords: *celiac disease, obesity, overweight, gluten free diet, weight, body mass index*

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1. Introduction

Celiac disease (CD) is an autoimmune gastrointestinal (GI) disorder precipitated in genetically predisposed individuals by the ingestion of prolamins, a major storage proteins found in wheat, rye, barley and less in oat. The genetic predisposition is related to human leukocyte antigen DQ2 and DQ8 haplotypes, but dozens of associated genes were described [1]. CD affects 1.0 to 1.5% of the population worldwide, with wide differences in European countries [2,3]. The epidemiology and phenotype of CD are constantly changing. It has been shown that the classic intestinal clinical picture of malnutrition, chronic diarrhea and nutritional deficiencies are disappearing and extra-intestinal presentations are emerging. Skin, endocrine, skeletal, hepatic, hematological, thrombophylic, gynecological, fertility, dental, cutaneous, neurological and behavioral abnormalities are often described [3,4]. Nowadays, we are witnessing an epidemiological shift in the disease phenotype towards a more advanced age, and increased prevalence of latent, hyposymptomatic or asymptomatic behavior [2,3].

While weight loss or abnormal weight gain are considered as classical symptoms of pediatric and adult CD, there is increasing evidence of overweight and obesity at the presentation or in treated CD children as well as in adults [6,7,8,9,10]. This phenomenon spans multiple Western and developing countries, but the obese or overweight presentation in pediatric CD populations in the Middle East region is rare, and in Israel, more specifically, nonexistent, to our knowledge.

The aims of the study were to estimate the prevalence of obesity at diagnosis among children with CD in comparison to a non-CD group of children, in Israel and to follow the changes in Body Mass Index (BMI) after initiation of a gluten-free diet (GFD).

2. Methods

The electronic charts of 390 children diagnosed with CD between 1995 and 2014, at The Lady Davis Carmel Medical Center and Rambam Health Care Campus in Haifa, Israel, were reviewed. Data collected from the medical records included age, sex, weight, height, presenting symptoms, small intestinal biopsy graded according to Marsh score, celiac related antibody titers (IgA+IgG anti-tissue transglutaminase (tTg) and IgA+IgG anti-neo-epitope-tTg , Helicobacter pylori presence, serum nutritional parameters (hemoglobin, iron, ferritin) and serum fat indices (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). Follow-up weight and height were recorded after one year of GFD, adherence verified by normalization of celiac antibody titers. The control group consisted of 407 children referred to the 2 hospitals with abdominal pain and underwent intestinal biopsy which excluded CD. Exclusion criteria were: missing biopsy results, missing anthropometric data at diagnosis,

and patients with other inflammatory bowel diseases, (Crohn's disease and ulcerative colitis) or specific end organs' dysfunctions.

Body mass index (BMI) and growth percentiles were calculated using Worlds Health Organization (WHO) AnthroPlus software (Blue-infinity (b-i) SA, Geneva, Switzerland. 2009) for patients' classification to weight groups. Cutoffs for underweight, normal weight, overweight and obesity using the WHO's standard thresholds for BMI-for-age and weight-for-age of 3rd percentile for underweight, 85th percentile for overweight and 97th percentile for obesity, were determined.

Statistics: Statistical analysis was performed with JMP 7.0.1 software (SAS Institute inc. 2007). T-test was used to compare continuous variables. Chi2 or fisher exact test (as required) was applied to examine the differences in symptoms frequencies between groups, BMI distribution by percentile groups and Helicobacter pylori presence. Pearson correlation coefficient was used to examine correlations between BMI and laboratory parameters. A two-tailed P-value of <0.05 was considered as statistical significant.

This study was approved by the local Helsinki Committees of Carmel and Rambam medical centers, Israel.

3. Results

3.1. Epidemiological Characteristics

57.4% of the CD and 56.3% of the controls were female. Mean age at diagnosis of CD was 7.12 ±4.3 years.

Symptoms at diagnosis were recorded in 172 CD and 167 control children. Some cases showed more than one symptom (Table 1). Abdominal pain was the most common symptom in both groups. The prevalence of anemia and diarrhea was higher in CD group compared to the controls: 32.6% and 21.6%, respectively, for anemia (p=0.022) and 15.7% and 8.4%, respectively, for diarrhea (p=0.039), with no correlation to weight. Twenty-seven of 172 CD patients (15.7%) and 7/167 (4.2%) of control patients (p=0.0004) did not suffer from any symptoms and were considered asymptomatic. Three of 31 (9.7%) of overweight and obese CD patients were asymptomatic at diagnosis.

3.2. BMI Categories' Distribution

Nearly 17.4% of patients with CD had high BMI at diagnosis (11.8% overweight, 5.6% obese), and 75.4% of patients presented with a normal BMI. The remaining 7.2% were underweight. No differences were found in the prevalence of underweight, normal weight and overweight between the groups. The proportion of children suffering from obesity was lower in CD group in comparison to the control group (5.6% and 10.1% respectively, p=0.025). While among girls, the prevalence of obesity was significantly lower (p=0.0426) in the CD group in comparison to controls, this difference was not depicted among boys (Figure 1).

3.3. Age at Diagnosis

Mean age of diagnosis among normal-weight CD children was 6.8±4.2 years, in comparison to over-weight and obese children who were diagnosed in average 1.5 years older at the mean age of 8.3±4.6 years (p=0.0401). In addition, no difference was found in the age of diagnosis in multiple comparisons between the underweight, overweight and obesity groups. It points to the lack of a linear relationship between the degree of obesity and age of diagnosis.

3.4. Correlations to BMI and Laboratory Parameters

No correlations were found between BMI percentiles and the degree of intestinal damage (r=0.0745, p=0.2329), blood lipid levels: for total cholesterol (r=-0.01, p=0.9361), for triglycerides (r=0.1281, p=0.3423), for HDL cholesterol (r=-0.0844, p=0.5517), for LDL cholesterol (r=0.0534, p=0.707), serum antibody levels: for neo-tTG-IgA (r=-0.0375, p=0.6657), for tTG-IgA (r=-0.015, p=0.8394), for AEA (r=0.001, p=0.9941), and Iron status indices: for hemoglobin (r=-0.0732, p=0.3356), for iron (r=-0.1617, p=0.063), and for ferritin (r=0.0177, p=0.848).

3.5. Helicobacter Pylori

Helicobacter pylori presence was recorded in 29.5% of tested children (47/160, (29.4 %) CD and 41/137 control, (30%)) with no significant difference between the groups) p=0.917). Overweight and obese CD children found to be the group with the highest incidence of H. pylori infection (46%) in comparison to normal weight (27%) and underweight CD children (13%) (chi2=6.017, p=0.0494).

Table 1. Patients Characteristics

	Control	Celiac
Demographics		
Male	178(43.7%)	116(42.6%)
Female	229(56.3%)	224(57.4%)
Mean age(y)(SD)	10.9(4.7)	7.1(4.3)
Presenting symptoms		
Abdominal pain	74(44.3%)	65(37.8%)
Anemia	**36(21.6%)**	**56(32.6%)**
Failure to thrive(FTT)	44(26.3%)	33(19.2%)
Diarrhea	**14(8.4%)**	**27(15.7%)**
Short stature	8(4.8%)	7(4.1%)
Constipation	1(0.6%)	7(4.1%)
Abdominal distention	1(0.6%)	7(4.1%)
Attention deficit hyperactive disorder	-	**6(3.5%)**
Weight loss	7(4.2%)	5(2.9%)
Low weight	2(1.2%)	6(3.5%)
Asthma	1(0.6%)	4(2.3%)
Diabetes mellitus T1	1(0.6%)	7(4.1%)
Asymptomatic	**7(4.2%)**	**27(15.7%)**
Other	18(10.8%)	19(11%)

Others include: hair overgrowth, hair loss, Down syndrome, acne, headaches, vomiting, throat pain, fatigue.
Anemia p=0.022, Diarrhea p=0.039, Asymptomatic p=0.0004, Attention deficit disorder p= 0.029.

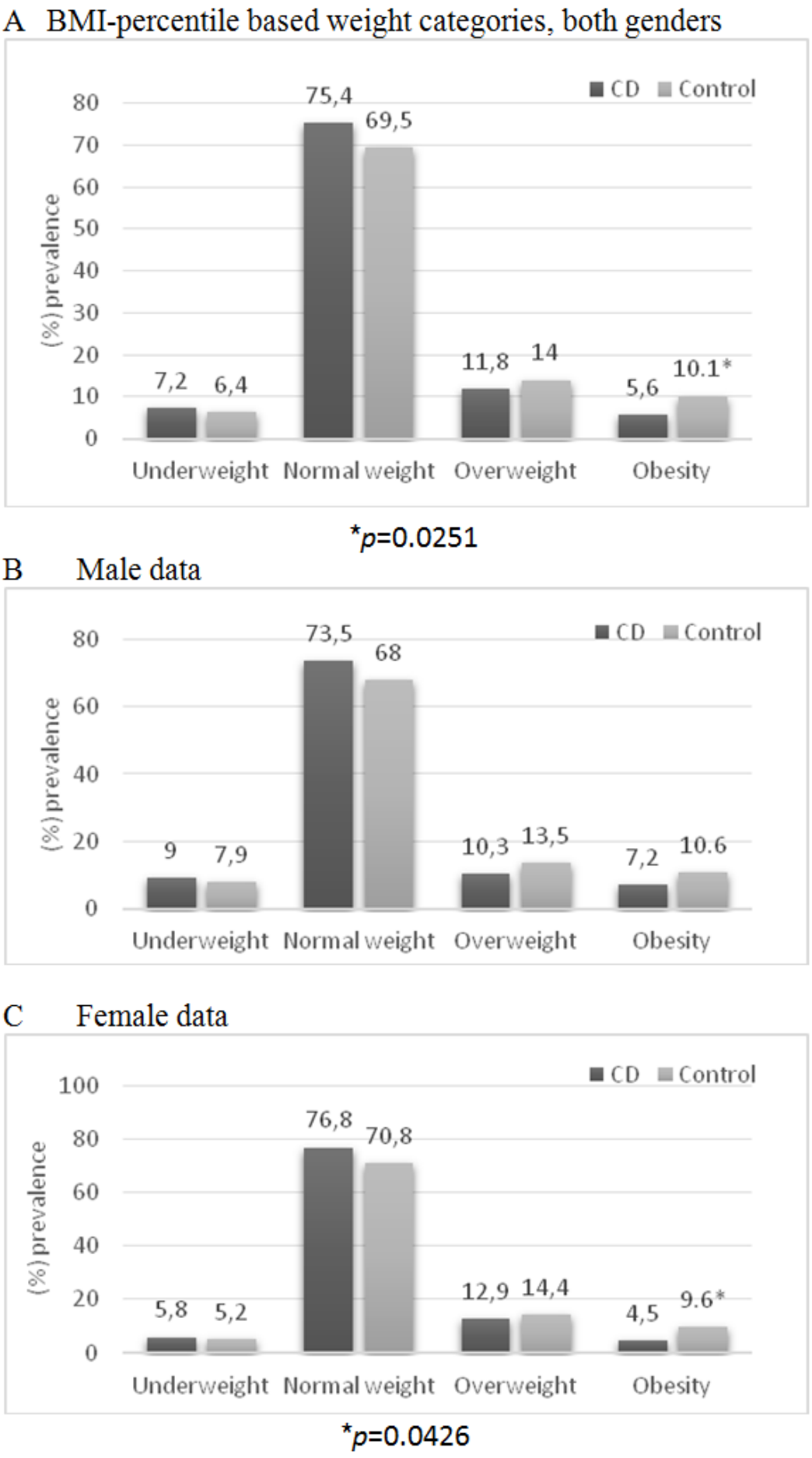

Figure 1. Distribution of BMI-percentile based weight categories in patients with celiac disease and controls, in both genders=A, among male=B and female=C groups

Table 2. Changes in BMI groups following a GFD

Follow up: BMI group classification after a GFD n (%)						
Obese	Overweight	Normal	Underweight			
0	0	3 (100)	0	3 (100)	Underweight	Initial BMI group No (%)
1 (2.4)	2(4.9)	38 (92.7)	0	41 (100)	Normal	
1 (20)	3 (60)	1 (20)	0	5 (100)	Overweight	
4 (66.6)	2 (33.4)	0	0	6 (100)	Obese	

3.6. Follow-up on GFD

BMI at follow-up, while on a GFD, was collected at a mean of 13±7 months after diagnosis from the clinical records of 55 patients initially referred to Carmel Medical Center. Mean BMI percentile was 46.2±34.4 at diagnosis and 51.5±33.4 at follow-up (non-significant). None of the patients found to be underweight at time of follow-up. Three of the children were under-weight at diagnosis, all of them were at normal weight group (BMI percentile |3.8-7.1) following GFD. Three of the 41 normal weight patients at diagnosis became overweight or obese at follow-up. Among 5 patients who were overweight: one became obese and one normalized body weight. Four of six patients continued to suffer from obesity while two were classified as overweight (Table 2).

4. Discussion

In this retrospective study the prevalence of overweight and obesity in large sample of CD children and adolescents compared to non-celiac control group were evaluated. Malnutrition and low weight, once considered as main characteristics of pediatric CD, represent actually, only in a small proportion of newly diagnosed patients, reflecting the changing epidemiology of the disease [1,2,3].

Coexistence of obesity and CD has been reported in the literature [5-22]. The coexistence was explained by the compensation theory. According to this hypothesis the proximal bowel malabsorption is compensated by enhanced distal small bowel absorptive capacity. It is also known that an individual's coefficient for fat absorption remains relatively static and eventually children whose energy intake is excessive may become overweight or obese [11].

According to the literature 3.9% to 13% of adults with CD are obese at presentation, another 15.2% to 31% are overweight [8, 16, 23]. In pediatric CD the observed rates of overweight and obesity are 8-20.8% and 0-6%, respectively [6–9,24–26]. It is intriguing, for example, that in developed and Western Italy, overweight/obesity is considered as rare manifestation of CD (7.8%) [19], while in the developing and Asian India population, 6.2% are overweight, 2.9% are obese and one third presented underweight [20].

In the present study the overweight and obesity rates, in newly diagnosed CD children, were 11.8% and 5.6% respectively, going along the above described rates. A higher prevalence of obesity among CD boys was presently observed, in agreement of the previously published data [19,24]. In comparison to non-celiac controls the groups differ in obesity rates solely within the female population, where lower rates of obesity were depicted in CD girls in comparison to control's females.

The surge in the diagnosis of celiac disease in children with overweight and obesity may be due to both, childhood obesity pandemic in Western countries, the increased awareness for the disease and the increasing mass of serological screening of asymptomatic or hyposymptomatic individuals.

Celiac disease screening performed recently in a large cohort of overweight and obese Italian children demonstrated similarity in the rates of CD between overweight/obese children and the general population [27]. In the same line, at the individual level, growth parameters, including weight, could not serve as a reliable tool in predicting or excluding CD [28]. Furthermore, most recently, overweight was described as a rare presentation of CD, at least in Italy [19].

Our results are comparable to the knowledge about the weight improvement of children with CD who are underweight at diagnosis [24, 26]. Earlier data on pediatric CD have shown that for most overweight children with CD, GFD has a beneficial effect [24]. Notably, the present study contradicts the above observation. While one third of the obese patients benefited from a GFD, the remaining children remained in their weight category.

Weight gain following a GFD might be a result of normalization of caloric balance due to the restoration of mucosal absorptive functions. Behavioral reasons can also lead to weight gain on GFD. The cessation of abdominal symptoms promotes food consumption, but the nutritional choices might play a key role in weight management [20]. Previous studies described a trend to replace gluten containing foods with an increased consumption of sugars, fats, proteins and hypercaloric beverages parallel to decrease fiber intake [16,29,30]. Unpalatability and the higher cost of gluten-free foods might promote inappropriate dietary habits and junk food, especially among children and adolescents.

Several mechanisms have been suggested to explain the relations between obesity and autoimmune diseases. One example is the secretion of adipokines by white adipose tissue, which modulate the immune response and contribute to a "low grade inflammation state"in obese subjects. The involvement of adipokines may play a role in the pathogenesis of intestinal inflammatory in those individuals. Indeed, high levels of leptin, resistin and visfatin were found to be associated with intestinal inflammation [31]. Studies have shown that psychosocial factors including depression, anxiety, and poor self-esteem are often present in obese children. Vitamin D deficiency might also play a role in the obesity-autoimmunity interplay, including in CD [21,32]. Interestingly, comparable associations between those factors and functional GI disorders are well described.

There is an emerging interest in the role of the intestinal microbiome in the pathogenesis of GI disorders. It has

been shown that obesity is associated with a change in microbiota, reduction in bacterial diversity, and altered metabolic pathways. Although both obesity and GI disorders are associated with specific microbiome patterns, the dysbiotic patterns are different. More research is required to evaluate the associations between gut microbiota, obesity, and CD [33].

Further research and exploration of the theories described above on the potential relations between obesity and CD will clarify the need of screening for CD in overweight/obese children.

5. Conclusion

The present study highlights the fact that CD can be diagnosed in overweight or obese children. Therefore, overweight or higher BMI should not serve as a selective exclusion criteria for CD screening and diagnosis. A nutritionally balanced GFD might promote weight normalization for the patients. Nevertheless, nutritional and growth follow-up is important to achieve an optimal weight and prevent both CD- and obesity-related complications.

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