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Changes of body mass index in celiac children on a gluten-free diet

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Abstract *Background and aim:* Studies of adults and children with celiac disease (CD) performed mostly in tertiary care centers have reported an increased risk of overweight during gluten-free diet (GFD). We measured body mass index (BMI) of CD children followed by family pediatricians in order to estimate prevalence of underweight and overweight at diagnosis and to describe BMI changes during GFD.

Methods and Results: We compared 150 CD children (age range 2–16 yrs) under GFD from a median (IQR) time of 4.4 (4.2) years with 288 healthy children matched for gender and age. We also evaluated retrospectively BMI changes between CD diagnosis and the current evaluation. The median (IQR) BMI of CD patients was significantly lower than that of controls [−0.38 (1.46) vs. 0.09 (1.18) SDS, $p < 0.0001$, Italian reference data]. Using the International Obesity Task Force classifications, CD children were less frequently overweight or obese (12% vs. 23.3%, $p = 0.014$) and more frequently underweight (16% vs. 4.5%, $p < 0.001$) than controls. During GFD, there was a marked decrease of number of underweight subjects (13 vs. 27) and a minimal increase of number of overweight subjects (9 vs. 6) ($p < 0.001$).

Conclusions: The frequency of overweight and obesity at diagnosis of CD and during GFD in children followed by family pediatricians is substantially lower than that reported in tertiary care centers. On the other hand, the high frequency of underweight at diagnosis confirms the need of careful personalized nutritional management.

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Introduction

Celiac disease (CD), a genetically mediated autoimmune enteropathy triggered by the ingestion of gluten, has a worldwide prevalence of 1–2% [1,2]. Its clinical manifestations are very heterogeneous but younger children have often gastrointestinal symptoms and adolescents and young adults are commonly diagnosed by screening [3–6].

Few studies, performed mostly in adult patients followed at tertiary care centers, have evaluated the distribution of body mass index (BMI) in CD patients [7–9]. Mariani et al. first reported high prevalence of overweight and obesity in CD adolescents on a gluten-free diet (GFD) [10]. The risk of overweight and obesity at diagnosis of CD varies largely with the nutritional status of the underlying population, as suggested by some very recent pediatric papers [11–14]. Cross-sectional studies have shown that children on GFD consume less complex carbohydrates and fiber and more sugars, proteins and saturated fats, and this may predispose them to overweight and obesity [10,15–18].

We evaluated the BMI of a large sample of CD children and adolescents followed by family pediatricians, compared it to that of matched healthy controls, and retrospectively evaluated its changes from the start of GFD.

Methods

Study design

81 family pediatricians (FP) working for the National Health System of the Lombardia region (Northern Italy) volunteered to this study. Each FP evaluated his known CD patients aged 2–16 years during a periodical health check performed in 2007 (study time). A total of 150 celiac children (47 males and 103 females) were enrolled into the study. The number of CD patients ranged from 1 to 7 for every FP. Exclusion criteria were: 1) age <2 years and age >16 years at study time, 2) GFD started from less than 6 months, and 3) presence of chronic disease (e.g. diabetes mellitus). Inclusion criterium was a maintained seronegativity (see below) in the months before the study as assumption of compliance to GFD. Each FP evaluated also 2 healthy children (“controls”) for each CD patient. They were matched to CD patients by sex (same) and age (± 1 month) by a statistician who used a random number generator implemented via software among healthy children from the electronic database of each FP. The study was approved by the Ethical Committee of Luigi Sacco Hospital (Milano, Italy) and informed consent was obtained from parents.

Clinical evaluation

CD was diagnosed on the basis of clinical features (chronic diarrhea, iron-deficiency anemia and malnutrition), positive serology (anti-gliadin, anti-endomysial and anti-transglutaminase antibodies), and the presence of severe mucosal atrophy (Marsh III stage) at duodenal biopsy [19]. Normalization of autoantibodies was used to assess compliance to GFD. The familial history of CD was also collected.

Anthropometric assessment

Current weight and height were measured at the periodic health check in 2007 (study time) and their values at diagnosis of CD (diagnosis time) were obtained from the electronic database of each FP. Weight and height were measured according to standard procedures [20]. Body mass index (BMI) was calculated as weight (kg)/height (m)². Standard deviation score (SDS) of weight and height were calculated from Italian reference data [21], available from age 2 years onward, and from WHO reference data [22], available from birth onward. BMI was categorized as underweight (grades 1, 2, and 3), normal weight, overweight and obesity, using the standards of the International Obesity Task Force (IOTF) [23,24]. In particular, overweight and obese children were defined as those children whose BMI was over the age- and sex-specific cut-off points corresponding to the adult BMI values of 25 (overweight), or 30 (obesity) [23] and underweight children were defined as those children whose BMI was below the age- and sex-specific cut-off points corresponding to the adult BMI value of 18.5 (grade 1), 17 (grade 2), and 16 (grade 3) [24]. At the study time the parents of the children had a measurement of weight and height [20].

Statistical analysis

Continuous variables are reported as median and interquartile range (IQR) because of skewed distributions (Shapiro–Wilk test). IQR was calculated as the difference between the 75th and 25th percentile. Categorical variables are reported as the number and percentage of subjects with the characteristic of interest. Between-group comparisons were performed with the Wilcoxon–Mann–Whitney test for continuous variables and with Fisher’s exact test for categorical variables. Univariable and multivariable logistic regression was used to calculate the odds of overweight or obesity (0 = normal weight; 1 = overweight or obese) and the odds of underweight (0 = normal weight; 1 = underweight from degree 1–3) for CD patients vs. controls. Multivariable logistic regression accounted for the matching criteria, i.e. gender (0 = female; 1 = male) and age (continuous, years) besides disease status. Among CD patients, multivariable bootstrapped quantile regression was used to evaluate the relationship between median BMI (SDS-WHO) at the periodic health check in 2007 (study time) and BMI (SDS-WHO) at diagnosis of CD (diagnosis time) taking into account gender (0 = female; 1 = male), age at diagnosis (continuous, years), paternal BMI (continuous, kg/m²) and maternal BMI (continuous, kg/m²) [25,26]. Because Italian reference data are available only from age 2 onward [21], we used WHO reference data [22] to test this association. Multivariable fractional polynomials were used to test whether the fit of any logistic or quantile regression model including one or more continuous predictors could be improved by taking into account non-linear relationships of such predictors with the outcome. Having found no increase of fit for any model, we evaluated all continuous predictor–outcome relationship as linear [27]. Statistical analysis was performed using Stata 11.2 (Stata Corp, College Station, TX).

Results

150 celiac children (47 males and 103 females) and 288 healthy children (92 males and 196 females) were enrolled into the study. The slight deviation from the postulated 1:2 matching ratio between CD patients and controls was due to the impossibility to match all CD patients with 2 controls within the database of the same FP. The 12 cases of failed matching were all cases of 1:1 matching instead of 1:2 matching. A family history of CD was detected in 7.5% of mothers and in 3.5% of fathers of CD children.

The measurements of the children are given in Tables 1 and 2. The weight and BMI of CD patients were significantly lower than those of controls when expressed both as kg/m² and SDS, while height was significantly lower only when expressed as SDS (Table 1). The lower BMI of CD patients translated into a lower number of overweight and obese subjects and into a greater number of underweight subjects as compared to controls (Table 2). Overweight and obesity were in fact less frequent (12% vs. 23.3%, $p = 0.014$) and underweight more frequent (16% vs. 4.5%, $p < 0.001$) in CD patients than in controls.

The odds of being overweight or obese was 0.45 (95% confidence interval (CI) 0.25 to 0.79, $p = 0.005$) for CD patients vs. controls. The odds of being overweight or obese was virtually unmodified (odds ratio [OR] = 0.43, 95% CI 0.25 to 0.77, $p = 0.004$) after correction for sex (OR = 0.9 for males, 95%CI 0.53 to 1.52, $p = 0.703$) and age (OR = 1.08 for each year of age, 95%CI 1.01 to 1.16, $p = 0.047$). On the other hand, the odds of underweight was higher = 4.03 (95%CI 1.98 to 8.17, $p < 0.001$) for CD patients vs. controls and it was not modified either by sex or age (data not shown).

Among CD patients, we tested whether there was an association between BMI (SDS-WHO) at study time and BMI (SDS-WHO) at diagnosis time, taking into account the effect of gender, age at diagnosis, age at study time, and maternal and paternal BMI at study time. The median (IQR) height of mothers was 1.62 (0.07) m and that of fathers was 1.74

Table 1 Continuous measurements (age and anthropometric variables) of celiac patients and controls at the study time.

	Celiac patients (<i>n</i> = 150)		Controls (<i>n</i> = 288)		WMW test <i>p</i> -value
	Median	IQR	Median	IQR	
Age (Years)	8.0	4.8	7.7	4.4	0.493
Weight (kg)	23.7	15.1	27.5	20.0	0.014
Weight (SDS, IT)	-0.59	1.28	0.18	1.27	<0.001
Height (m)	1.25	0.27	1.28	0.33	0.196
Height (SDS, IT)	-0.54	1.39	0.13	1.45	<0.001
BMI (kg/m ²)	16.0	2.8	17.0	3.4	<0.001
BMI (SDS, IT)	-0.38	1.46	0.09	1.18	<0.001
BMI (SDS, WHO)	-0.00	1.49	0.59	1.34	<0.001

Abbreviations: WMW = Wilcoxon-Mann-Whitney; IQR = interquartile range; BMI = body mass index; SDS = standard deviation scores; IT = Italian reference data [21]; WHO = World Health Organization Reference data [22].

Table 2 Categorical measurements of celiac patients and controls at study time.

	Celiac patients		Controls	
	<i>n</i>	%	<i>n</i>	%
Gender				
Female	103	68.7	196	68.1
Male	47	31.3	92	31.9
Total	150	100.0	288	100.0
$p = 0.914^*$				
Overweight ^a				
Non overweight nor obese	132	88.0	221	76.7
Overweight	17	11.3	61	21.2
Obese	1	0.7	6	2.1
Total	150	100.0	288	100.0
$p = 0.014^*$				
Underweight ^b				
Grade 3	1	0.7	0	0.0
Grade 2	3	2.0	3	1.0
Grade 1	20	13.3	10	3.5
Non underweight	126	84.0	275	95.5
Total	150	100.0	288	100.0
$p < 0.001^*$				
Overweight & underweight combined ^{a,b}				
Underweight (Grade 1 + 2 + 3)	24	16.0	13	4.5
Normal weight	108	72.0	208	72.2
Overweight	17	11.3	61	21.2
Obese	1	0.7	6	2.1
Total	150	100.0	288	100.0
$p < 0.001^*$				

*Fisher's exact test.

^a Overweight and obese children were defined as those children whose BMI was over the age- and sex-specific cut-off points corresponding to the adult BMI values of 25 (overweight), or 30 (obesity) (Ref. [23]).

^b Underweight children were defined as those children whose BMI was below the age- and sex-specific cut-off points corresponding to the adult BMI values of 18.5 (grade 1), 17 (grade 2), and 16 (grade 3) (Ref. [24]).

(0.09) m. The median (IQR) time between the diagnosis of CD and the study visit was 4.4 (4.2) years (range: 0.5–12.6 years). BMI at study time was positively associated with BMI at diagnosis ($p < 0.001$) and negatively associated with age at study time ($p < 0.001$) while gender, age at diagnosis, and parental BMI had no effect on this association (Table 3).

Table 4 reports the changes in weight status between diagnosis time and study time as detected by the IOTF classifications in the 95 CD subjects diagnosed >2 years of age. (Such classifications are available from age 2 onward and we could not apply them to younger patients). At diagnosis, 27 patients were underweight (28.4%), 62 had a normal weight (65.3%), and 6 were overweight or obese (6.3%). During GFD, most of the patients improved their weight status. The number of normal weight children increased in fact from 62 to 73, that of underweight children decreased from 27 to 13, and that of overweight or obese children increased slightly from 6 to 9. The median (IQR) change in weight [0.33 (4.58) SDS] and height [0.04 (7.47) SDS, Italian reference data] showed a substantial

Table 3 Association between BMI at study time, BMI at diagnosis of celiac disease and other predictors. Values are regression coefficients (median effect) and 95% confidence intervals and were obtained by bootstrapped multivariable median regression.

	BMI at study time
BMI (SDS-WHO) at diagnosis	0.6* [0.4, 0.7]
Male gender	0.0 [-0.4, 0.4]
Age at diagnosis (years)	0.1 [-0.1, 0.2]
Age at study time (years)	-0.1* [-0.1, 0.0]
Father's BMI (kg/m ²)	0.0 [0.0, 0.1]
Mother's BMI (kg/m ²)	0.0 [-0.1, 0.1]
Intercept	-0.4 [-2.5, 1.7]
<i>n</i>	150

**p* < 0.001.

SDS-WHO = standard deviation scores obtained from World Health Organization (WHO reference data).

within-individual variability. (WHO reference data could not be used owing to the lack of weight data over 5 years of age). It should be noted that the median (IQR) BMI-WHO at diagnosis was similar in CD patients diagnosed ≤ 2 ($n = 55$) or >2 years ($n = 95$) of age [-0.16 (1.59) vs. -0.13 (1.64) SDS, $p = 0.320$] and the same was true for BMI at study time [0.41(1.60) vs. -0.15 (1.43) SDS, $p = 0.126$].

Discussion

There is a concern about CD patients being overweight at diagnosis and gaining weight while on GFD. In the very last years some studies conducted in tertiary care Centers at CD

diagnosis have reported an unexpected high frequency of overweight (from 11 to 21%) and obesity (up to 7%) [11–14]. Our data, on the contrary, suggest that overweight and obesity in children at diagnosis of CD by family pediatricians seems to be lower than that reported in tertiary care Centers (cumulative 6.3%, Table 4). A speculation for this could be the possible differences in diagnostic modalities: in tertiary care Centers a large part of patients were identified due to familial screening or to the presence of other autoimmune disorders in the child/family, while such screening procedure seems less frequent in our setting; a family history of CD was detected in 7.5% of mothers and in 3.5% of fathers of CD children. Clearly, also the nutritional status of the underlying populations is very important for the correct interpretation of BMI in CD children at diagnosis.

Some experiences have outlined that the obesity risk might increase during GFD in CD children. In fact, frequency of overweight was reported nearly doubled after 1 year of GFD [13] and more than 50% of CD adolescents were found overweight during GFD [10]. However, in the latter paper the Authors used a relative body weight $>110\%$ instead of BMI to define overweight leading to an over-estimation of overweight [10]. The median duration of GFD in our children (4.4 years) was longer than in other studies [12–14]. Our data shows that: 1) children on GFD have lower weight, height and BMI as compared to age- and sex-matched controls; 2) this translates into a lower frequency of overweight and obesity both at diagnosis and during GFD; even if this frequency increases slightly during treatment, it remains lower than that observed in the general population; 3) on the other hand, they have a higher frequency of underweight at diagnosis that decreases during GFD but remains still higher than in the general population. The fact that our CD children tended to have low weight and height at diagnosis may be partly explained by a more efficient search for CD in children of small size. The absolute reduction in number of underweight children during GFD (from 27 to 13), as well as the number of CD patients going from underweight to normal weight (20 out of 27 at diagnosis) suggest that the increase in BMI observed during GFD has probably to be attributed to a physiological catch-up growth. It has to be emphasized, however, that

Table 4 Change of weight status between the diagnosis of celiac disease and the study time in celiac patients aged >2 years at diagnosis ($n = 95$).

	Weight status at diagnosis								
	Underweight		Normal weight		Overweight		Obesity		Total
Weight status at study time	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i> (%)
Underweight	7	53.8	5	38.5	0	0.0	1	7.7	13 (100%)
Normal weight	20	27.4	51	69.9	2	2.7	0	0.0	73 (100%)
Overweight	0	0.0	6	66.7	1	11.1	2	22.2	9 (100%)
Obesity	0	0.0	0	0.0	0	0.0	0	0.0	0 (100%)
Total	27	28.4	62	65.3	3	3.16	3	3.16	95 (100%)

$p < 0.001$ (Fisher's exact test).

Percentages of children are calculated within rows.

Overweight and obese children were defined as those children whose BMI was over the age- and sex-specific cut-off points corresponding to the adult BMI values of 25 (overweight), or 30 (obesity) (Ref. [23]).

Underweight children were defined as those children whose BMI was below the age- and sex-specific cut-off points corresponding to the adult BMI values of 18.5 (Ref. [24]).

a small proportion of underweight children seem to remain unchanged even during treatment.

Limitations of our study include the retrospective design and the lack of assessment of dietary intake and physical activity level. A prospective design would probably help to understand changes in underweight/overweight frequencies during GFD. An analysis of dietary intake may be useful to clarify the effects of nutritional deficiencies or excesses on weight status. Also the analysis of physical activity level at diagnosis and during treatment is certainly useful, taking into account the possible effect of increased sense of wellbeing associated with treatment on energy expenditure of the child.

Overweight/obesity was present at diagnosis in few of our CD children but its presence should not exclude the search for CD. On the other hand, the high frequency of underweight at diagnosis of CD suggests that this diagnosis should be especially pursued in the presence of underweight. However, according to our data both overweight and underweight should not be considered markers of CD, and the diagnosis has to be searched independently from weight status. Nevertheless, the treatment should probably be personalized in order to reach the goal of normal weight status in the most part of patients. In particular, the frequency of underweight halved but did not disappear during GFD, suggesting the need of careful nutritional management in subjects with this clinical pattern at diagnosis.

Nutritional rehabilitation leads to growth acceleration in most CD patients [28–33]. GFD heals in fact the intestinal mucosa and corrects malabsorption [34], with a more rapid recovery of fat mass [35–39]. However, there is not a clear explanation why some CD children do not reach the expected height-for-age. Patwari et al. [40] found that children with an early diagnosis of CD had a greater increase of height than children diagnosed later. Other studies have reported a complete catch-up in height when CD is diagnosed in pre-school age [31,32]. Interestingly, the presence of anti-pituitary antibodies has been recently reported in newly diagnosed CD children and this may contribute to growth impairment [41]. However, we did not find any difference in BMI between children diagnosed with CD before or after 2 years of age.

In conclusion, CD children followed by FP were less frequently obese than their control peers. Moreover, most of them (77%) reached a normal weight status during GFD and none of the underweight subjects became overweight or obese and these facts are proofs of the beneficial effect of GFD in the great part of CD children. The high frequency of underweight at diagnosis suggests the need for careful and personalized nutrition management. Prospective long-term longitudinal studies are needed to better clarify the relationship between BMI and CD.

Conflict of interest

The authors declare no conflict of interest.

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