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Body Mass Index and Prevalence of Skin Diseases in Adults with Untreated Coeliac Disease

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Key Words
Coeliac disease · Immunological disorders · Skin diseases · Body mass index · Malabsorption

Abstract
Objective: Coeliac disease (CD) is associated with immune-mediated skin diseases such as dermatitis herpetiformis and others. The objective of the study was to investigate the relation of body mass index (BMI), as an index of absorptive status, with the prevalence of skin diseases in adults with untreated CD. ***Methods:*** Anthropometry, gastro-intestinal symptoms, nutritional indices and immune-mediated skin diseases (dermatitis herpetiformis, psoriasis, aphthosis and alopecia) at diagnosis were analysed. ***Results:*** 223 men and 924 women with untreated CD (aged 20–60 years) were included, the commonest skin disease was dermatitis herpetiformis (18.4 and 6.9%, respectively), the rarest one was alopecia (1.8 and 2.1%). The BMI was positively associated with male gender, age at diagnosis and nutritional indices, negatively with diarrhoea and dyspepsia ($p < 0.001$). A BMI difference of 3.5 (1 standard deviation) was related to an excess prevalence of dermatitis herpetiformis (odds ratio, OR = 1.46, 95% confidence interval, CI = 1.23–1.72) and of psoriasis (OR = 1.40, 95% CI = 1.10–1.79) but not of other immunological disorders. Findings were similar in analyses by gender or age group and controlled for gender and age. The relation of BMI to dermatitis herpetiformis was linear over the whole BMI range, also excluding overweight patients. The relation of BMI to psoriasis was flat for low-to-normal BMI and explained only by overweight patients. ***Conclusion:*** In CD at diagnosis, the BMI is positively related to the prevalence of dermatitis herpetiformis and psoriasis, not to that of other immune-mediated skin diseases.

Introduction

Coeliac disease (CD) is an immunological disorder that affects 0.5–1% of the population in Europe and the Americas [1]. In the past, CD was considered a rare malabsorptive syndrome of childhood but now is regarded as a relatively common condition, diagnosable at any age, affecting various organs and systems [2]. The present knowledge supports the view that, in CD patients, the ingestion of gluten with food induces an immunodependent inflammation in the proximal small-bowel mucosa which, in turn, leads to the onset of a syndrome of variable severity ranging from a silent subclinical condition to an overt malabsorptive disorder with signs of malnutrition and/or several gastro-intestinal symptoms [3]. CD may often occur in association with various immune-mediated diseases such as thyroiditis of Hashimoto [4], dermatitis herpetiformis [5–8], alopecia [9, 10], psoriasis [11–14], aphthosis [15–17], Crohn's disease [18], insulin-

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dependent diabetes mellitus [19], auto-immune hepatitis [20] and Sjögren's disease [21]. It is not clear whether the presence in CD of these co-morbidities represents another consequence of the gluten-induced inflammation at the intestinal level or not. According to an alternative possibility, the presence of other immune-mediated diseases in CD could reflect a widespread dysreactivity of the immune system rather than a disorder directly dependent on intestinal dysfunction [22, 23]. A recent review of the skin manifestations in CD concluded that dermatitis herpetiformis is a marker of CD independently of the severity of the intestinal symptoms because few patients with dermatitis herpetiformis have signs of malabsorption, although virtually all of them have an associated enteropathy [24, 25]. Actually, previous studies about skin diseases in CD reported data about small series of patients and/or about patients referred to dermatological units [5–17]. Therefore, the present analysis was designed to further investigate this point and to establish whether, within a large cohort of adults with untreated CD, the prevalence of dermatitis herpetiformis and other immune-mediated skin diseases correlated or not with absorptive status as assessed by body mass index (BMI), gastro-intestinal symptoms and other objective indices.

Patients and Methods

The study cohort of this retrospective analysis was selected from the database of patients examined at the Coeliac Disease Centre of the Federico II University (Naples, Italy). The selection criteria of the study cohort were as follows: complete records of data, release of written informed consent, CD diagnosis in adulthood (age ≥20 years), absence of surgical gastro-intestinal resection or of diabetes mellitus. Patients with gastro-intestinal resection and/or diabetes mellitus were excluded because these co-morbidities could affect the patients' nutritional status over the effects of CD per se. The original database of our centre consisted of 2,270 patients diagnosed since 1975. Of these patients, 683 were excluded for CD diagnosis before the age of 20 or after 60, 293 patients for incomplete records, 104 for refused consent, 26 for gastro-intestinal resection before CD diagnosis and 17 for the presence of diabetes mellitus. Thus, the cohort for the present study was made of 1,147 patients (223 men and 924 women) with ages of 20–60 years at CD diagnosis, complete data, without gastro-intestinal resection and without diabetes mellitus.

CD diagnosis was based on the evidence of specific intestinal damage at duodenal biopsy and on the presence of specific antibodies in serum. Intestinal mucosa at duodenal biopsy was evaluated according to Marsh [26] by the method of Oberhuber et al. [27]. The search of specific antibodies in serum focused on anti-gliadin IgA-IgG in patients who were diagnosed in the years 1975–1991 and on anti-endomysium and anti-tissue-transglutaminase IgA in patients who were diagnosed after 1992. All patients included into the study were positive for the antibodies sought for, with the exception of 11 patients with IgA deficiency [28], and had intestinal damage at histology. Data collection at the time of CD diagnosis included weight and height for the calculation of the BMI (weight in kilograms divided by squared height in metres), presence of diarrhoea (3 or more liquid bowel movements/day in the last month), presence of dyspepsia (chronic or recurrent pain in the upper abdomen, upper abdominal fullness or feeling full earlier than expected with eating) and the measurement of laboratory indices for the assessment of absorptive status (serum concentration of iron, albumin and cholesterol). The clinical work-up at CD diagnosis included the search for all immune-mediated diseases associated with CD (e.g. thyroiditis of Hashimoto, auto-immune hepatitis, biliary cirrhosis, Sjögren's syndrome, sclerosing cholangitis), but only the following 4 skin diseases were included in the analyses: dermatitis herpetiformis, alopecia, psoriasis and aphthosis. Their diagnosis was based on an accurate medical examination and the consultation with a dermatologist.

Statistical procedures investigated the relation of BMI (independent variable) to the prevalence of immune-mediated skin diseases. Two sets of analyses were designed: analyses with the use of BMI as a continuous variable and analyses with the use of the categorical variable overweight defined as a BMI ≥25 [29]. Statistical procedures included Pearson correlation analysis, χ^2 analysis, logistic regression analysis as well as calculation of the odds ratio (OR) and 95% confidence interval (95% CI). The exponential logistic regression coefficient was used for the calculation of the OR in logistic regression.

Results

Descriptive Statistics

Table 1 reports descriptive statistics by gender. Within this cohort of adults with CD, the female gender was 4.15 times more prevalent than the male gender and was associated with a slightly lower age at diagnosis ($p = 0.053$). Compared to men, women had a lower mean BMI, a lower prevalence of overweight (OR = 0.37, 95% CI = 0.25–0.53) and a lower serum iron concentration. With regard to immune-mediated skin diseases, the rarest was alopecia in both genders whereas the commonest was dermatitis herpetiformis in both. In univariate analyses, the BMI was positively correlated with age, serum albumin, serum iron and serum cholesterol (Pearson R = 0.165–0.272, $p < 0.001$) and was inversely correlated with the prevalence of dyspepsia and of diarrhoea (logistic regression coefficient = –0.076 for both variables, $p < 0.001$).

BMI and Skin Diseases: Univariate Analysis

Table 2 summarizes the results of analyses by BMI tertile. Tertiles were separately defined in men and women to have subgroups with a progressively higher BMI but

with a similar gender distribution. With the increasing BMI, indices of absorptive status and age at diagnosis were progressively higher, whereas the prevalence of diarrhoea and dyspepsia was progressively lower. As far as immune-mediated skin diseases were concerned, the trend of linearity across BMI tertiles was significantly positive only for the prevalence of dermatitis herpetiformis and psoriasis.

The severity of mucosal damage was not different among the three tertile groups (Marsh II: 43 in group 1, 39 in group 2 and 43 in group 3; Marsh IIIa: 85 in group 1, 88 in group 2 and 82 in group 3; Marsh IIIb: 108 in group 1, 111 in group 2 and 103 in group 3; Marsh IIIc 149 in group 1, 143 in group 2 and 153 in group 3; p not significant).

In the logistic analysis of the prevalence of a given immune-mediated skin disease regressed over BMI, coefficients were significant only for dermatitis herpetiformis and psoriasis (table 3).

On the basis of the exponentiation of the logistic coefficient, a difference of 3.5 in BMI (approx. 1 standard deviation of BMI in men and women combined) was associated with a significant excess in the prevalence of dermatitis herpetiformis (OR = 1.46, 95% CI = 1.23–1.72) and of psoriasis (OR = 1.40, 95% CI = 1.10–1.79). The OR of dermatitis herpetiformis prevalence for 1 standard deviation of BMI was not significantly different between men (OR = 1.38, 95% CI = 1.04–1.83) and women (OR = 1.32, 95% CI = 1.04–1.67) as well as between patients aged 20–40 (OR = 1.50, 95% CI = 1.24–1.81) and those aged >40 (OR = 1.37, 95% CI = 0.91–2.07). The OR of psoriasis prevalence for 1 standard deviation of BMI was not significantly different between men (OR = 1.27, 95% CI = 0.83–1.93) and women (OR = 1.42, 95% CI = 1.04–1.94) as

Table 1. Descriptive statistics: mean ± standard deviation or prevalence

	Men	Women
Number of patients	223	924
Age at diagnosis, years	34.4 ± 10.2	33.0 ± 9.04
With age 20–40, %	24.3	21.2
BMI	22.9 ± 4.0	20.9 ± 3.3[a]
With BMI ≥25, %	22.0	9.4
Diarrhoea, %	23.9	24.4
Dyspepsia, %	37.2	41.7
Serum iron, μg/dl	73.3 ± 36.2	47.7 ± 31.3[a]
Serum albumin, g/dl	4.04 ± 0.67	3.99 ± 0.70
Serum cholesterol, mg/dl	154.8 ± 33.7	157.3 ± 34.1
Immune-mediated skin diseases, %		
Dermatitis herpetiformis	18.4	6.9[a]
Psoriasis	5.4	3.1
Aphthosis	4.0	2.6
Alopecia	1.8	2.1

[a] $p < 0.001$, for comparison between men and women.

Table 2. Gender, age and other variables by BMI tertiles: mean or prevalence

	BMI tertiles			p value[a]
Women:	11.02–19.37	19.38–21.66	21.66–39.84	
Men:	14.82–20.89	20.90–24.07	24.07–46.24	
Number of patients				
Women	308	308	308	
Men	77	73	73	
Age, years	30.9	32.9	36.1	<0.001
a-tTg, U/ml	57.0 ± 74.9	74.2 ± 99.6	66.7 ± 81.9	0.383
Diarrhoea, %	49.4	38.6	34.4	<0.001
Dyspepsia, %	28.6	21.8	19.9	0.012
Serum iron, μg/dl	48.1	53.0	55.1	0.016
Serum albumin, g/dl	3.80	4.00	4.10	<0.001
Serum cholesterol, mg/dl	145.6	157.9	166.5	<0.001
Dermatitis herpetiformis, %	5.7	8.7	13.1	<0.001
Psoriasis, %	2.9	2.4	5.5	0.048
Aphthosis, %	3.1	1.6	3.9	0.501
Alopecia, %	2.1	0.8	3.1	0.293

a-tTG = Anti-tissue-transglutaminase antibody. [a] For linearity across tertiles by ANOVA or χ^2 analyses.

well as between patients aged 20–40 (OR = 1.38, 95% CI = 1.04–1.83) and those aged >40 (OR = 1.40, 95% CI = 0.84–2.35).

Table 4 summarizes the results of analyses of the effect of the presence/absence of overweight. In comparison to adults with untreated CD and without overweight, adults with untreated CD and overweight were significantly different because they were more frequently male, older, with fewer symptoms and with a better absorptive status.

As far as immune-mediated diseases are concerned, overweight was significantly and positively associated only with dermatitis herpetiformis (OR = 2.31, 95% CI = 1.40–3.81) and psoriasis (OR = 3.27, 95% CI = 1.64–6.58).

BMI and Skin Diseases: Multivariate Analyses

Table 5 summarizes the results of multivariate analyses on the relation of BMI to dermatitis herpetiformis and psoriasis controlled for gender and age. Analyses were done using alternatively the BMI as continuous variable or the presence/absence of overweight as categorical variable. The BMI was positively and independently related to prevalence of dermatitis herpetiformis and psoriasis in all models. In this set of multivariable analyses, coefficients were significant and independent of gender only with dermatitis herpetiformis (lower prevalence in women than in men) and of age only with psoriasis (more prevalent with increasing age).

Table 3. Relation of BMI to the prevalence of immune-mediated skin diseases in adults with untreated CD: univariate logistic regression coefficient and standard error

	Coefficient	Standard error	p value
Dermatitis herpetiformis	0.107	0.025	<0.001
Psoriasis	0.096	0.035	0.006
Alopecia	0.058	0.051	0.256
Aphthosis	0.008	0.049	0.869

Table 4. Gender, age and other variables by presence/absence of overweight (BMI ≥25): mean or prevalence

	Overweight		p value[a]
	no	yes	
Women, %	82.78	63.97	<0.001
Age, years	32.7	37.6	<0.001
Diarrhoea, %	41.9	32.4	0.020
Dyspepsia, %	24.2	17.6	0.053
Serum iron, μg/dl	51.0	60.8	0.009
Serum albumin, g/dl	3.98	4.18	0.016
Serum cholesterol, mg/dl	154.4	175.1	<0.001
Dermatitis herpetiformis, %	8.1	16.9	0.002
Psoriasis, %	2.9	8.8	0.002
Aphthosis, %	3.0	2.2	0.437
Alopecia, %	2.0	2.2	0.526

[a] For comparison between two groups by ANOVA or χ^2 analysis.

Table 5. Relation of BMI, gender and age to prevalence of dermatitis herpetiformis and of psoriasis: multivariate OR and 95% CI (in parentheses)

Dependent variable	Independent variable	Reference interval	Model with BMI	Model with overweight
Dermatitis herpetiformis	BMI	+3.5	1.40 (1.16–1.68)***	not included
	overweight	yes vs. no	not included	2.04 (1.20–3.47)**
	gender	female vs. male	0.39 (0.25–0.60)***	0.36 (0.23–0.55)***
	age at diagnosis	+10 years	0.81 (0.64–1.02)	0.84 (0.23–0.55)
Psoriasis	BMI	+3.5	1.30 (0.99–1.69)	not included
	overweight	yes vs. no	not included	2.62 (1.27–5.43)**
	gender	female vs. male	0.70 (0.34–1.43)	0.70 (0.34–1.42)
	age at diagnosis	+10 years	1.41(1.03–1.93)*	1.39 (1.01–1.91)*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

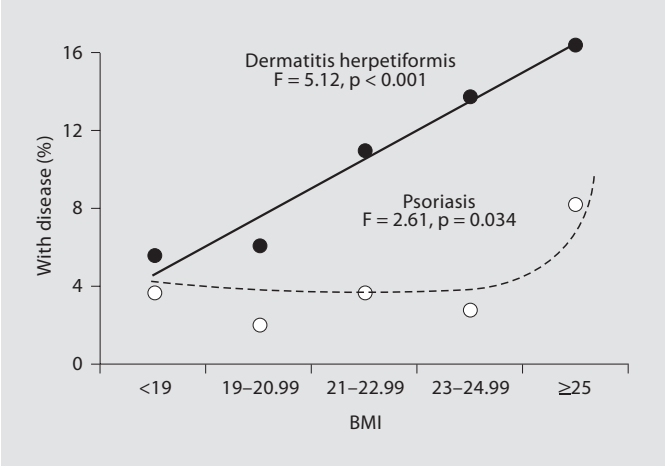

Fig. 1. Prevalence of dermatitis herpetiformis and psoriasis by arbitrary absolute strata of BMI in sex- and age-adjusted ANOVA for men and women combined. The number of patients per BMI stratum is as follows: 285, 334, 239, 155 and 134 (from BMI <19.00 to BMI ≥25.00).

Finally, figure 1 shows that, with control for gender and age, the prevalence of dermatitis herpetiformis was linearly higher with increasing BMI, whilst the prevalence of psoriasis was constant in patients with low-to-normal BMI and increased only in overweight patients. When multivariate analyses were repeated with exclusion of overweight patients, BMI as a continuous variable was positively associated with dermatitis herpetiformis (OR = 1.88, 95% CI = 1.29–2.73), but not with psoriasis (OR = 0.87, 95% CI = 0.50–1.53).

Discussion

The present cross-sectional study shows the novel finding that the BMI is directly related to the prevalence of dermatitis herpetiformis and psoriasis, but not to the prevalence of other immune-mediated skin diseases within a large cohort of adults affected with untreated CD. Findings on the relation of BMI to dermatitis herpetiformis and psoriasis were similar in univariate analyses done separately for the two sexes or for different age groups and were independent of gender and age in multivariate analyses. A higher BMI was also associated with male gender, older age and with less severe intestinal dysfunction as was consistently indicated by data about gastro-intestinal symptoms and indices of absorption status. The relation of BMI with dermatitis herpetiformis was continuous and linear from low to normal and high levels of BMI. In contrast, the relation of BMI to psoriasis was J-shaped: flat for low-to-normal BMI but with a twice higher prevalence of psoriasis in adult CD patients with a BMI in the range of overweight.

It is impossible to compare the results of the present study with previous reports because, to the best of our knowledge, no study is available on the relation of BMI with immune-mediated skin diseases in adults with untreated CD. A positive association was reported between CD and dermatitis herpetiformis [5–8], as well as between CD and psoriasis [11–14]. Thus, a practical implication of the study is that, in the presence of skin alterations suggestive of psoriasis, not only dermatitis herpetiformis, the presence of CD should be suspected even when the patient has a normal-to-high BMI and indices of nutritional status do not point towards malabsorption. Moreover, the present results further support 3 known concepts about untreated CD in adults: the relation of BMI to other indices of absorptive status, the variability of absorptive status in CD from severely altered to near-normal and the frequency of other immune-mediated diseases in CD.

Altogether, the present data do not support the hypothesis that a high BMI in untreated CD represents per se a definite risk factor for the development of any immune-mediated skin diseases because findings were significant only for dermatitis herpetiformis and psoriasis. The relationships of BMI with dermatitis herpetiformis and of BMI with psoriasis had a different shape suggesting different mechanisms. The linear relation of BMI to prevalence of dermatitis herpetiformis in the CD cohort of this study, together with the well-known sensitivity of dermatitis herpetiformis to gluten ingestion [30], suggests the possibility that the degree of caloric imbalance and/or of intestinal dysfunction might interact in some way with the production, the release or the action of the gluten-induced factor(s) responsible for the development of dermatitis herpetiformis. Thus, according to this interpretation, a high BMI would reflect mild or absent intestinal dysfunction and, therefore, would be frequently associated with dermatitis herpetiformis. Vice versa, a low BMI would reflect intestinal dysfunction and, therefore, would be rarely associated with dermatitis herpetiformis. The non-linear relation of a high BMI to the prevalence of psoriasis in the CD cohort of this study is substantially similar to the relation previously reported in adults without CD. In non-CD adults, the hypothesis was made that overweight may represent a pro-inflammatory condition favouring the development of several diseases,

including psoriasis [31]. In this view, the present finding of an association between high BMI and psoriasis in adults with untreated CD is unlikely to represent a condition specifically linked to gluten ingestion and/or malabsorption. It might rather represent the expression, also in adults with CD, of the generic pro-inflammatory effect of overweight on the development of psoriasis. Another possibility which may be common to both skin disorders is that gluten, in genetically predisposed subjects, causes an altered permeability of the mucosa allowing the passage of toxic fractions through the epithelium [32, 33], which act as triggers for the local and distant immunity. This is possible also for patients showing a clear picture of intestinal damage despite a high BMI [34]. Other possibilities cannot be excluded.

The major limitations of the study are the cross-sectional design and the lack of information in the present series of patients about the effects on dermatitis herpetiformis and psoriasis of the treatment with a gluten-free diet. Previous studies reported that dermatitis herpetiformis in CD is well controlled by a gluten-free diet [30]. Thus, a reasonable expectation could be that, also in adults of this cohort, the control of the CD should be followed by the attenuation of dermatitis herpetiformis despite the common increase in BMI secondary to the diet-induced improvement of the intestinal function. In adults with CD and psoriasis, the effects of the treatment of CD on psoriasis are less predictable. The gluten-free diet could have favourable effects on psoriasis if the development of psoriasis depended at least in part on the gluten-induced intestinal dysfunction. If psoriasis in these patients were completely independent of the intestinal dysfunction, the gluten-free diet could have negative effects on psoriasis because the control of CD generally improves the nutritional status and often leads to a high BMI [34], hence to a condition that is a putative risk factor for the development of psoriasis.

In summary, the present study confirms that patients with dermatitis herpetiformis have less frequently intestinal symptoms and a higher BMI when compared to CD patients without dermatitis [5–8]. The study confirms also that psoriasis is frequent in CD [11–14].

The study shows that, in adults with untreated CD, the BMI is directly related to the prevalence of dermatitis herpetiformis and psoriasis, but not to that of other immune-mediated skin diseases. The relation of BMI to dermatitis herpetiformis in CD is linear from low to high BMI values and could reflect the influence of gluten-induced intestinal damage on absorptive status and expression of dermatitis herpetiformis. The relation of BMI to psoriasis in CD is not linear but limited to BMI values ≥ 25 as in the non-CD population. Thus, the results support a role for overweight in psoriasis but not a specific relation between overweight and psoriasis in CD patients.

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