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Impact of Cigarette Smoking on Clinical Presentation and Treatment Response in Coeliac Disease

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ABSTRACT

Background & Aims: The environmental factors, apart from gluten ingestion predisposing to coeliac disease are poorly known. Smoking is associated with many immune-mediated diseases, but research on coeliac disease is scarce. This study aims to investigate how smoking affects the clinical presentation, presence of comorbidities and response to gluten-free diet in coeliac disease.

Methods: Altogether 815 adults with coeliac disease participated in a nationwide cross-sectional study. Participants were interviewed and smoking habits (never, former, or current smoker), clinical presentation of coeliac disease and presence of comorbidities were elicited. Serology and severity of small bowel mucosal lesions at diagnosis were gathered from the participants' medical records and follow-up serology was measured. Gastrointestinal symptoms and psychological well-being were assessed using validated questionnaires.

Results: Current smokers were more often male and were diagnosed at younger ages than never or former smokers. There were no differences between the groups in clinical presentation, severity of symptoms or mucosal lesions at diagnosis or in dietary compliance and clinical, serological, and histological recovery. Musculoskeletal disorders, particularly osteoporosis and osteopenia, were more common in never smokers than in other groups (14.5% vs. 5.1% and 4.1%, $p<0.001$), and cardiovascular disorders were diagnosed more often in former smokers (36.2% vs. 23.5% and 21.9%, $p=0.003$).

Conclusions: Smoking does not seem to have an impact on the clinical presentation, severity of symptoms or mucosal damage in coeliac disease. Histological and clinical recovery as well as seroconversion on gluten-free diet are not affected by smoking status.

Key words: coeliac disease – smoking – tobacco – small intestine – gluten-free diet.

Abbreviations: GFD: gluten-free diet; GSRS: Gastrointestinal Symptom Rating Scale; PGWB: Psychological General Well-Being; SF-36: Short Form 36 Health Survey.

INTRODUCTION

Coeliac disease is a chronic immune-mediated enteropathy triggered by dietary gluten in genetically predisposed individuals [1]. While the genetic component is well-established and ingestion of gluten is essential for developing the disease, other environmental factors are also required. These factors remain controversial, but intestinal infections and taking antibiotics in early childhood may be associated with coeliac disease development [2, 3], while the role of intestinal dysbiosis is also debatable [4]. Smoking is an environmental factor known to modify the immune system and is implicated in several inflammatory disorders [5–7]. Regarding inflammatory bowel diseases, smoking has a fascinating and controversial effect. It increases the risk of Crohn´s disease and predisposes to more severe disease [8, 9], while in ulcerative colitis smoking protects against the risk of developing the disease and is associated with a lower relapse rate [10, 11].

The majority of studies on coeliac disease and a recent meta-analysis have reported a significantly decreased prevalence of coeliac disease among smokers compared with non-smokers [12–15], but contradictory results from large scale studies have also been reported [16–18]. While various potential contributions of smoking to the pathogenesis of coeliac disease have been proposed [15, 19, 20], the actual causality between smoking and risk of coeliac disease remains difficult

to demonstrate. Furthermore, the clinical picture of coeliac disease is extremely variable, with a protective effect of smoking postulated only in highly symptomatic disease [18]. However, the few small studies on the subject have failed to show such an association [13, 21]. Smoking has also been shown to affect the severity and clinical course of many other inflammatory diseases [6, 7], yet we are unaware of any studies examining the effect of smoking on the clinical course and prognosis of coeliac disease.

This study aims to scrutinize the possible differences in clinical presentation, response to gluten-free diet and presence of comorbidities in adult coeliac disease patients based on their history of smoking.

METHODS

Patients and Study Design

This cross-sectional study was carried out in Tampere University Hospital and Tampere University. Previously diagnosed coeliac disease patients were recruited via newspaper advertisements and with the help of the Finnish Coeliac Society. All voluntary participants were systematically interviewed either by telephone or face to face by an experienced physician or a study nurse specialized on coeliac disease, and blood samples were drawn for serology. In the case of telephone interviews this was done at the nearest laboratory. The participants also completed structured questionnaires to elicit gastrointestinal symptoms and quality of life. Diagnoses and relevant medical data were confirmed from individual patient records with participants' consent. Only patients over 18 years of age with biopsy-verified coeliac disease were included in this study.

Current and previous smoking were elicited during the interview and for the study analyses, the participants were divided into three groups according to their smoking status: patients who had never smoked (never smoker), patients who had stopped smoking at any time before study entry (former smoker) and patients who smoked at the time of the study (current smoker).

Ethical Aspects

The Regional Ethics Committee of the Tampere University Hospital approved the study protocol (R05183) and all participants gave written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Clinical Characteristics

The clinical data collected included demographics, age at coeliac disease diagnosis, type, duration, and self-reported severity of clinical symptoms before diagnosis, duration and strictness of gluten-free diet (GFD) at the time of the study, severity of current coeliac disease-related symptoms and presence of chronic comorbidities. History of malignancies, bone fractures and problems with reproduction (e.g. miscarriages and infertility) was also elicited. The clinical symptoms of coeliac disease before diagnosis were divided into abdominal symptoms, malabsorption, dermatitis herpetiformis, other extraintestinal symptoms and asymptomatic patients diagnosed by screening of at-risk groups. The patients were asked to rate the severity of their symptoms before diagnosis as mild, moderate, or severe, significantly restricting normal life. Strictness of adherence to GFD was assessed and patients were divided into three groups: (1) strict diet (no dietary lapses); (2) dietary lapses and (3) normal unrestricted gluten-containing diet. The coeliac disease-related symptoms at the time of the study (i.e., persistent symptoms) were classified into three categories: no symptoms, mild symptoms (occasionally some coeliac-disease related symptoms) or severe symptoms (symptoms significantly affecting patients' normal life). Chronic comorbidities were classified into seven main categories: musculoskeletal (e.g. inflammatory arthropathies, degenerative disorders and osteoporosis/osteopenia), gastroenterological (e.g. lactose intolerance, gastro-oesophageal reflux disease, cholecystolithiasis, inflammatory bowel disease), immunological (e.g. asthma, allergy, autoimmune thyroid disease, diabetes mellitus type 1) cardiovascular (e.g. hypertension, coronary heart disease, stroke), psychiatric (e.g. depression, anxiety) and neurological (e.g. migraine, epilepsy) disorders.

Small Bowel Mucosal Biopsies and Coeliac Disease Serology

Data on duodenal histology at diagnosis and at the time of the control biopsy were gathered from medical records. At the time of this study the Finnish national guidelines recommended at least four biopsies taken during gastroscopy to confirm the diagnosis of coeliac disease and control biopsies taken at approximately one year after commencing GFD to confirm mucosal recovery. The severity of mucosal lesions was graded into normal mucosal architecture, partial villous atrophy or subtotal/total villous atrophy depending on the original pathology reports. If no villous atrophy was detected, the diagnosis of coeliac disease was confirmed by special measures (e.g. transglutaminase-specific IgA deposits).

Findings of coeliac disease-related antibodies at coeliac disease diagnosis were gathered from patient records when available. In addition, serum IgA class tissue transglutaminase (TG2) and endomysial antibody (EmA) were tested in the samples taken at the time of the study. TG2 was measured by commercial enzyme-linked immunosorbent assay (Quanta Lite h-tTGA IgA, INOVA Diagnostics, San Diego, CA) with values >30 U/l considered positive. Serum EmA was assessed by a validated in-house method as described elsewhere [22]. Titres 1:≥5 were considered positive for EmA. The corresponding IgG-class antibodies were measured in case of selective IgA deficiency.

Questionnaires

Participants' current gastrointestinal symptoms were also evaluated quantitatively using the validated and structured Gastrointestinal Symptom Rating Scale (GSRS) questionnaire, which evaluates indigestion, diarrhoea, abdominal pain, reflux and constipation through 15 separate questions. The scoring is based on a Likert scale from one to seven points, where one point signifies minimal gastrointestinal symptoms and seven points the most severe symptoms [23].

Self-perceived health and quality of life were measured with the Psychological General Well-Being (PGWB) and Short Form 36 Health Survey (SF-36) questionnaires. The PGWB consists of 22 items, which can be further divided into six subdimensions:

anxiety, depression, well-being, self-control, general health and vitality. Total scores may range from 22 to 132, higher scores indicating better psychological well-being [24]. SF-36 comprises of 36 items and taps addresses eight separate health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Each item is scored from 10 to 100, a higher score denoting better well-being [25].

Statistical Analysis

Continuous variables are presented as medians with interquartile ranges (IQR) or ranges. Binominal and categorical variables are presented as number of subjects and percentages. Statistical differences between patient groups were studied using χ^2 test or Fisher's exact for cross-tabulations, and the Kruskal–Wallis H test for continuous variables. Binary logistic regression was used for adjustment. Statistical significance was set at $p<0.05$ and testing was two-tailed All statistical analyses were performed with help of a statistician and using SPSS version 26 (IBM corp., Armonk, NY).

RESULTS

Altogether 815 coeliac disease patients were eligible for the study and of these 76% of were female. Patients were diagnosed with coeliac disease at median age of 43 years. In total, 565 (69%) had never smoked, 177 (22%) were former and 73 (9%) current smokers. Median duration of smoking for former smokers was 10 years and for current smokers 20 years.

The never smokers were significantly more often females than were former or current smokers (Table I). The current

Table I. Clinical characteristics at diagnosis of 815 adult coeliac disease patients with different smoking habits

	Never smoker n=565		Former smoker n=177		Current smoker n=73		
	n	%	n	%	n	%	p
Females	463	81.9	108	61.0	51	69.9	<0.001
Age at diagnosis, median (range), years	43 (18–81)		44 (18–79)		39 (18–71)		0.027
Duration of symptoms before diagnosis[a]							0.632
Less than 1 year	102	20.1	33	20.5	18	26.9	
1–5 years	169	33.3	56	34.8	26	38.8	
5–10 years	57	11.2	15	9.3	4	6.0	
Over 10 years	179	35.3	57	35.4	19	28.4	
Severity of symptoms at diagnosis							0.442
Mild	142	26.7	48	28.7	20	28.6	
Moderate	288	54.2	89	53.3	31	44.3	
Severe	101	19.0	30	18.0	19	27.1	
Type of symptoms at diagnosis							
Abdominal symptoms, all	467	82.7	143	80.8	61	83.6	0.817
Diarrhoea	218	38.6	76	42.9	34	46.6	0.301
Abdominal pain	293	51.9	94	53.1	32	43.8	0.382
Flatulence/bloating	195	34.9	53	29.9	22	30.1	0.451
Nausea/vomiting	42	7.4	11	6.2	4	5.5	0.858
Constipation	49	8.7	25	14.1	8	11.0	0.105
Heartburn	42	7.4	21	11.9	8	11.0	0.147
Malabsorption	257	45.5	65	36.7	35	47.9	0.092
Weight loss	92	16.3	32	18.1	19	26.0	0.117
Anaemia	191	33.8	47	26.6	19	26.0	0.110
Dermatitis herpetiformis	96	17.0	35	19.8	14	19.2	0.664
Other extraintestinal symptoms	97	17.2	27	15.3	11	15.1	0.784
Joint pain, synovitis	45	8.0	13	7.3	3	4.1	0.547
Asymptomatic[b]	33	5.8	7	4.0	3	4.1	0.627
Seronegative[c] at diagnosis[d]	39	12.7	16	19.3	4	9.3	0.227
Small bowel histology at diagnosis[e]							0.130
Normal mucosal architecture	13	2.7	5	3.5	2	3.1	
Partial villous atrophy	149	31.5	59	41.8	18	28.1	
Subtotal/total villous atrophy	311	65.8	77	54.6	44	68.8	

[a] data from 735 patients; [b] diagnosed by screening in at-risk groups; [c] seronegativity to coeliac disease-related antibodies; [d] data on 433 patients; [e] data from 678 patients.

smokers had been diagnosed with coeliac disease at younger ages than the never or former smokers and this phenomenon was observed equally in both genders. The study groups did not differ significantly in clinical presentation, duration or severity of symptoms, prevalence of seronegative coeliac disease or severity of histological lesion at diagnosis (Table I).

At the time of the study, current smokers were younger than never or former smokers (Table II). All patients had been on GFD for a median of nine years, and no differences were seen in duration of diet between the three study groups. Also, strict adherence to GFD, presence or severity of persistent symptoms or seropositivity at the time of the study did not differ between the groups. Follow-up biopsies were taken a median of one year (range 0.5–3 years) after diagnosis and the small bowel mucosal recovery between the study groups was equal (Table II).

When the comorbidities at the time of the study were compared, musculoskeletal disorders in general and osteoporosis/-penia were more common in non-smokers than in former or current smokers, while circulatory diseases in general and particularly hypertension were more common among former smokers than in the two other groups (Table III). When these finding were adjusted for gender and age at the time of the study, all other observed differences remained statistically significant despite the difference in the musculoskeletal disorders in general, in which the association persisted, but statistically only as borderline significant. There were no significant differences between the groups in any other comorbidities, but the current smokers had less often any comorbidities (Table III). Also, this finding remained statistically significant after the adjustment with gender and age at the time of the study. Malignancies were reported in 28 patients in the whole study group (Table III). Basal cell carcinomas were excluded from this analysis. The most common malignancies were breast cancer (n=4), prostate cancer (n=2), small bowel cancer (n=2) and colon cancer (n=2). There was one salivary gland carcinoma, but no lung cancers or carcinoma of the larynx were observed in this cohort.

Altogether 592 patients completed the GSRS, PGWB and SF-36 questionnaires. There were no significant differences between the study groups in either the total or any of the subscores of the three questionnaires (Supplementary file, Table I).

DISCUSSION

This large study was unable to demonstrate any association between smoking status and clinical presentation of coeliac disease, which corroborates earlier observations. One small study found no difference in smoking habits between patients with classic and subclinical coeliac disease [13]. Another study reported an association between smoking and weight loss in a coeliac disease cohort but found no association between smoking and other factors studied, thus reflecting disease severity [21]. There are also earlier studies showing a relationship between endomysial antibody seronegative coeliac disease and current smoking [21, 26], and the authors speculated that smoking could affect mucosal transglutaminase activity in coeliac disease and thus inhibit the production of endomysial antibodies. However, contradictory findings have also been reported [13], and in the present cohort prevalence of seronegativity for coeliac disease-related antibodies at diagnosis they did not differ between the studied groups.

Female predominance was more pronounced in coeliac disease patients who had never smoked than in former and current smokers, reflecting the gender difference in the use of tobacco products in the general population [27]. Current smokers were also younger than never or former smokers at the time of coeliac disease diagnosis. Similar findings were reported by Vazquez et al. [13], but they attributed the difference in age at diagnosis to a consequence of a bias as in

Table II. Follow-up data of 815 celiac disease patients on a gluten-free diet (GFD) with different smoking habits

	Never smoker n=556		Former smoker n=172		Current smoker n=73		
	n	%	n	%	n	%	p
Current age, median (range), years	55 (21–89)		55 (27–82)		51 (26–75)		0.014
Duration of GFD, median (IQR), years	9 (4–15)		9 (4–14)		9 (5–17)		0.692
Strictness of GFD at follow–up							1.000
Strict diet[a]	545	97.1	173	97.7	71	97.3	
Dietary lapses	15	2.7	4	2.3	2	3.7	
Normal gluten-containing diet	1	0.2	0	0	0	0	
Persistent symptoms at follow-up							0.828
No symptoms	413	74.3	127	73.8	56	76.7	
Mild symptoms	134	24.1	40	23.3	16	21.9	
Severe symptoms	9	1.6	5	2.9	1	1.4	
Follow-up histology on GFD[b]							0.189
Normal mucosal architecture	184	55.8	56	64.4	22	63.2	
Partial villous atrophy	131	39.7	24	27.6	12	31.6	
Subtotal/total villous atrophy	15	4.5	7	8.0	2	5.3	
Positive coeliac-related serology[c] on a long-term GFD	67	11.9	19	10.7	10	13.7	0.797

[a] no dietary lapses; [b] follow-up biopsy median of 1 year after diagnosis, data on 455 patients; [c] positive endomysial or transglutaminase antibodies.

Table III. Comorbidities at follow-up of 815 celiac disease patients with different smoking habits

	Never smoker n=565		Former smoker n=177		Current smoker n=73		
	n	%	n	%	n	%	p
Musculoskeletal disorders	199	35.2	52	29.4	12	16.4	0.004
Inflammatory arthropathies	36	6.4	14	7.9	1	1.4	0.139
Degenerative disorders	76	13.5	20	11.3	8	11.0	0.672
Osteoporosis or osteopenia	82	14.5	9	5.1	3	4.1	<0.001
Gastrointestinal disorders	214	37.9	55	31.1	19	26.0	0.056
Lactose intolerance	113	20.0	25	14.1	10	13.7	0.112
GERD	55	9.7	15	8.5	5	6.8	0.675
Cholecystolithiasis	25	4.4	5	2.8	1	1.4	0.416
IBD, other enteropathies	8	1.4	3	1.7	2	2.7	0.479
Immunological disorders	228	40.4	79	44.6	34	46.6	0.416
Asthma	47	8.3	18	10.2	8	11.0	0.619
Allergy	106	18.8	31	17.5	12	16.4	0.851
Autoimmune thyroid disease	82	14.5	29	16.4	10	13.7	0.796
Diabetes mellitus type 1	8	1.4	3	1.7	2	2.7	0.479
Cardiovascular diseases	133	23.5	64	36.2	16	21.9	0.003
Hypertension	94	16.6	50	28.2	13	17.8	0.003
Coronary heart disease	24	4.2	8	4.5	0	0	0.158
Stroke, TIA	13	2.3	3	1.7	0	0	0.501
Neurological disorders	57	10.1	17	9.6	5	6.8	0.678
Psychiatric disorders	26	4.6	10	5.6	3	4.1	0.804
Bone fractures	159	28.2	44	24.9	20	27.4	0.679
Malignancies[a]	21	3.8	5	2.8	2	2.7	0.906
Reproductive problems	35	6.2	7	4.0	2	2.7	0.372
No comorbidities	58	10.3	13	7.3	17	23.3	<0.001

GERD: gastro-oesophageal reflux disease; IBD: inflammatory bowel disease; TIA> transient ischaemic attack; [a b]Basal cell carsinomas excluded.

their study current smokers, both patients and controls, were also younger at study entry. It is possible that older smokers did not participate in this study due to their ill health and this also biases our results. Smokers may also have sought help from health care due to smoking-related health harms and earlier coeliac disease diagnosis was due to surveillance bias. However, in light of the present study, we are unable to rule out the possibility that earlier diagnosis may indeed be associated with smoking.

The present study found no association between smoking and clinical recovery from the disease. The histological recovery after a median of one year on GFD did not vary according to smoking status at the time of the study, nor did the prevalence of persistent symptoms or seropositivity at the time of the study. Adherence to GFD was high regardless of smoking status, and thus did not affect these results. This is also in line with our earlier studies, where dietary compliance and mucosal recovery on GFD are usually at a high level in Finnish coeliac patients [28, 29]. As far as we know, there are no previous data on smoking and clinical recovery from coeliac disease. However, as smoking affects the clinical course of many other diseases, the present finding is somewhat surprising.

In this study cardiovascular diseases were more common in former smokers, but this is in line with numerous studies on non-coeliac cohorts and probably demonstrates the increased motivation to for smoking cessation after being diagnosed with cardiovascular disease [30, 31]. Interestingly, musculoskeletal disorders, especially osteoporosis/-penia were more common among never smokers even after adjusting for gender and age. Surprisingly, current smokers in this study also had significantly more often no other comorbidities. The findings of a high prevalence of musculoskeletal disorders and osteoporosis in never smokers and the general lack of comorbidities in current smokers are difficult to explain. Smoking generally has a negative effect on musculoskeletal health [32] and decreases bone mineral density [33]. Smoking is also a predisposing factor to many other diseases [34]. It seems unlikely that smoking would really protect coeliac disease patients against comorbidities, and as data concerning possible confounding factors such as socioeconomic status, lifestyle choices and body-mass index were lacking in this study, these results should be interpreted with caution.

In earlier studies gathering data on general population, smoking has been associated with higher prevalence of dyspeptic symptoms and increased risk of peptic ulcer disease [35, 36]. In this study, there was a non-significant trend toward never smokers having other gastrointestinal diseases more often than former or current smokers, but

no association was evidenced between smoking status and prevalence or severity of persistent symptoms at the time of the study. Furthermore, the severity of gastrointestinal symptoms measured with the GSRS questionnaire did not differ either. Quality of life measured using the SF-36 and PGWB questionnaires was not affected by smoking status in this cohort, although earlier studies have reported impaired quality of life in smokers [37].

In this study 9% of patients were smoking at the time of the study, which is in line with other coeliac disease cohorts in other Western countries [12, 14, 21]. This percentage is clearly lower than in the Finnish general population at the time of the study, as approximately 20% of adults were daily smokers [38]. There are several potential immunomodulatory mechanisms by which smoking might impact the pathogenesis of coeliac disease. In brief, smoking has been shown to modify both cellular and humoral immunity, alter gut permeability, inhibit transglutaminase activity and decrease mucosal immunoglobulin A production [5-6, 19-20]. Moreover, as suggested in earlier studies, the observed relatively small proportion of current smokers among coeliac disease patients supports the proposed protective role of cigarette smoking against symptomatic adult-onset coeliac disease. However, the true causality between risk for coeliac disease and smoking remains unclear as the presence of unidentified confounding factors cannot be ruled out.

The strengths of this study include a large, presentative nationwide cohort of coeliac patients with biopsy-proven diagnoses. Personal structured interviews and validated questionnaires were used. Data on duodenal biopsies and coeliac disease-related antibody levels at diagnosis were acquired from the medical records and the follow-up serology was also measured. The main weakness of this study is that more detailed smoking history was lacking and therefore smoking status at the time of diagnosis remained unknown. In addition, data on some potentially confounding factors were lacking. There is a possibility of selection and recall bias as smokers with poor health may be less willing to participate in a voluntary-based study than more health-conscious individuals, and the data were gathered largely based on an interview conducted a median of nine years after the coeliac disease diagnosis. In addition, the small number of current and former smokers affected the statistical power of our analyses.

CONCLUSIONS

Smoking does not seem to affect the phenotype of coeliac disease, nor does it seem to interfere with treatment response and mucosal recovery on GFD.

Conflicts of interest: None to declare.

Authors' contribution: T.I., C.P., T.S., H.H., K. Kurppa and K. Kaukinen designed the study. T.I., T.S., K. Kurppa and K. Kaukinen gathered the data. C.P. and H.H. analyzed the data. T.I., C.P., K. Kaukinen drafted the paper. All authors critically revised the manuscript and approved the final version for publication and agreed to be accountable for all aspects of the work.

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