Adult coeliac disease and cigarette smoking

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Abstract

Background—Genetic predisposition and gliadin exposure are known to be crucial factors in the development of coeliac disease. Circumstantial evidence suggests that other unidentified environmental factors may also be of pathogenetic importance.

Aim—To define the relation between cigarette smoking and the risk of development of symptomatic adult onset coeliac disease.

Subjects—Eighty six recently diagnosed adult coeliac disease patients and 172 controls matched for age and sex.

Method—Matched case control study, using a simple questionnaire to determine smoking history, and in particular smoking status at the time of diagnosis of coeliac disease.

Results—At the time of diagnosis, the proportion of current smokers was 7% in the coeliac group, and 32·6% in the control group, giving a matched odds ratio of 0·15 (95% confidence intervals 0·06, 0·38). The difference could not be accounted for by social class, nor by coeliac patients giving up smoking after the onset of symptoms as most non-smokers in the coeliac group had never smoked.

Conclusion—Cigarette smoking, or a factor closely linked to it, seems to exert a major protective effect against the development of symptomatic adult onset coeliac disease. The implication is that gliadin exposure is not the only important environmental factor involved in the pathogenesis of this condition.

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It is well established that coeliac disease results from enteric exposure to an environmental factor, gliadin, in people with a predisposing genetic constitution, primarily related to the HLA loci on chromosome 6.[1 2] However, if these were the only aetiological factors, coeliac disease might be expected to develop in all predisposed people shortly after weaning onto a normal diet. This is not the case: coeliac disease may show discordance between HLA-identical siblings including monozygotic twins,[3 4] may develop after a previously normal small bowel biopsy,[3 4] and often presents in adult life.[1 5]

Despite indirect evidence that additional acquired aetiological factors must be operative,[6 7] the nature of such factors remains to be established. Given the important role played by the immune system in the pathogenesis of coeliac disease,[1 2] it has been suggested that the complex mechanisms of somatic generation of immunoglobulin and T cell receptor diversity may be of importance, but supportive evidence is lacking.[8] Apart from the controversial evidence implicating infection with adenovirus 12[1 9 10] there are few published reports on the role of environmental factors other than gliadin in the aetiology of coeliac disease.

Cigarette smoking has been convincingly linked to the risk of development of inflammatory bowel disease.[11 12] In a small pilot study we observed that adults with coeliac disease were mostly non-smokers. This case control study was undertaken to test the hypothesis that cigarette smoking is associated with a reduced risk of development of symptomatic adult coeliac disease.

Method

The study group comprised 86 adult patients (between the ages of 18 and 75) diagnosed with coeliac disease between 1 January 1985 and 1 June 1995. There were 57 females and 29 males, with a median year of birth of 1943 (interquartile range: 1933–1953). All patients included in the study fulfilled each of the following diagnostic criteria: (a) presentation with evidence of malabsorption or diarrhoea, or both; (b) small bowel biopsy histology showing characteristic appearances of coeliac disease; (c) a convincing clinical or histological response to gluten withdrawal, or both.

The control group was drawn from attenders at an outpatient orthopaedic and trauma clinic. Two controls were matched to each coeliac patient on the basis of sex and year of birth (to within two years). An unmatched disease control group comprised 62 patients with ulcerative colitis diagnosed since 1 January 1985 (35 females, 27 males; median year of birth – 1946, interquartile range: 1934–1958).

All subjects completed with an investigator a short questionnaire about their background and smoking history (including year started, year stopped, and average daily quota). In particular, cigarette smoking status at the time of diagnosis was established for each coeliac disease patient, and at the time of diagnosis of the matched coeliac patient for each control. Where available, smoking status at the time of diagnosis was confirmed from hospital records. If there was any doubt, the subject was assumed to be a smoker. A 'smoker' was

arbitrarily defined as a person who had at least one cigarette a day for at least three months, while an 'ex-smoker' previously but no longer fulfilled this criterion. An odds ratio was derived from the results using the Mantel-Haenszel estimate for matched case control studies with 1:2 matching.[13]

Results

Table I shows the proportion of current cigarette smokers, ex-smokers, and lifelong non-smokers in each study group at the time of diagnosis. Only six (7·0%) of the coeliac group were current smokers compared with 56 (32·6%) of the control group. The proportion of smokers in the control group was close to that predicted from 1991 population survey data[14] adjusted for age and sex of the study group, which gives an expected prevalence of current smokers of 31·4%.

The data (Table II) provides a matched odds ratio for coeliac disease in current smokers of 0·15 (95% confidence intervals, 0·06, 0·38). The difference between the groups was not due to the influence of social class (Table III). Nor could the difference be accounted for by coeliac patients giving up smoking after the onset of symptoms, as it was present 10 years or more prior to diagnosis (Figure) and indeed most non-smokers in the coeliac group had never smoked (Table I).

As shown in other studies, the prevalence of current smokers in the ulcerative colitis group was low at diagnosis (8·1%). However, the pattern of previous smoking habits differed considerably between the coeliac and colitic groups (Figure). Five years prior to diagnosis, only 12·8% of coeliac patients were actively smoking compared with 36·0% of matched controls and 32·3% of colitis patients.

Discussion

The relation between cigarette smoking status and the risk of development of adult coeliac disease shown by this study does not of course prove causality, and the influence of confounding factors must be considered. However, the strength of the association supports a causal link. Studies on a larger scale are required to discover if there is a dose risk relation – in other words, whether heavy smokers are at lower risk of coeliac disease than light smokers.

Even if a true causal relation exists, the data do not indicate the direction of causality. It might be argued that the results are due to 'would-be' smokers being dissuaded by the presence of symptoms of disease before diagnosis. We feel this explanation is most unlikely, for the following reasons. Firstly, most non-smokers in the coeliac group had never smoked – if the symptoms of developing coeliac disease had caused abstention, one would have expected an excess of ex-smokers. Secondly, in Crohn's disease, in inflammatory enteropathy with a range of manifestations similar to those of coeliac disease, the evidence is that there is no acquired aversion to cigarette smoking. Indeed, there is accumulating evidence for a positive association between cigarette smoking and Crohn's disease, both before and after diagnosis.[11] [12]

Might cigarette smoking protect against the development of adult coeliac disease, and if so, how? There are various possible mechanisms. The immune system and enteric mucosal integrity are closely involved in the pathogenesis of coeliac disease,[1] [2] [6] [15] and both have been shown to be influenced by smoking status.

Smoking has a range of immunomodulatory actions, including suppression of the CD4/CD8 ratio and natural killer activity of circulating lymphocytes,[16–18] and a reduction in IgA concentrations of oral and intestinal secretions,[18–20] though the pathophysiological significance of these effects remains unclear.[21] Smoking status has been linked to the risk of development of a variety of other disorders considered to be immunologically based, but the association is not consistent. For example, smokers seem to be at increased risk for

TABLE III *Subject distribution by social class (as percentage of group)*

	Coeliac disease	Controls
Class I	1·2	1·2
Class II	20·9	19·8
Class III	51·2	54·1
Class IV	17·4	17·4
Class V	7·0	5·2
Unclassified	2·3	2·3

TABLE I *Smoking status at the time of diagnosis (as percentage of group)*

	Coeliac disease (n=86)	Controls (n=172)	Ulcerative colitis (n=62)
Current smoker	7·0	32·6	8·1
Ex-smoker	27·9	27·9	56·5
Lifelong non-smoker	65·1	39·5	35·5

TABLE II *Smoking status of matched pairs at diagnosis*

		Neither smoker	Matched controls One smoker	Both smokers
Coeliac	Smoker	3	2	1
	Non-smoker	41	26	13
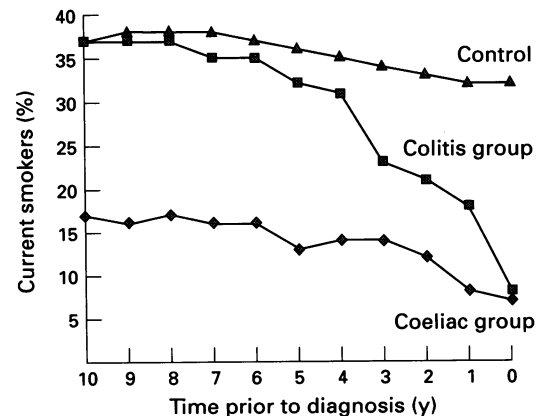
Percentage of current smokers in each group related to time prior to diagnosis.

Goodpasture's syndrome[22] and Graves' ophthalmopathy,[23][24] reduced risk for rheumatoid arthritis[25] and ulcerative colitis,[11][12] and at the same risk as non-smokers for Hashimoto's thyroiditis.[23][24]

Smoking also influences the function of the gastrointestinal tract in ways that might influence the development of disease.[26] Demonstrated actions on intestinal mucus production or on gut epithelial permeability could conceivably influence the immunogenicity of gliadin or restrict mucosal exposure to some other exogenous pathogenetic factor, though the available evidence suggests that these changes occur primarily in the colon rather than the small bowel.[27][28]

Smoking status may account, at least in part, for some of the previously unexplained epidemiological findings regarding coeliac disease. The increase in incidence of adult onset coeliac disease over the past 30 years[5] mirrors the fall in the prevalence of current smokers.[14][29] The female predominance among coeliac disease patients diagnosed in adulthood shown in this and a previous study[5] may correspond to higher tobacco exposure among men.[14]

The contrast between the smoking habits of adult onset coeliac patients and colitis patients prior to diagnosis is striking. While both conditions are commoner in non-smokers, the risk of adult coeliac disease is greatest in life-long non-smokers, whereas the risk of ulcerative colitis is highest in (recent) ex-smokers, as previously demonstrated.[12] This might suggest that the action of smoking differs between the two diseases.

In conclusion, this case control study shows a strikingly reduced risk of the development of adult onset coeliac disease among cigarette smokers. This finding, which requires confirmation in other populations, suggests that environmental factors other than gliadin exposure are of importance in the pathogenesis of this condition.

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