

## ORIGINAL ARTICLE

## Value of routine duodenal biopsy in diagnosing coeliac disease in patients with iron deficiency anaemia

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Accepted 19 December 2003**Background:** Iron deficiency anaemia (IDA) is a recognised feature of coeliac disease in adults and can be its only presentation.**Objective:** To determine the yield of routine distal duodenal biopsies in diagnosing coeliac disease in adult and elderly patients with IDA whose endoscopy revealed no upper gastrointestinal cause of iron deficiency.**Study design:** Prospective study in a teaching hospital endoscopy unit.**Method:** Altogether 504 consecutive patients with IDA, aged 16-80 years, attending for endoscopy were included in this study. At least two distal duodenal biopsies were taken if endoscopy revealed no cause of iron deficiency.**Result:** In nine (1.8%) patients duodenal biopsies revealed typical histological features of coeliac disease. Of these, five patients were above 65 years old.**Conclusion:** In adult and elderly patients undergoing endoscopy for IDA, the endoscopist should take distal duodenal biopsies to exclude coeliac disease if no upper gastrointestinal cause of anaemia is found. Coeliac disease is not an uncommon cause of IDA in patients >65 years of age and a history of chronic diarrhoea increases diagnostic yield in this age group.

Coeliac disease is common in Western European populations with an estimated prevalence of about 1:200 or even higher in some areas.<sup>1,2</sup> Chronic iron deficiency anaemia (IDA), often subclinical, is not an uncommon presentation of coeliac disease even in elderly patients.<sup>3-5</sup> Despite such a high prevalence, it is often unrecognised and under-investigated in patients presenting with IDA. In a recent large study on IDA, coeliac disease was not even considered as a possibility.<sup>7</sup> In the United Kingdom, 2%-3% of patients presenting with IDA could have coeliac disease,<sup>6</sup> hence it should be considered in the differential diagnosis in such patients. Although endomysial and tissue transglutaminase antibodies are reliable serological tests, characteristic histological changes on distal duodenal biopsy is still considered to be the "gold standard" for diagnosis of coeliac disease.<sup>1</sup> Occult gastrointestinal blood loss, however, is the commonest cause of iron deficiency,<sup>6,7</sup> therefore, such patients are referred to endoscopy unit for oesophagogastroduodenoscopy (OGD) and colonoscopy to exclude serious gastrointestinal causes.<sup>7</sup> If OGD does not reveal any obvious cause of anaemia, it is now recommended that distal duodenal biopsies should be performed to exclude coeliac disease as a cause of iron deficiency.<sup>6</sup> This prospective study began before such a recommendation came into practice and the purpose was to determine yield of routine distal duodenal biopsies in diagnosing coeliac disease in adult and elderly patients presenting with IDA whose OGD failed to reveal any cause of iron deficiency.

## METHOD

A total of 504 consecutive patients presenting with IDA, aged between 16-80 years, were included in this prospective study, in a teaching hospital setting, from November 1994 to August 1998. These patients were referred to our endoscopy unit by general practitioners or hospital colleagues for an OGD to exclude an upper gastrointestinal cause for anaemia. IDA was defined as a haemoglobin concentration of <115 g/l in women and <125 g/l in men with microcytosis and low

serum ferritin. All patients in this study had their OGD performed (with or without intravenous midazolam sedation according to patients' preferences) by an experienced endoscopist (TCNL) with at least two distal duodenal biopsies taken if endoscopy failed to reveal any obvious cause of anaemia. These patients were divided into two groups according to their age (<65 and >65 years) and if they had additional symptoms of weight loss and/or chronic diarrhoea (table 1). Any patient with a previous diagnosis of coeliac disease was excluded from the study and none had serological tests (antigliadin and/or endomysial antibodies) for coeliac disease before endoscopy. For all patients, endoscopy and duodenal biopsy reports were sent to the referring general practitioner or hospital colleague. Fisher's exact test was used for statistical analysis.

## RESULTS

Of the 504 patients, 201 (40%) were below 65 years (group A) and 303 (60%) were above 65 years of age (group B). In group A, 163 patients had anaemia without diarrhoea or weight loss, of which two (1.2%) had coeliac disease confirmed on duodenal biopsy. In contrast, a diagnosis of coeliac disease was confirmed on duodenal biopsy in 2/19 (10.5%) patients with a history of chronic diarrhoea.

In group B, 259 patients had anaemia as their sole presentation of which two (0.7%) had coeliac disease confirmed on biopsy. In contrast, coeliac disease was diagnosed in 3/14 (21.4%) patients with a history of chronic diarrhoea. A history of weight loss did not increase diagnostic yield in either group.

Overall, 4/201 patients <65 years and 5/303 patients >65 years (total 9/504; 1.8%) in this cohort had the characteristic changes of coeliac disease seen on duodenal biopsies. Unlike weight loss, a history of chronic diarrhoea increased diagnostic yield from 1.2% to 10.5% ( $p < 0.05$ ) for patients <65

**Abbreviations:** IDA, iron deficiency anaemia; OGD, oesophagogastroduodenoscopy

**Table 1** Coeliac disease (CD) in patient subgroups according to their age and symptoms

Presentation	Age <65 years (group A)		Age >65 years (group B)	
	Negative for CD	Positive for CD (%)	Negative for CD	Positive for CD (%)
Anaemia only	163	2 (1.23)	259	2 (0.77)
Anaemia and diarrhoea	19	2 (10.53)	14	3 (21.43)
Anaemia and weight loss	12	0	20	0
Anaemia, diarrhoea, and weight loss	3	0	5	0

years of age and from 0.7 to 21.4% ( $p < 0.0001$ ) for patients >65 years.

## DISCUSSION

Manifestations of coeliac disease in adults are protean. Classical symptoms of diarrhoea and/or malabsorption are now uncommon.<sup>1,4</sup> Most patients have minor or atypical symptoms that could be unrelated to the gastrointestinal tract.<sup>1,5</sup> IDA as the only presenting feature of coeliac disease is not uncommon in adult or even in elderly patients. As the prevalence of coeliac disease is high in the community, it should therefore be considered as a potential cause in any patient presenting with IDA. Recent guidelines from the British Society of Gastroenterology recommended that duodenal biopsies should be taken during endoscopy if no obvious cause of iron deficiency could be found.<sup>6</sup>

The prevalence of coeliac disease in our cohort is 1.8%, which is similar to a previous report of 2%–3% in adult patients with IDA.<sup>6</sup> Although others have reported a higher prevalence of coeliac disease in such patients,<sup>8</sup> this disparity could possibly be related to differences in local prevalence of coeliac disease as well as patient selection criteria. Our study confirms a previous observation that a history of chronic diarrhoea increases the diagnostic yield of coeliac disease particularly in elderly (>65 years) patients with IDA.<sup>8</sup> Five patients in our series were above 65 years of age; this emphasises the fact that IDA can be a presenting feature of coeliac disease in elderly patients.<sup>3</sup> All our patients were returned to their referring consultant or general practitioner after endoscopy for further work-up of anaemia where appropriate; therefore, besides coeliac disease we do not have data on other causes of IDA in this cohort and whether these patients' anaemia responded to a gluten-free diet. However, it is now well established that IDA in coeliac disease responds very well to a gluten-free diet.<sup>3</sup>

Bearing in mind that the diagnostic yield of duodenal biopsy in our study was one in 56, it still remains questionable whether routine biopsy on every patient with IDA is the most cost effective strategy. If duodenal biopsies are taken in every patient whose endoscopy reveals no obvious cause of anaemia, it will not only have cost implications but will also increase the workload of the histopathologists. Certain appearances of duodenal mucosa on endoscopy, such as reduction or absence of folds and/or mosaic pattern, have been shown to have a high predictive value in diagnosing coeliac disease on biopsy,<sup>9,10</sup> but a less experienced endoscopist may not be able to recognise such changes and, moreover, such appearances will be absent in some patients with coeliac disease. Hence reliance on endoscopic appearances would result in under-diagnosis of coeliac disease.<sup>11</sup> Perhaps a better approach would be targeting patients for biopsy through serological screening before endoscopy. At present, it is generally accepted that endomysial antibody is the best available screening test, however, it is relatively expensive. Reliance on the relatively cheaper antigliadin antibody would again result in under-diagnosis as it has a lower sensitivity, particularly in elderly patients.<sup>3</sup> IgA

antitissue transglutaminase antibody has a similar sensitivity and specificity as endomysial antibody and it is becoming widely available for a simpler, quicker, and relatively cheaper test for routine clinical use.<sup>12</sup> Screening with transglutaminase antibody to select patients for biopsy before endoscopy would be an alternative and perhaps a cost effective approach. However, it must be emphasised that the sensitivity of endomysial and transglutaminase antibodies does not approach 100%, therefore reliance solely on serology may potentially miss the occasional patient with coeliac disease. At present, unless serological tests are requested by the general practitioner or hospital doctor in such patients before their referral for endoscopy, it remains essential that the endoscopist takes at least two distal duodenal biopsies<sup>13</sup> to exclude coeliac disease, if no cause of anaemia can be found.

Finally, the importance of confirming a diagnosis of coeliac disease as the cause of IDA must be emphasised for several reasons. Firstly, coeliac disease is an easily treatable condition and a gluten-free diet not only corrects anaemia but also improves symptoms. Secondly, confirming a diagnosis of coeliac disease will avert unnecessary and unpleasant (often invasive) investigations for IDA.<sup>7</sup> Thirdly, establishing coeliac disease as the cause of IDA will allay patients' anxiety regarding uncertainty of diagnosis. Finally, compliance with a gluten-free diet prevents long term complications of coeliac disease such as osteoporosis, infertility, malignancy, etc.

In conclusion, our study shows that distal duodenal biopsies performed during endoscopy are worthwhile in establishing coeliac disease as an underlying cause of IDA in adult and elderly patients. A history of chronic diarrhoea in such patients increases diagnostic yield, particularly in those greater than 65 years of age.

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## FILLER.....

### Tobacco is a “weapon of mass destruction”. Should western countries be invaded for that?

The western tobacco industries, with declining tobacco consumption in parts of the west, are now targeting Asian and eastern European markets intensively.<sup>1</sup> This part of world is fast approaching a “tobacco holocaust”. The following staggering statistics call for an urgent action on this weapon of mass destruction.

(1) Tobacco kills more people than AIDS, alcohol, cocaine, homicide, suicide, motor vehicle crashes, and fires combined. It has already killed 70 million people since 1950. Annual global tobacco related deaths are about 3 million (one third in developing nations) and is expected to rise to more than 10 million by the 2020s.<sup>2</sup> By 2030, 70% of all deaths due to tobacco will occur in developing nations (presently it is 50%). Tobacco related diseases are responsible for one in 10 adult deaths worldwide.<sup>4</sup>

(2) With current patterns, about 500 million people alive in the world today will eventually be killed by tobacco use (nearly a half will be today’s children and teenagers).<sup>2</sup> If tobacco control is extremely successful and adult tobacco consumption is cut to half by 2020, there will still be over 250 million people dying of tobacco consumption.

(3) Seventy percent of Chinese men smoke and, if they do not change their habits, a third of them, now under 30 years (more than 50 million), will eventually die of smoking. Tobacco is predicted to account for 13% of all deaths in India by 2025. In Thailand, 250 million children alive today will eventually die from tobacco if they take up smoking at the present rate.<sup>5</sup>

(4) In a developing country with a per capita gross domestic product of \$2000, effective tobacco prevention costs approximately \$20 to \$40 per year of life gained. Lung cancer treatment costs \$18 000 per year of life gained.<sup>4</sup> For the USA, direct health care costs related to tobacco were estimated in 1980 to be US \$16 billion (7% of national health care costs) and indirect mortality and morbidity costs were US \$26 billion.

(5) Approximately five trillion cigarettes (1000/human on earth) are produced annually. In 1999 the tobacco industry spent \$8.24 billion a year on marketing. This amounts to \$22.5 million a day—nearly \$1 million an hour!

(6) Philip Morris, Japan Tobacco and British American Tobacco, the world’s three largest cigarette companies, now own or lease plants in at least 40 countries each.<sup>6</sup> In 1998, they had combined tobacco revenues of more than \$88 billion, a sum greater than the total gross national product of Albania, Armenia, Bahrain, Bolivia, Botswana, Bulgaria, Cambodia, Cameroon, Estonia, Guyana, Honduras, Jamaica, Jordan, Laos, Latvia, Madagascar, Moldova, Mongolia, Nepal, Nicaragua, and Togo combined.

We need an international coalition that could address tobacco issues that cross borders. We also need to create an international coordinating agency to reduce and monitor tobacco consumption. Key areas for action include facilitating international agreements on smuggling control, discussions on tax harmonisation to reduce the incentives for smuggling, and ban on advertising and promotion involving the global communications media.

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