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CLINICAL

Is routine screening for coeliac disease of value in people with type 1 diabetes?

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ABSTRACT This study aimed to assess the impact of screening positive for coeliac disease on a population of adults with type 1 diabetes. Fifty-three patients were identified with a positive screen for coeliac disease, out of a population of 2,752 individuals with type 1 diabetes (minimum prevalence 1.9%). Prior to screening, 32% of patients were asymptomatic. Only a fifth of patients found no improvement in well-being with a gluten-free diet and in those who followed a strict gluten-free diet the improvement in well-being was greater (p=0.034). Screening was felt to be beneficial by 73%. The response did not relate to gluten-free diet adherence but did relate to symptom improvement (p=0.037). These data show that patients report an improvement in well-being with treatment and feel that screening for coeliac disease is beneficial.

KEYWORDS Coeliac disease, type 1 diabetes

DECLARATION OF INTERESTS No conflict of interests declared.

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INTRODUCTION

Coeliac disease (CD), occurs in 0.3–1% of the Western population,[1] and is characterised by an immune-mediated response to gliadin. The resulting T cell-mediated inflammatory response leads to damage to the jejunal mucosa and thus malabsorption.[2] In adult life, CD often presents with anaemia, metabolic bone disease, diarrhoea or weight loss, but patients may have only minor symptoms.[3]

Coeliac disease is more common in association with certain diseases, including type 1 diabetes mellitus.[3] In children with type 1 diabetes the incidence of CD can be as high as 6.2%;[1] however, this is not the case in adults. In the UK, the incidence of CD in adult patients with type 1 diabetes is 1.3–2%; higher than the general population but lower than in children.[1] This compares with a prevalence in European studies of 1.6–5% and in the USA of 3.8–6.4%.[1] Coeliac disease is often classified as silent or active.[3]

Management involves following a strict gluten-free diet (GFD). This leads to an improvement in symptoms and reduces complications. Patients with CD have a 50- to 100-fold risk of developing malignant lymphoma compared with the general population. Compliance with a GFD can reduce this risk.[4] This increased risk of malignancy is the major contributor to the increased mortality in CD (standardised mortality rate [SMR] 2.0).[5] Corrao et al.[5] also demonstrated that the mortality rate was higher (SMR 3.8, 95% confidence interval [CI]: 2.2–6.4) in patients in whom the diagnosis was delayed more than 10 years after the onset of symptoms, but highest in patients not adherent to a GFD (SMR 6.0, 95% CI: 4.0–8.8). This increased mortality was also mainly due to malignancy. There was no increased mortality in the relatives of CD patients.[5] Osteoporosis is also more prevalent in CD, and there is an increase in bone mineral density (BMD) after commencement of GFD. This improvement appears to be mainly within the first year of treatment.[6]

However, the benefit of a strict GFD in asymptomatic individuals is less clear.[3] The incidence of silent CD is not increased in patients with non-Hodgkin's lymphoma[7] and mortality was not increased in patients who presented with minor symptoms (SMR 1.1) or who were asymptomatic and diagnosed after antibody screening (SMR 1.2).[5] Thus, controversy remains as to whether there is a need for screening of asymptomatic or minimally symptomatic people to detect cases of silent CD and whether there is a beneficial role for GFD in these patients. In the present study the impact of screening positive for CD on a population of adults with type 1 diabetes was assessed.

PATIENTS AND METHODS

Following work by one of us (HRG) to assess the incidence of CD locally, a decision was made to implement screening for CD in the diabetes clinics in two local hospitals (Western General Hospital, Edinburgh; St John's Hospital, Livingston); the majority of patients with type 1 diabetes (1,197 patients in total) were tested over an 18-month period. Opportunistic screening was carried out from 1996 on patients at a further hospital (Royal Infirmary of Edinburgh; type 1 diabetes population of 1,555). Of these 1,555 patients, 607 had been

TABLE 1 Patient demographics and clinical parameters at baseline

Parameter [no. of patients]	Baseline value
Total number of subjects	53
Mean age (years)	37.6 (±14.3)
Mean duration of diabetes (years)	18.5 (±11.2)
Male	26 (49.1%)
Female	27 (50.9%)
Underwent endoscopy	40 (75.5%)
Histological confirmation of CD	35 (66.0%)
Follow GFD	31 (58.5%)
Weight (kg) [50]	73.07 (±14.26)
BMI (kg/m^2) [34]	26.54 (±4.89)
AGA (0–30 U/ml) [22]	66.73 (±35.54)
AtTG (5–30 U/ml) [31]	96.06 (±15.91)
HbA_{1c} (5.0–6.5%) [50]	8.39 (±1.45)
Ferritin (male) (20–300 ug/L) [10]	41.10 (±25.62)
Ferritin (female) (10–150 ug/L) [13]	24.23 (±35.48)
Hb (male) (130–180 g/L) [15]	142.60 (±19.58)
Hb (female) (115–165 g/L) [18]	127.50 (±20.19)
Magnesium (0.7–1.0 mmol/L) [16]	0.72 (±0.08)
Calcium (2.1–2.6 mmol/L) [26]	2.32 (±0.08)
Phosphate (0.8–1.4 mmol/L) [7]	1.19 (±0.21)
Vit B12 (200–900 ng/L) [25]	433.28 (±118.54)
Red cell folate (130–500 ug/L) [6]	208.33 (±102.43)
Serum folate (5–20 ug/L) [15]	8.49 (±4.70)

Data are expressed as mean (standard deviation, SD). Numbers in round brackets in the left column indicate normal reference values.

AGA: anti-gliadin antibody; AtTG: anti-tissue transglutaminase antibody; BMI: body mass index; CD: coeliac disease; GFD: gluten-free diet; Hb: haemoglobin.

screened in 1996 as part of a previous study.[3] Patients with type 1 diabetes and a positive screen for CD were identified retrospectively from our biochemistry database and the database from this previous study. The study was discussed with the local ethics committee and deemed not to require ethical approval.

Data were collected from the patients' case notes and a patient questionnaire. Information recorded included sex, age of patient and duration of diabetes at the time of screening, the presence of a thyroid disorder, whether the patient was referred to a gastrointestinal clinic and underwent endoscopy, and any medication commenced after screening. Patient weight, body mass index, haemoglobin A_1C (HbA_{1c}), haematological and biochemical indices, and BMD measurements were also noted at baseline and time of follow-up.

The diagnosis of type 1 diabetes was in most cases based on the presence of symptoms of hyperglycaemia in the presence of weight loss and/or ketonuria in patients within the appropriate age group. Any patients with an equivocal diagnosis had already had the diagnosis confirmed by measurement of anti-glutamic acid decarboxylase (GAD) antibodies. HbA_{1c} was measured by high-performance liquid chromatography and was Diabetes Control and Complications Trial (DCCT)-aligned on all three sites. The serological tests in use had changed in the years preceding this project. Patients picked up in the original screening study were screened using anti-gliadin antibodies (AGA) and those tested more recently had anti-tissue transglutaminase antibodies measured. Patients' BMDs were categorised according to the World Health Organization classification system. Time to follow-up was ideally 12 months after initial screening, but this varied between patients. The minimum time for follow-up was six months and the maximum 30 months.

All patients with biopsy-positive CD were asked to respond to a questionnaire. One patient was excluded as he had not been informed of his positive screen at the time of the study. The questionnaire aimed to elicit information with regard to symptoms, adherence to GFD and general well-being in order to determine overall patient acceptability of screening.

Statistical analysis

All analyses were performed using SPSS version 13.0. The Shapiro-Wilk test was used to test for normality of the distribution of data. Student's t-test was used for normally distributed data, Wilcoxon two-sample test for non-parametric data and Fisher's exact test for categorical data. Significance was assumed if p-values were <0.05.

RESULTS

Patients

Fifty-three type 1 diabetes patients (26 male, 27 female) with a mean (standard deviation, SD) age at screening of 37.6 (±14.3) years fulfilled the inclusion criteria of a positive serological blood result for CD (Table 1). The minimum overall prevalence of positive coeliac serology among patients with type 1 diabetes was 1.9%. Thirteen patients were detected at the Western General Hospital, Edinburgh (minimum prevalence 2.3%), 15 patients at St John's Hospital, Livingston (minimum prevalence 2.4%) and 25 patients at the Royal Infirmary of Edinburgh (minimum prevalence 1.6%). The mean (SD) duration of type 1 diabetes was 18.5 (±11.2) years. Of these 53 patients with positive serology, 52 (98%) were referred to a gastrointestinal clinic where 40 (75.5%) underwent endoscopy for small bowel biopsy. Coeliac disease was confirmed histologically in 35 patients (66%). Four patients (7.5%) were found to have normal small bowel mucosa on histological examination of biopsy specimens, and in one patient (1.9%) the biopsy was inconclusive. Thirteen patients (24.5%) did not undergo endoscopy, seven declined, one had not yet been informed of the

TABLE 2 Data at baseline and follow-up for patients on a gluten-free diet

Parameter [number of patients]	Time to follow-up (months)	Mean at baseline	Mean at follow-up	p-value
Weight (kg) [27]	16.6 ± 8.4	71.3 ± 10.7	70.7 ± 10.7	0.422
BMI (kg/m^2) [18]	13.4 ± 5.7	24.9 ± 3.0	24.7 ± 2.4	0.390
AGA (U/ml) [8]	22.5 ± 7.7	74.6 ± 36.8	30.7 ± 31.0	0.012
AtTG (U/ml) [7]	11.1 ± 3.6	93.9 ± 32.6	80.4 ± 18.9	0.109
HbA_{1c} (%) [27]	16.0 ± 8.7	8.61 ± 1.55	8.58 ± 8.58	0.901
Ferritin (ug/L) [7]	20.4 ± 9.0	28.3 ± 32.2	59.3 ± 49.3	0.045
Hb (g/L) [19]	18.0 ± 9.1	134.4 ± 22.9	140.2 ± 14.6	0.132
Magnesium (mmol/L) [3]	11.7 ± 3.8	0.75 ± 0.04	0.75 ± 0.02	0.691
Calcium (mmol/L) [9]	12.8 ± 6.7	2.31 ± 0.08	2.37 ± 0.05	0.116
Vit B12 (ng/L) [6]	19.8 ± 10.8	470.2 ± 107.8	593.2 ± 217.5	0.83
Serum folate (ug/L) [4]	11.5 ± 3.3	5.2 ± 2.5	8.4 ± 3.8	0.68

Data are mean (SD). AGA: anti-gliadin antibody; AtTG: anti-tissue transglutaminase antibody; BMI: body mass index; Hb: haemoglobin.

result, one had moved away, two were awaiting endoscopy, one was pregnant and one had Down's syndrome. Eight patients (15.1%) with positive serology also had an autoimmune thyroid disorder. Two subjects (3.8%) had both Down's syndrome and hypothyroidism.

Baseline data

Unsurprisingly, both anti-gliadin antibody (AGA) and anti-tissue transglutaminase antibodies were elevated with a mean (SD) of 66.73 (±35.54) U/ml and 96.06 (±15.91) U/ml respectively. Mean serum ferritin was at the lower end of the reference range for both sexes, and in 11 patients (20.8%) serum ferritin was below the normal range. Mean serum folate levels were also low normal, and four patients (7.5%) had a serum folate below the normal range. All other biochemical investigations were normal except for HbA_{1c}, which was predictably elevated (Table 1). Seven of the 11 patients with a low serum ferritin at baseline were prescribed iron supplements. Five patients were prescribed folic acid, and three of these patients were in the group of four with a low serum folate.

Fifteen (seven male, eight female) of the 53 patients (28.3%) had a dual-energy X-ray absorptiometry (DEXA) scan at baseline. These patients all had CD confirmed histologically; thus overall, 42% of those with histological confirmation of CD had a DEXA scan. The mean (SD) T score at the spine was –0.96 (±1.31), at the femoral neck –0.5 (±1.04) and at the total hip –0.24 (±0.84). Three patients (20% of those undergoing DEXA) were osteoporotic at one or more sites and six (40%) were osteopaenic. Seven patients (46.7%) were treated with a calcium and vitamin D supplement; of these, three (20%) were also prescribed a bisphosphonate. Of the three patients who were treated with a bisphosphonate, two were osteoporotic and one was osteopaenic, although this latter patient's T score was –2.4 at the spine. Of the four patients treated with a calcium and vitamin D supplement alone, one was osteoporotic and the remaining three were osteopaenic.

Follow-up data

A GFD was followed by 31 patients (58.5% of all antibody-positive patients). Of those who did follow a GFD, four had a negative biopsy and 13 had not had a biopsy performed, mainly because they had refused or were awaiting endoscopy. Anti-gliadin antibody and serum ferritin levels were the only indices that showed a significant improvement ($p<0.05$) (Table 2).

Questionnaire

Thirty-one of 47 questionnaires were completed; a response rate of 66%. No symptoms prior to screening were reported by 32% of patients. Of the remaining 68% who reported symptoms, 45% recognised these in retrospect.

Patients were asked to indicate on a four-point scale if their well-being had improved with a GFD. A fifth of patients found no improvement in well-being (Figure 1A). The data were dichotomised into 'not at all and barely' and 'moderately and very much' to assess the relationship between adherence to GFD and improvement in well-being. Twelve patients adhered strictly to a GFD and all but one reported a marked improvement in well-being. Six of twelve patients who were not strict with their GFD noticed an improvement ($p=0.034$) (Figure 1B). In addition, there was a trend to a reported improvement in well-being in those who reported an improvement in one or more symptoms, although this was not statistically significant ($p=0.059$) (Figure 1C).

A four-point scale was also used to assess the patients' views on the benefits of screening. Twenty-two patients (73%) reported screening to be moderately or greatly beneficial (Figure 2A). The response did not relate to GFD adherence but did relate to symptom improvement ($p=0.037$) (Figure 2B).

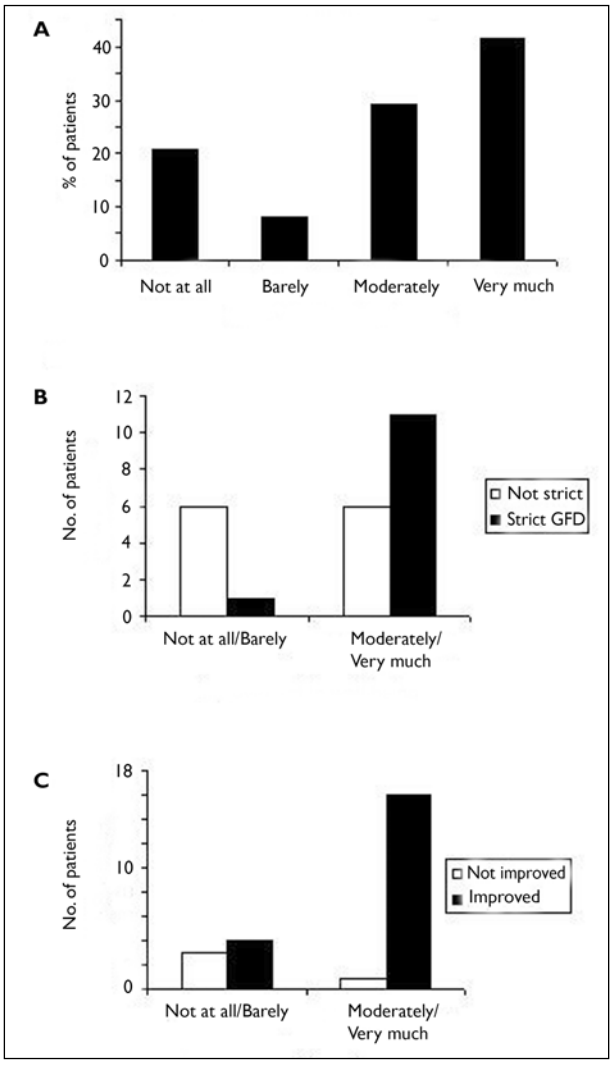

FIGURE 1 Patients' experience of an improvement in well-being following the diagnosis of coeliac disease:
A Reported improvement in well-being;
B Improvement in well-being relates to adherence to a gluten-free diet (p=0.034);
C Improvement in well-being does not relate to symptom improvement (p=0.059).

DISCUSSION

Previous studies have suggested that approximately 1.3–2% of UK adult patients with type 1 diabetes have positive coeliac serology[1] and that 75% of these have an abnormal biopsy.[8] In our type 1 diabetes population the prevalence of positive coeliac serology was comparable at a minimum prevalence of 1.9%; however, although most patients on two sites were screened, those at a third hospital were screened opportunistically, therefore this is likely to be an underestimate. Unfortunately, records of those screened and those not screened were not kept, thus an exact prevalence cannot be determined.

In keeping with previously published reports, no sex difference was observed.[9] The presence of an association

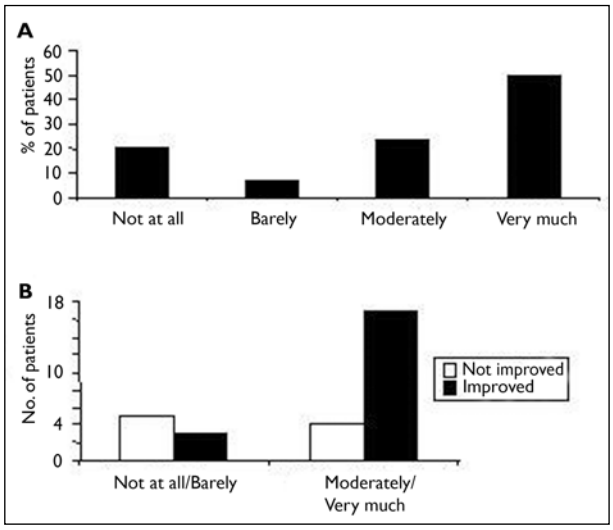

FIGURE 2 **A** Patients' views on whether screening for coeliac disease is beneficial.
B Patients' views on whether screening for coeliac disease correlated with symptom improvement (p=0.037).

between type 1 diabetes and thyroid disease has long been recognised. Perros et al. reported the prevalence of thyroid disease in patients with type 1 diabetes to be 31.4% in females and 12.4% in males.[10] Overall, 15.1% of our patients with positive coeliac serology had autoimmune thyroid disease (27% of females; 4% of males). Thus, although it is reasonable to assume that in patients with two autoimmune diseases, thyroid disease may be increased, no excess of thyroid disease was seen in this population of patients with type 1 diabetes and CD compared with a population of type 1 diabetes alone. Of the 53 patients with positive serology, two patients had Down's syndrome. This is in keeping with the well-documented observation that autoimmune diseases such as CD are more prevalent in Down's syndrome.[11]

At baseline, the serum ferritin of our patients who screened positive was at the lower end of the reference range and in 20.8% of patients was low; more than half of these patients were prescribed iron. Only 7.5% had a serum folate level below the reference range; of these, 75% were prescribed folic acid. Sub-clinical CD, which occurred in the majority of the patients we investigated, is increasing in prevalence, and in one study iron deficiency anaemia was present in 25.21%.[12] In a small number of Belgian patients, Buysschaert et al. found iron deficient anaemia in 40% and folate deficiency in 20%.[13] Our findings are entirely in keeping with these reports.

At follow-up, serum ferritin was significantly increased, presumably due to adherence to a GFD and the use of iron supplements, and improvement in this parameter may result in an improved sense of well-being. HbA_{1c} did not show a significant improvement with GFD. However, Holmes[1] reported that in patients with CD detected by screening, the influence of a GFD on diabetic control as judged by HbA_{1c} was variable.

Low BMD and the increased fracture risk it infers typically occurs in post-menopausal women.[14] Fickling et al. reported that metabolic bone disease is common in CD and is associated with premature osteoporotic fractures.[15] A UK study reported 13% more low trauma fractures in patients with CD than those without.[16] Worryingly, in the patients described here, the mean age of the patients with low BMD was 38.1 years and there was an excess of men in this group.

Previous studies have shown that many patients with CD and type 1 diabetes are oligo- or asymptomatic.[13,17–20] In agreement with this, less than one quarter of our patients felt they experienced symptoms of CD prior to screening. Many patients are only able to recognise ill-health retrospectively[1] following the benefits conferred by a GFD and this is evident from the present study in which almost half of patients recognised symptoms in hindsight.

Eighty per cent of patients reported a sense of improved well-being on a GFD and the majority felt that screening was beneficial. This undoubtedly strengthens the case for screening and is consistent with previous studies describing an improvement in well-being following the introduction of a GFD in individuals without apparent symptoms.[1,21] Improvement in well-being was related to adherence to GFD, and three-quarters of patients reported screening to be moderately or greatly beneficial. Unsurprisingly, this was related to symptom improvement. There has been debate as to the benefit of a GFD in asymptomatic individuals[22] and the utility of screening asymptomatic patients from high-risk groups.[23] In a 14-year follow-up study, quality of life was comparable with the general population.[23] However, no data were available on these patients at the time of diagnosis. In contrast, quality of life in a group of 14 screen-detected patients was assessed at baseline, and no difference was seen compared with controls.[24]

The major flaw in our study is due to its retrospective design, which does give rise to an incomplete data set, and introduces the possibility of selection bias as those who had an improvement in symptoms may have been more likely to return their questionnaires. However, despite this, we feel our data are of interest and lend weight to the argument for screening an apparently asymptomatic group of patients.

In summary, in this study we present data on, to our knowledge, the largest reported group of patients with type 1 diabetes screened for CD. We confirm the benefit of treatment with a GFD and appropriate supplementation, with regard to ferritin and folate levels, and show that patients with type 1 diabetes feel that screening for CD is beneficial.

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