Genetic determinants of coeliac and gastric autoimmunity in children and young adults with type 1 diabetes

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BACKGROUND

- It is well known that individuals with type 1 diabetes (T1D) are at increased risk of other autoimmune diseases, but the absolute risks are unclear.
- Among the conditions most frequently associated with T1D are coeliac disease (CD) and autoimmune body gastritis.
- Autoantibodies against tissue transglutaminase (TGA) and gastric H^+/K^+-ATPase (ATPA) are associated with coeliac disease and autoimmune body gastritis, respectively.
- These disorders are characterized by genetic predisposition, including HLA class II DR3-DQ2 (DR3) and DR4-DQ8 (DR4) as well as environmental influences.
- A single nucleotide polymorphism (SNP) in the *CTLA4* immune regulatory gene has a smaller effect on the risk of developing autoimmunity.

HYPOTHESIS & OBJECTIVES

Hypothesis

We hypothesized that certain combinations of HLA and non-HLA genetic factors underlie coeliac and gastric autoimmunity in individuals with type 1 diabetes

Objectives

- To identify T1D patients who are seropositive for coeliac and gastric autoantibodies
- To investigate the genetic profile (HLA class II and *CTLA4*) of these patients

METHODS

A cohort of 1061 children and young adults with T1D (aged 0.7-28 years, median age 11.8 years) from the well-characterized population-based, Bart's-Oxford (UK) family study [1] was investigated using the following techniques:

- TGA and ATPA were measured in serum by ***radioimmunoassay*** using ^{35}S-labelled antigens. The positivity threshold for TGA (1.31 units) was set at the 97.5 percentile of 5470 healthy school children (median age 7.5 years) [2], for ATPA (20.9 units) - of 322 healthy schoolchildren (median age 9.5 years)
- HLA class II genotype for high risk (DR3-DQ2, DR4-DQ8, *DRB1*0404*) and low risk (DRX) alleles was analyzed using ***PCR-SSP***
- A T1D associated SNP, rs3087243 in the *CTLA4* gene was analysed using ***Taqman*** SNP genotyping.
- Data analysis was performed utilizing SPSS software. Differences in categorical data were investigated by Chi-squared or Fisher's Exact test. Models adjusted for independent factors and covariates were analysed by logistic regression; a two-tailed p<0.05 was considered significant.

RESULTS

1. Prevalence of coeliac and gastric autoimmunity in children and young adults with T1D

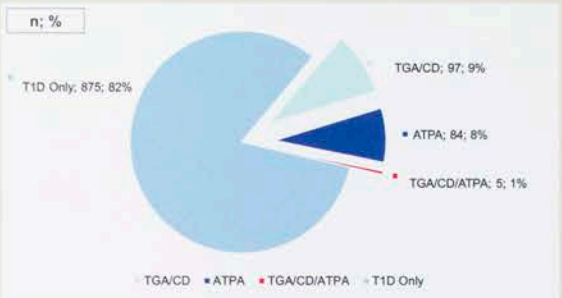

Figure 1. TGA/CD were present in 9.1% of T1D patients. ATPA were present in 8.4%. The combination of both types of autoimmunity was present in less than 1% (5 patients).

2. Non-genetic risk factors for the development of coeliac and gastric autoimmunity in children and young adults with T1D

1) Age and age-at-onset of T1D

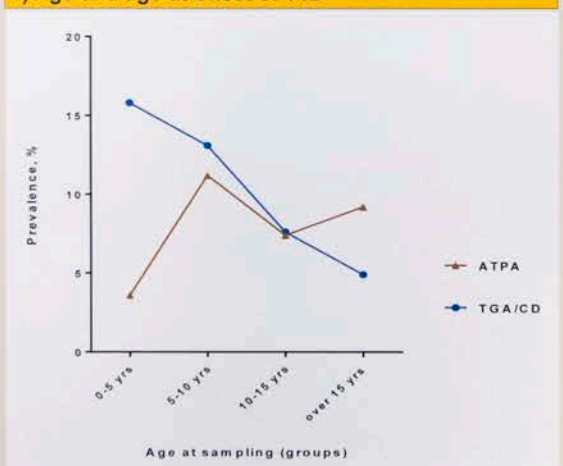

Figure 2. Being younger and having earlier onset of T1D increases the risk of TGA/CD, and decreases the risk of ATPA (p<0.05).

Age-at-onset results mirror those for age at sampling results, since 86% of the cohort were sampled within 1-2 years of diagnosis.

2) Gender

TGA/CD OR 1.7 (95%CI 1.1-2.6)*

ATPA OR 2.1 (95%CI 1.3-3.2)**

Figure 3. Females are at greater risk of developing TGA/CD and ATPA.
*p<0.05; **p≤0.001

3. Genetic risk factors for the development of coeliac and gastric autoimmunity in children and young adults with T1D

1) HLA class II genes

HLA DR	**TGA/CD** (n=91) OR*	**ATPA** (n=75) OR
DR3/3	**6.1**	NS
DR3/4	**4.1**	**4.6**
DR3/X	**4.4**	NS
DR4/4	**5.4**	NS
DR4/X	NS	NS
DR3-DQ2	**2.1**	**3.0**
DR4-DQ8	NS	NS
*DRB1*0404*	NS	**2.4**/1.2 (M/F)

Table 1. HLA DR3-DQ2 haplotype predisposes to both TGA/CD and ATPA. ATPA is also linked to DRB1*0404. *p<0.05; reference genotype – DRXX; (F) – in females, (M) – in males

2) SNP rs3087243 in *CTLA4* gene

TGA/CD	**ATPA**
DR3/3 + *CTLA4 A*	***CTLA4 G***
0.1 (0.04-0.7)*	**0.6** (0.3-0.9)**

Table 2. Statistical interaction was observed between HLA DR3/3 and the *CTLA4 A* allele protecting from TGA/CD in T1D (p<0.05). The T1D predisposing *CTLA4 G* allele conferred protection from ATPA (p=0.05).
*Odds ratio for interaction (95% CI) is presented; **Odds ratio (95% CI) is presented.

SUMMARY

- ❖ Coeliac and gastric autoimmunity are increased in individuals with type 1 diabetes.
- ❖ Females are at greater risk.
- ❖ The prevalence of TGA/CD decreases with increasing age at T1D diagnosis, in contrast to ATPA.
- ❖ Coeliac autoimmunity is associated with HLA DR3-DQ2. The DR3/DR3 genotype demonstrates the highest risk. This is in line with a previous report [3].
- ❖ Individuals with T1D carrying the HLA DR3/DR4 genotype are at increased risk of developing ATPA.
- ❖ The finding that the HLA *DRB1*0404* gene increases risk of ATPA seropositivity also replicates a recent report [3].
- ❖ These preliminary data show that HLA and non-HLA genes can modulate the risk of multiple autoimmunity, suggesting common pathogenic pathways. Replication in larger cohorts should allow these relationships to be clarified.

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ACKNOWLEDGMENTS

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Autoantibodies to tissue transglutaminase target epitopes dependent on residues in the N-terminal domain

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BACKGROUND

Tissue transglutaminase (tTG), is the main autoantigen of coeliac disease (CD). Specific tTG epitopes, including N-and C-terminal sites as well as the catalytic triad, have been reported to be targeted by autoantibodies in CD, but the findings are controversial [1-5].

HYPOTHESIS

We aimed to confirm which of the tTG sites, catalytic core, C- or N-terminus, are critical for antibody binding as this could aid the design of more specific assays and inform studies of disease pathogenesis.

Objectives:

1. Mutating distinct residues of the tTG protein (at 1 to 6 places).
2. Testing the binding of mutated antigens with tTG antibodies in sera from TGA positive patients.

METHODS

- Plasmid DNA encoding human tTG was mutated at sites in the catalytic core (Cys277, His335, Asp358 to alanine), N-(Arg19, Glu153 to serine) and C-terminal domains (Met659 to serine) using ***PAGE-purified mutagenic primers.***
- Antibody binding to a panel of ^{35}S-labelled tTG mutant antigens synthesized *in vitro* was assessed by ***radioimmunoassay*** in sera from 111 TGA-positive individuals (mean age 40 years, range 1.1-80 years) out of 445 patients sent for measurement of CD-associated autoantibodies to Cork University Hospital, Eire.
- A Wilcoxon signed-ranks test (SPSS) was used for statistical analysis (a two-tailed $p<0.05$ was considered significant).

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RESULTS

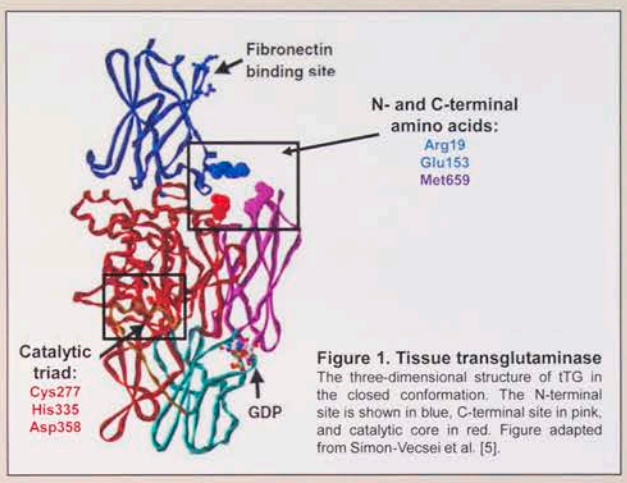

Figure 1. Tissue transglutaminase
The three-dimensional structure of tTG in the closed conformation. The N-terminal site is shown in blue, C-terminal site in pink, and catalytic core in red. Figure adapted from Simon-Vecsei et al. [5].

1. Antibody binding of the tTG protein with mutated catalytic triad amino acids: Cys277, His335, Asp358

Single (C277A, H335A, D358A) and triple (C/D/H) tTG mutants

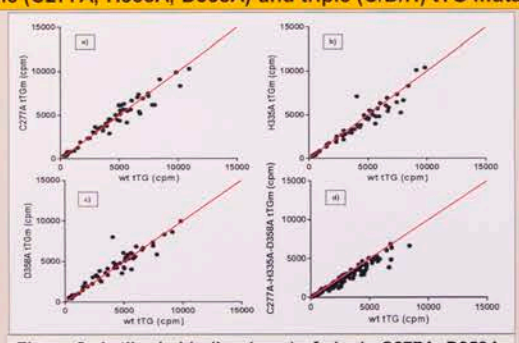

Figure 2. Antibody binding (cpm) of single C277A, D358A, H335A and triple C/D/H mutants of the tTG antigen vs wild type tTG in sera of TGA positive patients
The median relative binding for tTG mutants was 99.8% ($p>0.05$) for C277A (a), 92.6% ($p<0.001$) for H335A (b), 105.8% ($p<0.05$) for D358A (c) and 85% ($p<0.001$) for the triple mutant (d)

2. Antibody binding of the tTG protein with mutated N- and C-terminal site amino acids: Arg19, Glu153, Met659

1) Single (R19S, E153S, M659S) tTG mutants

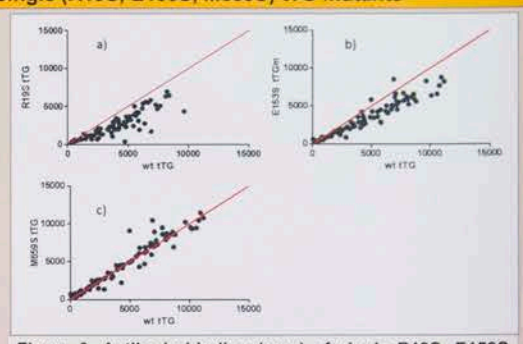

Figure 3. Antibody binding (cpm) of single R19S, E153S and M659S mutants of the tTG antigen vs wild type tTG in sera of TGA positive patients
The median relative binding for tTG mutants was 66.2% ($p<0.001$) for R19S (a), 76% ($p<0.001$) for E153S (b) and 102% ($p<0.05$) for M659S (c)

2) Double (R/E, R/M, E/M) and triple (R/E/M) tTG mutants

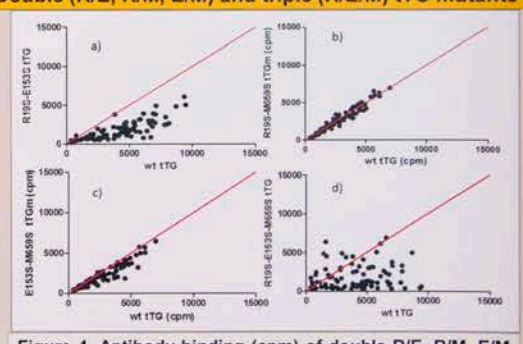

Figure 4. Antibody binding (cpm) of double R/E, R/M, E/M and triple R/E/M mutants of the tTG antigen vs wild type tTG in sera of TGA positive patients
The median relative binding for tTG mutants was 48% ($p<0.001$) for double R19S/E153S (a), 94% ($p=0.031$) for R19S/M659S (b), 87% ($p<0.001$) for E153S/M659S (c) and 48% ($p<0.001$) for triple R19S/E153S/M659S (d) mutants

3. Antibody binding of the tTG protein with mutated catalytic triad and terminal sites amino acids: C/D/H/R/E/M

Six-site (C/D/H/R/E/M) tTG mutant

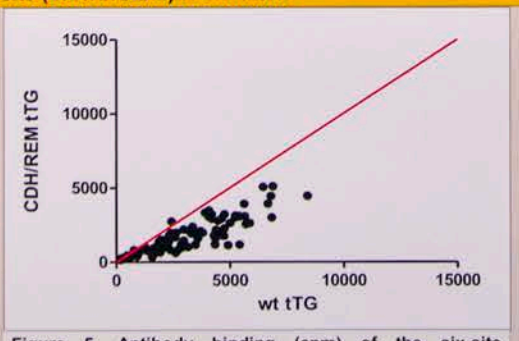

Figure 5. Antibody binding (cpm) of the six-site C/D/H/R/E/M mutant of the tTG antigen vs wild type tTG in sera of TGA positive patients
The median relative binding for tTG six-site mutant was 60% ($p<0.001$)

Mutants	N tested samples	Decreased binding	Increased binding	RB %	Z	P
Catalytic triad						
C277A	66	33	33	100	-0.3	0.723
H335A	66	50	16	93	-4.0	6.1E-5
D358A	66	22	44	106	-2.3	0.019
C/D/H	111	99	12	85	-8.1	3.7E-16
Terminal sites						
M659S	94	34	60	102	-2.9	0.004
E153S	94	85	9	76	-6.8	1E-11
R19S	94	92	2	66	-8.4	4.2E-17
R/E	96	94	2	48	-8.4	3.1E-17
R/M	92	60	32	94	-2.1	0.031
E/M	92	80	12	87	-7.4	1.6E-13
R/E/M	96	91	5	48	-8.0	1.1E-15
Catalytic/Terminal sites						
C/D/H/R/E/M	111	107	4	60	-9.0	2.2E-19

Table. Antibody binding characteristics of the mutant tTG antigens (in comparison with wild type tTG)
RB – relative binding (median); p - two-tailed. Mutation of the catalytic core_Cys277, His335 and Asp358 amino acids resulted in minor changes in binding (median decrease 15% for the triple tTG mutant); mutation of the N- and C-terminal sites Arg19, Glu153 and Met659 amino acids resulted in reduction of antibody binding (median decrease was 52% for both double R/E and triple R/E/M tTG mutants, and 6-13% for R/M and E/M tTG mutants); combined 6-site mutation of the tTG antigen resulted in reduction of antibody binding (median decrease 40%)

SUMMARY

The N-terminal domain of tTG involving amino acids Arg19 and Glu153 is important to the integrity of tTG autoantibody epitopes in CD. Simultaneous mutation of these two amino acids has the highest impact on antibody-binding to tTG, while modifying the catalytic core, previously reported as being important, had only a small effect on binding. The effects of C-terminal mutations were more variable. These findings suggest that a major epitope is located in the N-terminal, but additional regions of the antigen are likely to contribute to antibody-binding. Characterization of mechanisms and epitopes involved in anti-tTG autoimmunity is important for development of targeted therapeutic manipulations in CD patients or at-risk individuals.

CLINICAL INERTIA IN COELIAC DISEASE

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Introduction

Clinicians' knowledge and practice may directly affect patients' diagnostic pathway. An Endomysial antibody (EMA) has a >90% positive predictive value for coeliac disease[1]. Furthermore NICE have recommended that patients with suspected coeliac disease should have an endoscopy and biopsy within 6 weeks[2]. This should serve to reduce the temptation by the patient to start a Gluten free diet (GFD).

We aimed to determine GI Consultant practice by assessing their 'grading' for patients referred from primary care with a positive EMA. In addition, we sought to determine Gastroenterologists' views about coeliac disease.

Methods

Data regarding time to diagnostic endoscopy was collected from adult patients who had a positive EMA test in primary care from 2 referral centres (n=158). As a comparator cohort, we collected data regarding the time from GP referral to index endoscopy in adults referred with suspected IBD (n=64).

In addition, an unselected cohort of Gastroenterology consultants and specialist registrars (n=50) completed a questionnaire regarding their views and attitudes towards both coeliac disease and IBD.

Results

The median time from positive EMA identified in primary care to referral made for diagnostic endoscopy was 23 (12-35) days. EMA positive patients waited significantly longer from referral to endoscopy (55 [26-90] days) than did patients who had suspected IBD (34.5 [18-70] days; p=0.006) (Figure 1). Overall time from EMA positive blood test identified in primary care to diagnostic endoscopy was 78 (58-120) days.

EMA positive patients who waited longer for endoscopy had lower Marsh Grade of duodenal biopsy (r=-0.189; p=0.017) (Figure 2).

Results

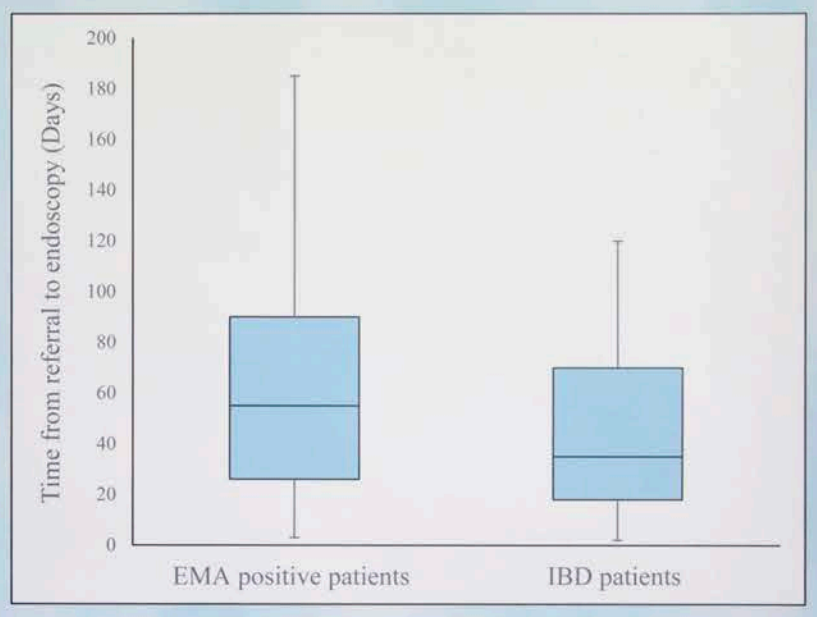

Figure 1. Box plot showing time from primary care referral to index endoscopy by patient cohort.

Marsh Grade	Endoscopy <42 days after referral (n=65)	Endoscopy >42 days after referral (n=93)
0-2	15.4%	30.1%
3a	9.2%	17.2%
3b/c	75.4%	52.7%

Figure 2. Table showing Marsh Grade of duodenal biopsy by time to endoscopy

32% (16) of Gastroenterologists failed to identify that coeliac disease was more prevalent in the adult population than IBD. 16% (8) of respondents felt that a diagnosis of coeliac disease does not significantly impact patient quality of life. 36% (18) felt that doctors were not required for the adequate management of coeliac disease.

Conclusions

- There are delays in the diagnostic pathway for patients with coeliac disease
- This may delay treatment intensification
- Provider-related beliefs may contribute to clinical inertia
- We advocate enhancing both undergraduate and postgraduate training about coeliac disease to help reduce this effect.

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A review of changes in presentation of Coeliac Disease within our centre and comparison with 2009 data set

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Introduction

Coeliac disease (CD) is a lifelong autoimmune condition primarily affecting the small intestine. It is characterised by symptoms which include bloating, diarrhoea, nausea, constipation, tiredness and weight loss. Some patients will also be asymptomatic but with strong family history or an autoimmune condition. Treatment is life long exclusion of gluten from the diet.

Aim

To assess the presenting symptoms of CD in patients within our centre and compare to previous data presented in 2009.

Method

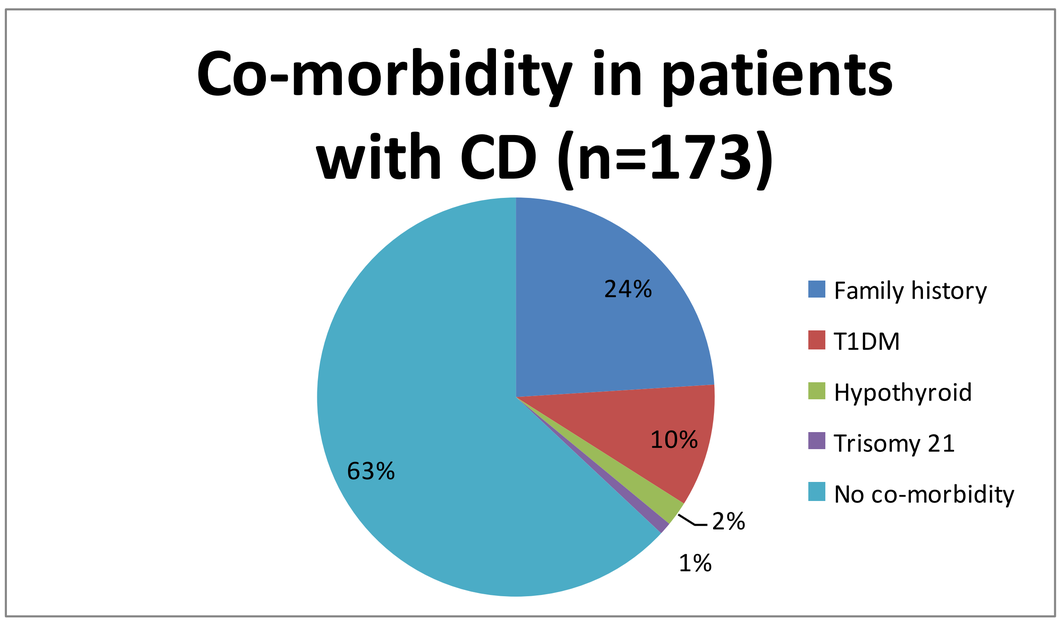
A prospectively maintained departmental database was used to identify all children diagnosed with CD since the new ESPGHAN/BSPGHAN guidelines[1/2] were adopted by our centre in 2013.

Results

- 173 patients were diagnosed within the study time.
- Median age at diagnosis was 7.83yrs
- 102/173 (59%) reported more than one presenting symptoms
- 14/173 (8%) were reported as asymptomatic

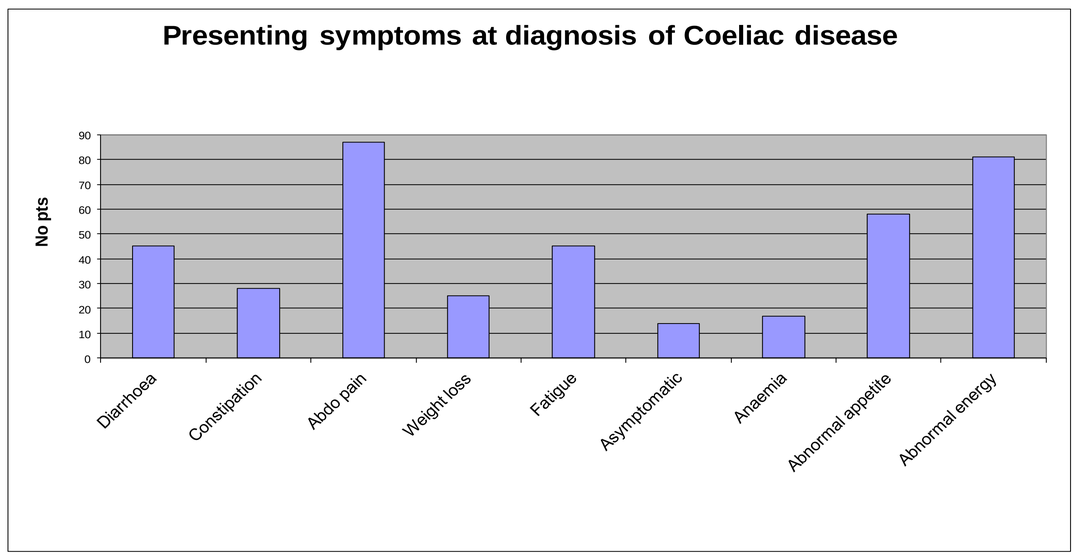
Reported co-morbidity

- 18/173 (10%) patients had type 1 diabetes mellitus at time of diagnosis of CD, 5/18 were asymptomatic
- 3/173 (2%) were diagnosed with hypothyroidism
- 2/173 (1%) were diagnosed with Trisomy 21
- 42/173 (24%) had a family history CD



Presenting symptoms

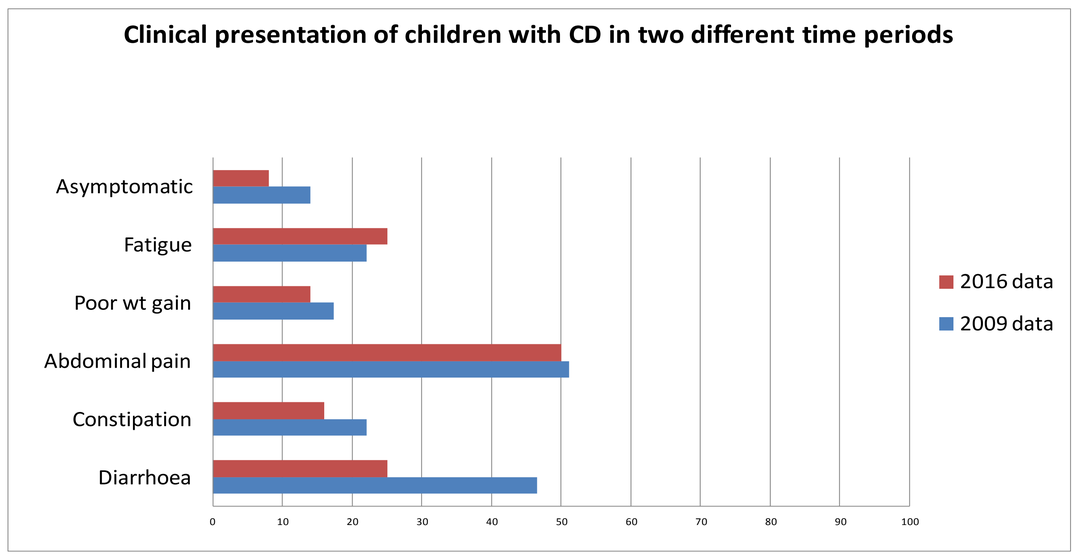
- Abdominal pain was most frequently reported symptom (45/173, 50%)
- Abnormal appetite was reported in 33% of patients and abnormal energy levels in 47% patients
- Constipation was reported in 16% of patients at time of presentation
- 14% of patients reported weight loss or poor weight gain at time of diagnosis
- 10% of patients presented with anaemia
- 8% of patients reported no symptoms



Comparison of current data with 2009 data

- Median age at diagnosis is comparable (7.25yrs in 2009 cohort c/w 7.83yrs in current cohort)
- More typical symptoms of coeliac disease such as poor weight gain and diarrhoea becoming less common
- Poor weight gain at time of diagnosis decreased from 17.4% patients in 2009 c/w 14% in current cohort
- The incidence of diarrhoea at time of diagnosis decreased from 46.5% in 2009 c/w 25% in current cohort
- Abdominal pain was comparable with 51% in 2009 and 50% in 2016 cohort

In the current cohort there was a reduction in number of patients presenting with co-morbidities (51% in 2009 group c/w 38%) and also a reduction in number of patients reporting to have no symptoms at time of diagnosis (14% patients in 2009 cohort c/w 8% in current cohort).



Conclusion

The presenting symptoms of Coeliac Disease have changed compared with our data set in 2009. Abdominal pain was the most frequently reported symptom in both data sets. There has been a reduction in patients presenting with co-morbidities and asymptomatic patients.

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Length of time for tTG antibody levels to normalise following diagnosis of Coeliac Disease in a paediatric cohort

NHS Greater Glasgow and Clyde

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Introduction

Coeliac disease (CD) is a lifelong autoimmune condition primarily affecting the small intestine. Treatment of the condition is by life long exclusion of gluten from the diet. Diagnostic criteria of CD in paediatric population changed in 2012 and our centre adopted the new guidelines in 2013. Diagnosis can now be made on serology in symptomatic patients when tissue transglutaminase (tTG) antibodies are greater than 10 x upper limit normal (ULN) with positive EMA and HLA tissue typing. Those with associated co-morbidity, those who are asymptomatic or tTg lower than 10 x ULN still require an upper GI endoscopy with small bowel biopsies.

Aim

To assess the length of time taken for tTG antibodies to normalise following the diagnosis of CD in our patient cohort.

Method

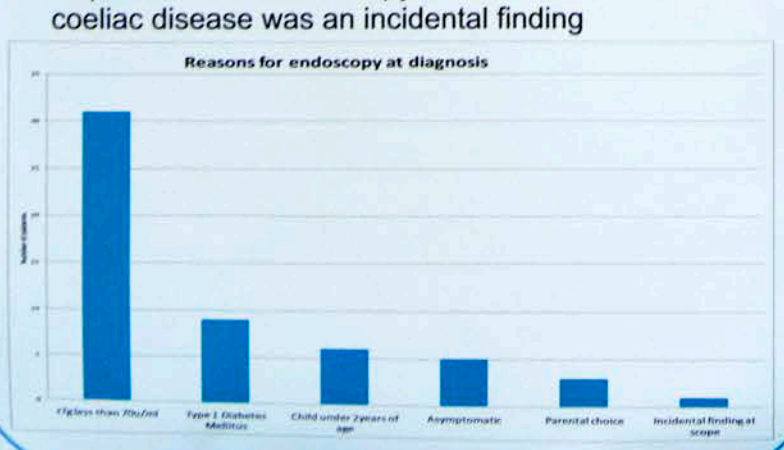
A prospectively maintained departmental database was used to identify all children diagnosed with CD since the new ESPGHAN/BSPGHAN guidelines[1] came into place in our centre in 2013. Data collected included tTg antibody at time of diagnosis, 6 months and 1 year following diagnosis. IgA Tissue Transglutaminase antibodies were analysed using the Phadia method on the Immunocap250 analyser. The method of confirmation of initial diagnosis was also recorded (serology/biopsy).

Results

- 111 patients were identified
- Median age at diagnosis was 7.205yrs
- 65/111 (58%) patients diagnosed between 2013-2016 at Royal Hospital for Children were female

57/111 (51%) underwent biopsy to confirm diagnosis. Reasons for endoscopy at time of diagnosis include:

- tTG less than 70u/ml occurred in 31/57 (54%) patients
- 9/57 (16%) patients had endoscopy due to Type 1 Diabetes Mellitus
- 6/57 (10%) had endoscopy due to being under 2years of age
- 5/57 (8%) had endoscopy due to being asymptomatic
- 3/57 (5%) required underwent endoscopy due to parental choice
- 1 patient had endoscopy for another reason and coeliac disease was an incidental finding



tTG antibody—time to normalise

At diagnosis:

- 59/111 patients had tTG antibody level greater than 128u/ml.
- 18/111 patients had tTG antibody level greater between 70u/ml to greater than 128u/ml.
- 32/111 patients had tTG antibody level less than 70u/ml.
- Median value tTG antibody level = greater than 128u/ml.

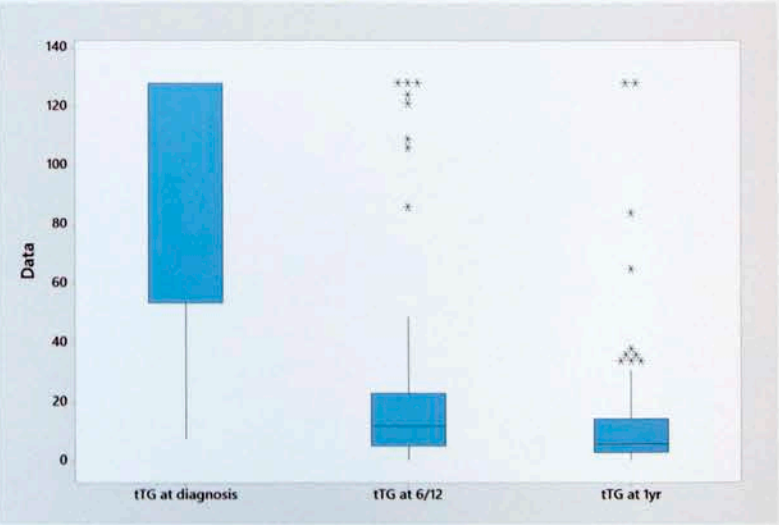
At 6 months following diagnosis:

- 30 patients had tTG antibody levels within normal range (less than 7U/ml). This is a significant reduction in tTG antibody levels compared with diagnosis (p=0.000).
- 67 patients had tTG antibody level out with normal range.
- 14 patients had no 6 month blood test results available.

At 1year following diagnosis:

- 54 patients had tTG antibody level within normal range (less than 7u/ml). This is a significant reduction in tTG antibody level compared with diagnosis (p=0.000).
- 39 patients had tTG antibody level out with normal range.
- 18 patients had no result available.

Figure 1 - tTG levels demonstrate a sustained reduction 1yr post diagnosis



Conclusion

The majority of patients underwent diagnosis by endoscopy and the main reason for this was due to tTG antibody levels being less than 70u/ml. Once diagnosed this data set demonstrates that over half of our patients tTG antibody level had fallen to within normal range at a year following diagnosis. This is useful data as many parents and young people are keen to know when levels should have improved.

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The role of a point of care test, Simtomax (IgA/IgG-deamidated gliadin peptide), in predicting histological remission in coeliac disease on a gluten free diet.

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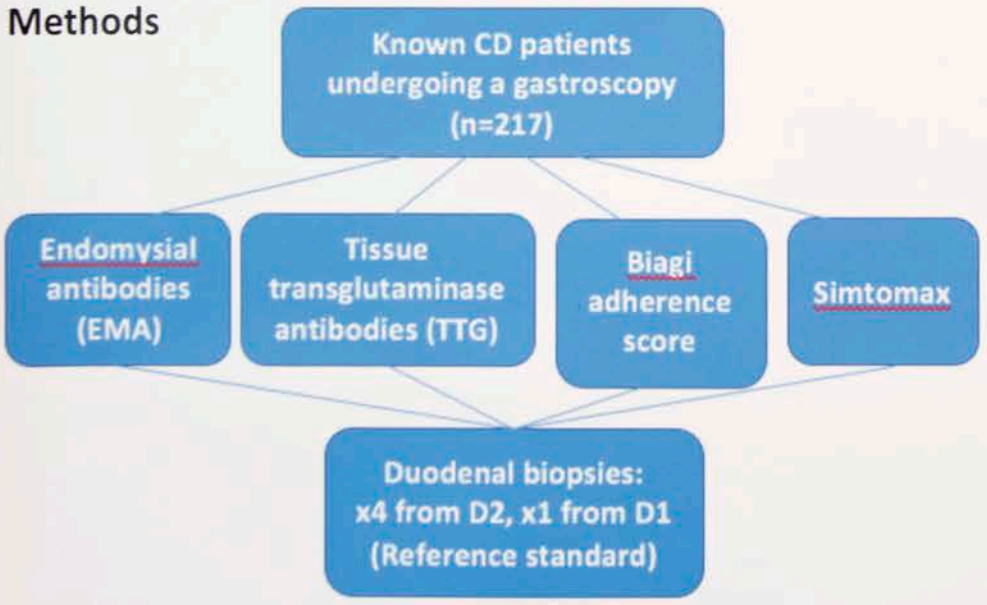
Introduction

Coeliac disease (CD) is a chronic inflammatory enteropathy treated with a life-long gluten free diet (GFD). Non adherence can lead to symptoms and complications such as osteoporosis and malabsorption, and patients with persistent villous atrophy are twice as likely to develop lymphoproliferative malignancies compared to those who achieve mucosal healing. Therefore, the optimal assessment of treatment response is evaluation of duodenal histology.

However, there is little consensus in the UK on routine re-biopsy during follow up. Duodenal biopsy requires a gastroscopy which is invasive and can be poorly tolerated. There is currently no reliable surrogate marker for histological remission in daily clinical practice. We aimed to assess the role of an IgA/IgG-deamidated gliadin peptide (DGP) based finger prick point of care test (POCT), Simtomax, in predicting histological remission in CD.

Methods



Results

- 217 patients with CD on a GFD (median duration 6 years) were recruited from 2013-2017.
- 70% female, age range 16-83, median age 53
- 85 (39.2%) patients had persistent villous atrophy.
- Simtomax was the most sensitive surrogate marker in predicting villous atrophy (p=0.0005).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Simtomax	67.1 (56.0-76.9)	59.1 (50.2-67.6)	51.4 (45.0-57.6)	73.6 (66.6-79.6)
TTG	44.7 (33.9-55.9)	86.4 (79.3-91.7)	67.9 (56.4-77.5)	70.8 (66.5-74.8)
EMA	37.7 (27.4-48.8)	89.4 (82.9-94.1)	69.6 (56.5-80.1)	69.0 (65.1-72.6)
Adherence score	24.7 (16.0-35.3)	86.4 (79.3-91.7)	53.9 (39.8-67.3)	64.0 (60.8-67.2)

Discussion

Of all clinically available surrogate markers, Simtomax had the highest sensitivity in predicting villous atrophy. Simtomax has the additional advantage of convenience being a finger prick test, providing rapid results within 10 minutes. In combination with clinical and dietetic assessments, Simtomax could aid clinical decision making on the necessity of follow-up duodenal biopsy within the same consultation.

Quality standards in coeliac disease: a retrospective evaluation in a single specialist clinic

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Background

Quality standards in the management of coeliac disease (CD) were recently published by the National Institute for Health and Care Excellence (NICE)[1]. These specify a new 6-week target for the time from referral to endoscopy, which was previously covered by the 18-week referral to treatment (RTT) pathway[2]. They also state that all newly-diagnosed patients should discuss a gluten-free diet with a specialist such as a dietitian.

We retrospectively evaluated practice in the Oxford University Hospitals NHS Foundation Trust coeliac clinic against the new NICE criteria, as well as against national guidelines that recommend duodenal bulb biopsies are taken in addition to biopsies from the second part of the duodenum (D2) at endoscopy, and that all patients should be screened for nutritional deficiency including iron studies, vitamin B12, folate and vitamin D[3].

Methods

The medical records of 110 patients newly referred to the coeliac disease clinic between September 2015 and September 2016 were examined. The date of referral and endoscopy were recorded, along with relevant demographic, clinical and laboratory information. Data were collected and analysed in Microsoft Excel®.

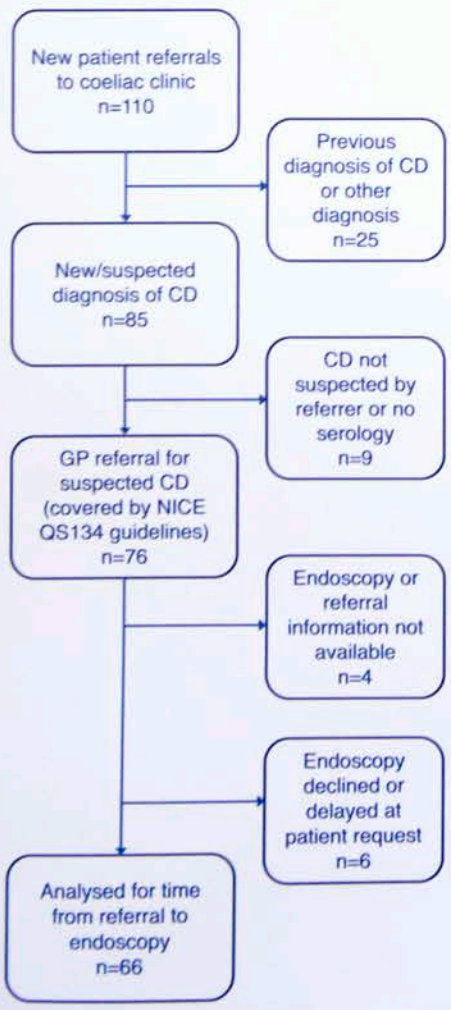

Figure 1: Flow chart of case identification for analysis of time from referral to endoscopy.

NICE Quality Standard QS134: Coeliac disease[1]

- ✓ **Statement 1**: People at increased risk or with symptoms of coeliac disease are offered a serological test for coeliac disease.
- ✓ **Statement 2**: People with a positive serological test for coeliac disease are referred to a specialist and advised to continue with a gluten-containing diet until diagnosis is confirmed.
- ✓ **Statement 3**: People referred to a specialist who need an endoscopic intestinal biopsy to diagnose coeliac disease have it within 6 weeks of referral.
- ✓ **Statement 4**: People newly diagnosed with coeliac disease discuss how to follow a gluten-free diet with a healthcare professional with specialist knowledge of coeliac disease.
- ✓ **Statement 5**: People with coeliac disease are offered an annual review.

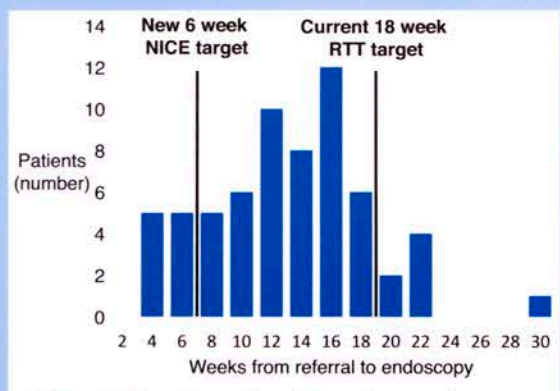

Figure 2: Time from referral to endoscopy for patients with suspected coeliac disease

Results

Eighty-five patients (68% female, median age 34) were seen with suspected or newly-diagnosed coeliac disease, of whom 76 (89%) were referred with positive coeliac serology. Time from referral to endoscopy was analysed for 66 patients (Figure 1). The median time from referral to endoscopy was 12 weeks 2 days (SD 37 days), with 59 patients (89%) having an endoscopy within 18 weeks, but only 11 patients (17%) within 6 weeks (Figure 2).

Duodenal bulb biopsies were taken in addition to D2 biopsies at endoscopy in 31 patients (44%). A diagnosis of coeliac disease was made in 74 patients (87%) referred to the clinic, of whom 67 (90%) were referred to a specialist dietitian.

Haematinics (iron studies, vitamin B12 and folate) were measured in 67 patients (90%), vitamin D in 61 patients (82%) and bone densitometry was measured in 51 patients (69%). Nutritional deficiencies were common, particularly iron deficiency (with or without anaemia) and vitamin D deficiency (<30nmol/L) (Figure 3).

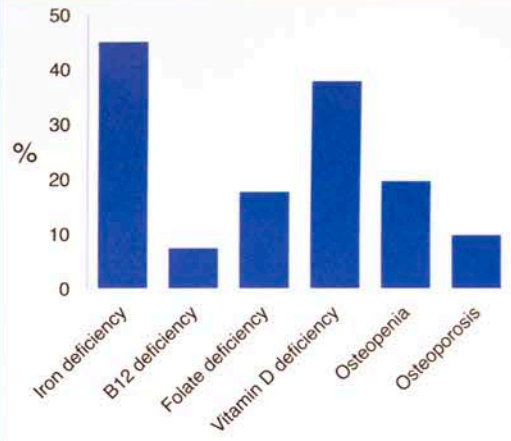

Figure 3: Incidence of nutritional deficiency and bone disease in newly diagnosed patients with coeliac disease

Conclusion

Appropriate dietitian referral, specialist follow-up and screening for nutritional deficiency and bone disease occur within the Oxford coeliac disease service. However, compliance with recommended biopsy protocols was only 44%. Whilst most referrals met the 18-week RTT pathway, few would have met the new 6-week quality standard. Significant changes to the coeliac disease referral pathway will be needed to achieve these targets.

Support and funding

Michael FitzPatrick is supported by an Oxford-Celgene Research Fellowship funded by Celgene Corporation. We thank the Translational Gastroenterology Unit, University of Oxford, and the Oxford University Hospitals NHS Foundation Trust for their support.

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Using MRI to improve our understanding of Coeliac disease

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AIM: To investigate differences in gut transit and Quality of Life between newly diagnosed coeliac disease patients and a matched cohort of healthy volunteers

INTRODUCTION: Recent developments in magnetic resonance imaging (MRI) are providing novel insights on pathophysiological mechanisms of different gastrointestinal diseases. These methods could help to explore the relationship between symptoms and objective MRI bowel parameters in coeliac disease (CD), both at diagnosis and at follow-up after treatment with gluten free diet. In particular studies have shown disordered gut transit in untreated CD (Tursi, 2004) (Sadik et al., 2004). This research uses non-invasive MRI to investigate difference in gut transit in adults newly diagnosed with CD and healthy volunteers (HVs) who do not have coeliac or other bowel disease and do not exclude gluten from their diet.

METHODS: 14 newly diagnosed coeliac patients (9 females and 5 males, aged 20-67 years old, and 14 HVs, 10 females and four males aged 20-59 years old) participated. The CD patients were recruited after a positive coeliac serology and duodenal mucosal biopsy and before starting a gluten free diet. They completed two validated questionnaires to assess their quality of life, the Patient Health Questionnaire, a Somatic Symptom scale (PHQ15-SS) to assess their physical health and the hospital anxiety and depression scale (HADS), a psychological screening tool measuring anxiety and depression.

MRI to assess whole gut transit time was undertaken on a 1.5T GE scanner. Participants underwent a short fasting MRI scan in the morning, 24 hours after ingestion of 5 MRI transit marker capsules. The MRI study measured the WGTT as previously validated (Chaddock et al., 2014).

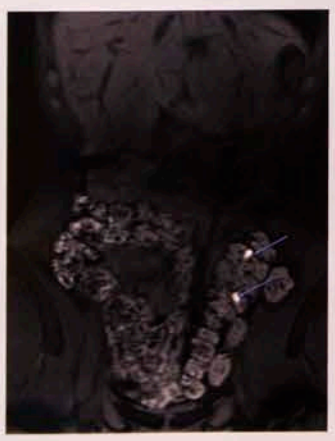

Figure 1 Transit pills in the colon (blue arrows)

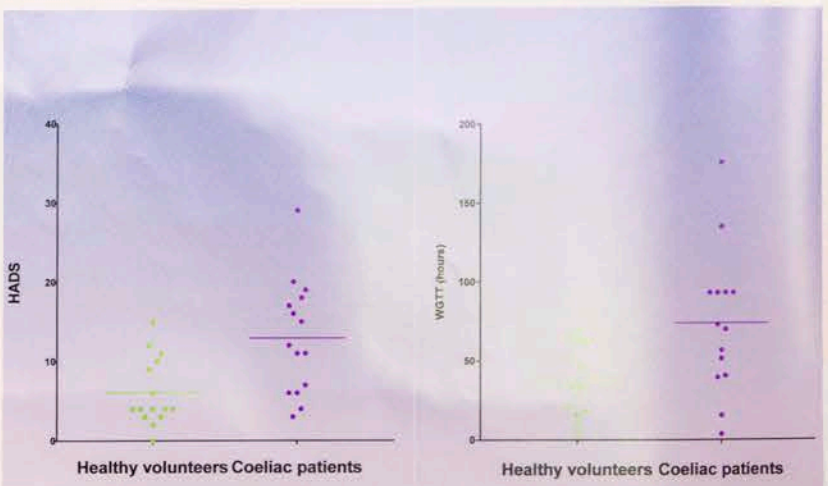

Figure 2 HAD scores

Figure 3 Transit times

RESULTS: The two groups were matched for age, gender and body mass index (BMI). Compared to the HVs, the CD patients had significantly high scores for HAD-D (p=0.0007) and PHQ15-SS (p=0.0002) symptom questionnaires. In the coeliac patients WGTT was double compared to the HVs, this difference being significant (p=0.01).

CONCLUSIONS: The CD patients showed reduced general health and increased likelihood of depression in comparison to age and sex-matched controls which was consistent with published literature (O'Leary et al., 2002). WGTT in the untreated coeliac patients was significantly longer than in the HVs.

Gut function in CD, in particularly transit, is an under researched area. This preliminary experience suggests that MRI can offer new insights into the pathophysiology of CD. The imaging exam is quick, non-invasive, uses non-ionising radiation and is acceptable to patients and could help monitoring and follow up, complementing existing more invasive techniques.

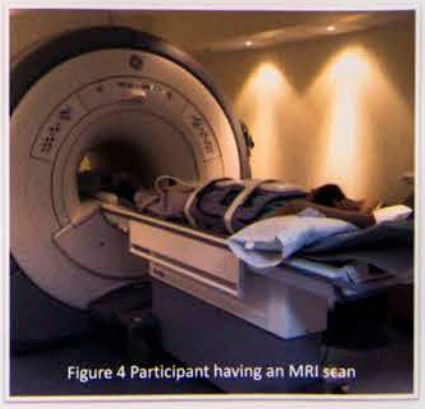

Figure 4 Participant having an MRI scan

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Monitoring of Vitamin D in an adult secondary care coeliac population

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University Hospital Birmingham NHS Foundation Trust

INTRODUCTION

Vitamin D deficiency is a complication in patients with coeliac disease but there is no UK consensus on frequency of monitoring or supplementation.

We sought to determine practice in monitoring and supplementing vitamin D over the last 14 years in a single hospital centre adult coeliac population in Birmingham.

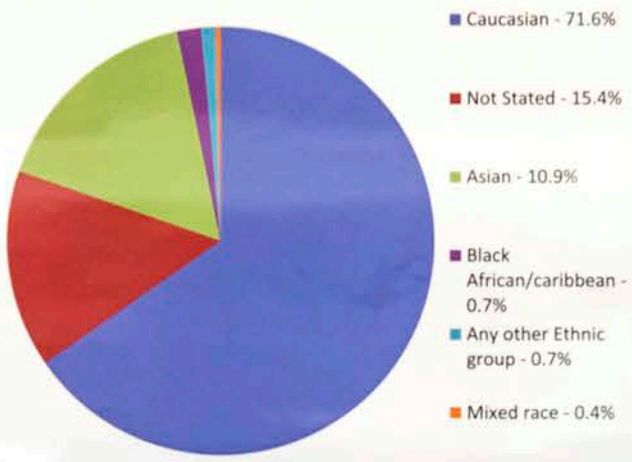
Adults diagnosed per year at UHB

Year	Number of Diagnosed	Average age of diagnosis
2002	38	68
2003	52	66
2004	73	66
2005	72	64
2006	75	63
2007	82	60
2008	75	60
2009	102	57
2010	90	57
2011	112	59
2012	138	55
2013	117	55
2014	162	50
2015	151	52
2016	85	55
Average	94	57

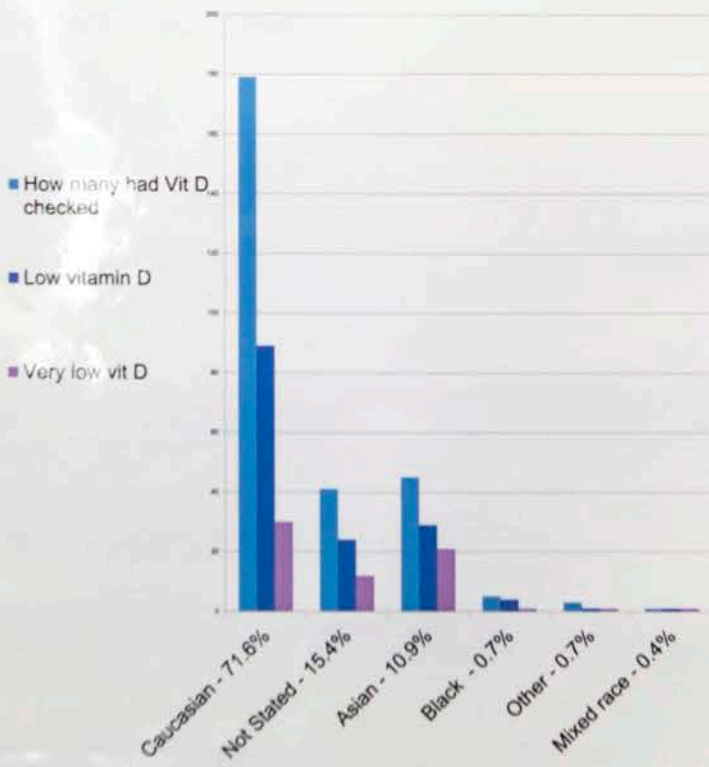
METHODS

Hospital informatics data was obtained for 1423 patients from 2002 to date diagnosed with Coeliac disease coding in UHB GI Medical or dietetic clinics. It was determined whether vitamin D was checked and prescribed in secondary care.

COELIAC POPULATION AT UHB



Vitamin D levels in each ethnicity



ACKNOWLEDGEMENTS

Many thanks to the coeliac patients and other medical, nursing and admin staff in UHB NHS Foundation Trust GI medical and dietetic services

RESULTS

Overall, 19.2% (n=274) of all patients diagnosed with coeliac disease had their vitamin D levels checked. Of these, 24% were very deficient (<30nmol/L) and a further 30% were deficient (<50nmol/L). 229 people (16%) were prescribed supplementation in the hospital records.

Of the Asian population (n=156), 28.8% (n=45) had their vitamin D levels checked. 64.4% (n=29) of these were deficient (<50nmol/L). Of the Caucasian population (n=1020), 17.5% (n=179) had their levels checked. 49.7% were deficient (n=89).There were no overt trends by BMI.

CONCLUSIONS

One fifth of coeliac patients have vitamin D levels checked at hospital. Of those around half need supplementation.

FUTURE DIRECTIONS

Given variation by ethnicity and limited evidence of prescriptions, the process of diagnosing and supplementing vitamin D deficiency in the adult coeliac population needs further study as part of service design.

Public Health England are now recommending all adults to take 10 µg of vitamin D per day. The cost to check 25-OH Vitamin D is £15.17. It may be more cost-effective to move straight to supplementation for most patients in dietetic-led clinics.

Delivering the best in care

Queen Elizabeth Hospital Birmingham

University of Roehampton London

University Hospitals of Leicester NHS Trust

Adherence to a gluten free diet in Caucasians and South Asians with coeliac disease, using the coeliac disease adherence test (CDAT) score

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[1]Health Sciences Research Centre, University of Roehampton, London. [2]Gastroenterology, Dudley Group of Hospitals,. [3]Gastroenterology, University Hospitals of Leicester

INTRODUCTION

- A gluten free diet, in people with coeliac disease, leads to symptomatic improvement, histological remission of villous atrophy, improvements in quality of life, reduction in the risk of osteoporosis and gastrointestinal malignancies.
- However, a gluten free diet is difficult to follow and many patients refer to social and practical issues. Dietary adherence to the gluten free diet in coeliac disease has been reported to range from 36% to 96% (Hall *et al.*, 2009). Factors that influence adherence include sociodemographic, age of diagnosis and membership of advocacy groups (Hall *et al.* 2009).
- There is very limited literature exploring adherence to the gluten free diet by South Asians with coeliac disease. Over 10 years ago Butterworth *et al.*, (2004) indicated South Asian patients self reported more frequent consumption of gluten containing foods compared with Caucasians.

STUDY AIM: **To identify differences between the adherence to a gluten free diet in patients with coeliac disease from Caucasian and South Asian populations in the UK.**

METHODS

- The participants were recruited from the coeliac disease database held within the University Hospitals of Leicester's (UHL) pathology department, patients diagnosed from 2004 onwards were selected. From 1248 histologically confirmed patients with coeliac disease 972 met the inclusion criteria.
- The postal survey included the questionnaire from Butterworth *et al* (2004) and the coeliac disease adherence test (CDAT) questionnaire (Leffler *et al* 2009) with available support in 7 ethnic languages
- Data was analysed using SPSS (v22.0). Chi squared, t-test and logistic regression were performed.
- Ethical approval was granted through the procedures of the University of Roehampton and the Health Research Authority (REC number: 14/LO/2128).

RESULTS

- Questionnaires were returned by 375 people with histologically confirmed coeliac disease: 337 Caucasians (239 females, 98 males) and 38 Asians (27females, 10males).
- The completion rate for the Caucasian population was 40.6% (n=337) and 26.5%(n=38) for South Asian population.

Table 1. Self reported ingestion of gluten containing foods by South Asians and Caucasians

Frequency of gluten ingestion as perceived by patient	South Asians (n=38)	Caucasians (n=337)
Never	57.9% (22)	62.9% (212)
Once a month	21.1% (8)	25.5% (86)
Once a week	15.8% (6)	9.2% (31)
Daily gluten ingestion	5.3% (2)	1.8% (6)

RESULTS

- Gluten free dietary adherence: CDAT score ranged from 7 to 30, mean scores for Caucasians and South Asians were similar (14.2 and 15.4 respectively; NS). The proportion of Caucasians and South Asians self reporting to never consume gluten were also similar (63% and 58%: NS), as shown in Table 1.
- South Asians with coeliac disease did report more difficulties following the gluten free diet (Table 2), a high proportion of all participants indicated the need for more gluten free foods to be prescribed.

Table 2. Difficulties reported following the GFD in South Asians and Caucasians

The % (n) who responded 'yes'	South Asians (n=38)	Caucasians (n=337)
I don't understand what foods I can eat	76.3% (29)	4.5% (15)
I don't understand food labelling	52.6% (20)	3.9% (13)
I don't have time to prepare the different meals	2.6% (1)	7.4% (25)
Gluten free foods are unpleasant	81.6% (31)	57.0% (192)
Gluten free foods are expensive	97.4% (37)	78.3% (264)
My GP does not prescribe enough	94.7% (36)	73.6% (248)

- 93% reported they received information about Coeliac UK, a similar proportion of Caucasians and South Asians joined Coeliac UK (55% and 42% respectively: NS)
- Membership of Coeliac UK, affordability of gluten free foods and understanding food labelling were significant factors in gluten free dietary adherence.

CONCLUSION

- Our study found no ethnic difference in adherence to the gluten free diet, this is in contrast to an earlier study by Butterworth *et al.* (2004). A lower percentage of Caucasians and South Asians reported daily ingestion of gluten in our study compared with Butterworth *et al.* (18% of Caucasians and 19% of South Asians).
- A high proportion of all participants indicated the need for more gluten free foods to be prescribed. Membership of the Coeliac UK and affordability of gluten free products were associated with adherence to the gluten free diet.
- The number of South Asian responses is relatively small (n=38); it is important to recruit a larger cohort of South Asians with coeliac disease to further our understanding of specific factors influencing their adherence to the gluten free diet such as understanding what food they can consume and food labelling.

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Food Intake and Processing of Food Cues in Coeliac Disease: A Pilot Study

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Introduction

- Individuals with coeliac disease (CD) need to be **vigilant** around food[1]
- This can lead to disordered eating attitudes and **restrictive eating** behaviours[2]. These behaviours are common in unfamiliar settings[3]
- The CD Food Attitudes and Behaviours scale (CD-FAB) identifies these attitudes and behaviours[4]
- Only self-report measures have explored food attitudes and behaviours in CD. These measures tell us little about actual food consumption.

Methods

- 41 individuals with CD (**37.1 years**); 10 healthy controls.
- CD-FAB: questionnaire to assess coeliac related food attitudes and behaviours.
- **Computer task:** dot-probe task assessing vigilance towards food.
- **Taste test**: to assess willingness to consume food in unfamiliar environments.
- Covariates: food familiarity, food liking, current hunger, satiety, mood and disordered eating status.

Aims and objectives

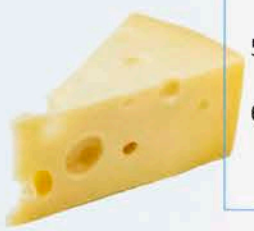
We report the first behavioural, laboratory-based study in coeliac disease. We explored the **relationship between CD-FAB scores, vigilance towards food images and food consumption** in those with CD

Development of the Vigilance Measures

1. **Gluten-free, gluten containing** and **control images** were matched for shape, colour, size and nutritional content
2. A dot-probe task was programmed in E-Prime.
    1. Fixation cross (500 ms)
    2. Food image (500 ms)
    3. Probe (incongruent or congruent to food position)
    4. Response
3. Vigilance to gluten-free and gluten images was calculated separately by subtracting the reaction times for the congruent trials from the incongruent trials. **Positive scores indicate vigilance towards the image**, negative indicate attention being directed away from the image

Development of the Taste Test

1. **Four gluten-free foods**; 2 savoury, 2 sweet. Presented in original packaging.
2. Individuals invited to inspect the packaging and confirm the food was gluten-free.
3. Foods were unwrapped and poured into each bowl.
4. Researcher left the room; participants invited to taste, rate and snack on the food for 10 minutes.
5. Participants informed that any left over food would be thrown away.
6. After 10 minutes, researcher returned and removed food. Remaining food was **covertly weighed.**



Results

- As expected individuals reported less hunger and more fullness over time, this is likely due to food consumption
- Food intake was associated with **binge eating scores** and **food familiarity**. These factors, along with covariates, were placed in step one of a regression model, with overall calorie intake as the dependent variable.
- The CD-FAB did not explain additional variance in calories consumed above covariates ($f(1,39)=3.75$, $p=.002$)
- There was no relationship between CD-FAB scores and vigilance towards food images. However, those with **CD showed greater vigilance** towards gluten-containing images compared to controls (figure 1; $t(1,48)=2.03$, $p=.048$)

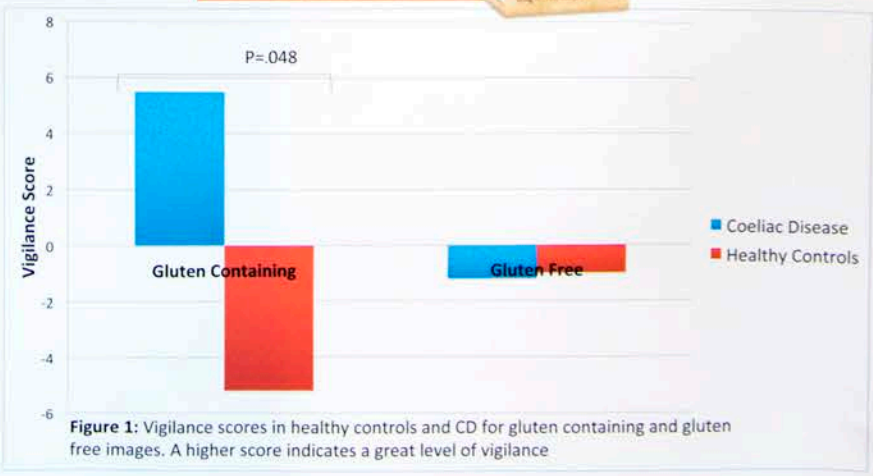


Figure 1: Vigilance scores in healthy controls and CD for gluten containing and gluten free images. A higher score indicates a great level of vigilance

Discussion

- The relationship between food attitudes and intake is still **unclear**; the perceived safety of lab environment and packaging of gluten-free foods may have reduced differences across CD-FAB scores
- Processing of gluten-containing images is **different in CD** compared to controls; replication is larger samples in needed
- **Laboratory based study are feasible** in individuals with CD

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The economic burden of Coeliac Disease in the UK: a retrospective population-based study

Mara Violato[1], Alastair Gray[1]

[1]Health Economics Research Centre (HERC), Nuffield Department of Population Health, University of Oxford

Introduction and Aims

Although the prevalence and health impact of Coeliac Disease (CD) is considerable, research on the impact of CD and its symptoms on out-of-pocket costs, healthcare resource use and overall economic burden of the disease is still limited.

Aims: to quantify the cost - and its variation over time - of CD in the UK to:

(i) people with coeliac disease, in terms of out-of-pocket expenses

(ii) the NHS, in terms of use of healthcare services due to symptoms and management of the disease

(iii) family and friends of the person with coeliac disease

Methods

Study design: A retrospective postal survey, similar to one we conducted in 2006 was carried out at the end of 2015.

Participants: A representative, geographically stratified, sample of 4000 individuals diagnosed with Coeliac Disease, drawn from the membership list of Coeliac UK, with the expectation of obtaining a response rate of 40% (~1,600 responses), which was successfully achieved.

Collected data: data on socio-demographic characteristics of respondents, time to and since diagnosis, type and duration of symptoms, quality of life, resource use and costs incurred pre- and post-diagnosis by the patient (e.g. private consultations, food supplements), the NHS (e.g. GP visits, prescriptions), and family/friends (e.g. feeling limited in daily life situations).

Statistical analysis: descriptive and regression-based methods used to disentangle the key drivers of differences in the economic burden of CD before and after diagnosis among different socioeconomic strata of the population over time.

Selected Results

Table 1: Socio-demographic characteristics of the participants in the 2015 survey

Characteristics	*No. of patients (%)*
Current (2015) age of respondent	55.7 (20.1)†
Age of respondent at diagnosis (years)	44.2 (19.5)†
Gender	
Male	432 (27.3%)
Female	1151 (72.7%)
Annual family income (gross)	
Less than £10,000	115 (7.7%)
£10,000 - £20,000	319 (20.4%)
£20,001- £30,000	223 (14.9%)
£30,001 - £40,000	199 (13.3%)
£40,001- £50,000	152 (10.2%)
£50,001 - £60,000	80 (5.4%)
£60,001- £70,000	75 (5.02%)
More than £70,000	156 (10.5%)
Not disclosed	174 (11.7%)
UK Region of residency	
England	1183(74.7%)
Wales	74 (4.7%)
Scotland	124 (7.8%)
Northern Ireland	41 (2.9%)
Not reported	162(10.2%)

† Mean and standard deviation

Table 2 – Cost per person year of private healthcare services and other products before and after diagnosis

Costs	*Before diagnosis*	*After diagnosis*
	Mean (Std. Dev.)	**Mean (Std. Dev.)**
Private doctors	£23.8 (279.6)	£34.3 (519.5)
Private dietitians	£5.07 (60.3)	£9.8 (73.3)
Private allergy testing	£1.2 (14.9)	£8.1 (170.5)
OTC medication to alleviate symptoms	£7.5 (37.2)	£9.4 (54.6)
Dietary products	£5.6 (32.9)	£68.6 (304.5)
Nutritional supplements	£2.9 (18.8)	£19.9 (94.7)
Books or DVDs on symptoms	£1.06 (11.02)	£8.2 (33.6)

Table 3 – NHS use after diagnosis

	TIME SINCE DIAGNOSIS			
NHS service	**1 to < 5 years** Mean (Std Dev)	**5 to <10 years** Mean (Std Dev)	**10 to <20 years** Mean (Std Dev)	**≥20 years** Mean (Std Dev)
Routine medical examination	2.03 (3.83)	0.96 (1.46)	0.68 (0.98)	0.35 (0.62)
GP	1.51 (3.54)	0.73 (1.55)	0.56 (1.27)	0.21 (0.42)
Dietitian	1.13 (1.81)	0.43 (0.55)	0.24 (0.37)	0.07 (0.12)
Gastroenterologist	0.84 (2.77)	0.34 (0.71)	0.26 (0.45)	0.09 (0.17)

In terms of NHS use, in the early years after diagnosis, respondents (excluding those diagnosed for less than one year) reported to have on average one GP consultation and one routine medical examination per year, with half of respondents also reporting one dietitian consultation and/or one referral to the gastroenterologist per year, in relation to their coeliac disease. However, the use of these healthcare services dropped dramatically as time since diagnosis increased (**Table 3**).

When asked how restrictions on prescription of GF food affected the affordability of an adequate GF diet, 21% of respondents admitted they could not always afford to purchase the same amount or variety of GF food that they were used to having on prescription, and another 21% were only just managing. However, less than 1% of respondents said they no longer followed a strict GF diet. As **Figure 1** shows, these restrictions on prescriptions had a larger negative impact on people at lower income levels.

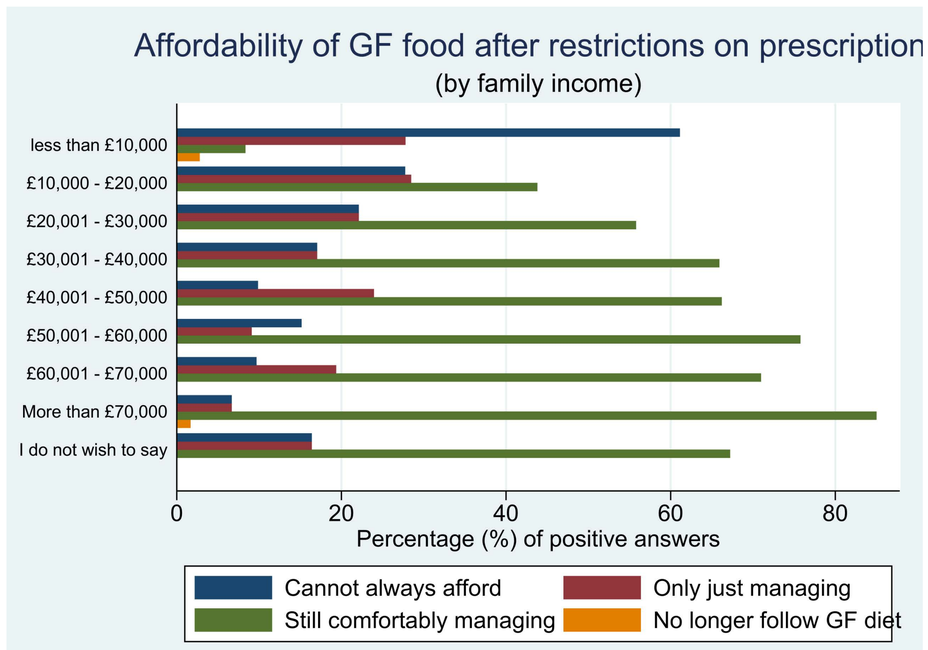

Figure 1- Affordability of GF substitute foods by family income after restrictions on prescription of GF foods

After diagnosis, people with coeliac disease incurred a number of out-of-pocket expenses related to the management of their condition, some of which are presented in **Table 2**. The largest amount of expenditure after diagnosis was, however, the increase in food shopping bills. The mean increase in the yearly food shopping bill of respondents after diagnosis was £861 (Std. Dev. 705.8). A similar pattern of changes had been experienced, after diagnosis, also by the respondents to the 2006 survey, whose average increase in the shopping bill for food was £679 (Std. Dev. 576) (in 2006 prices) per person per year.

The majority of family members/friends of the person with CD confirmed that they felt limited in a number of daily life situations (e.g. restaurants) as a result of restrictions associated with their relative/friend with CD. Furthermore 61% of them indicated they were moderately or extremely worried about the health and wellbeing of the person with CD following her/his diagnosis.

Discussion

- After diagnosis people with coeliac disease incurred a number of substantial out-of-pocket expenditures related to the management of their conditions including private medical consultations, OTC medications/dietary products to alleviate symptoms (**Table 2**) and a large increase (£861: Std. Dev. 705.8) in their yearly food shopping bill.
- Use of NHS services was higher in the years immediately after diagnosis but dropped dramatically as time since diagnosis increased (**Table 3**).
- Coeliac disease and its management was reported to have a negative impact also on people (family and friends) close to the person with the condition.
- Our results show significant additional out-of-pocket and NHS costs associated with CD after diagnosis. Unless ameliorated, the high costs of adhering to a gluten-free diet may challenge adherence in low income groups.

Acknowledgements: this research was funded by Coeliac UK

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Gluten neuropathy: clinical characteristics and impact on mental health

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Introduction

After cerebellar ataxia, peripheral neuropathy (PN) is the commonest neurological manifestation of gluten sensitivity. We aimed to examine the clinical characteristics and estimate the prevalence of pain in patients with PN and gluten sensitivity. We also investigated its impact on patients' mental status.

Methods

Between October 2015 and January 2017 all consecutive patients attending a specialist gluten/neurology clinic, were invited to participate. All patients were examined clinically and neurophysiologically. Pain was assessed via the DN4 questionnaire and the visual analogue scale (VAS). Overall Neuropathy Limitations Scale (ONLS) was used to assess the severity of neuropathy. The Mental Health Index (MHI-5) was used to measure participants' general mental health status.

Results

In total, 55 patients (74.5% males) with PN and gluten sensitivity were recruited. The age of the patients ranged from 45 to 88 years (mean 70.0±9.8 years). Twenty-nine patients (52.7%) were on a strict gluten-free diet (Biagi score 3 or 4).

Symmetrical sensorimotor axonal neuropathy was the commonest form of neuropathy (69.1%), followed by sensory ganglionopathy (29.1%) and mononeuritis multiplex (1.8%). The ONLS score ranged from 1 to 7 (mean 3.2±1.8).

Pain was present in 35 patients (63.6%). Based on the DN4 questionnaire in 34 (97.1%) patients with painful PN, the pain was neuropathic in nature. Based on the VAS, the pain intensity on examination ranged from 0 to 7 (mean 2.6±2.3) and the maximum intensity of pain ranged from 2 to 10 (mean 7.0±2.3). In 10 patients (18.2%) pain was the first symptom of their neuropathy.

Comparison between groups of painful and not painful PN did not show significant differences regarding age, gender, neuropathy severity, or neuropathy type. Patients with painful neuropathy were less likely to be on a strict gluten free diet (42.9% versus 70.0%, p=0.052), Also, patients with pain presented with significantly worse general mental health status based on the MHI-5 score (76.6±13.6 versus 85.8±9.6, p=0.01).

	Total population (n=55)	Painful PN (n=35)	Painless PN (n=20)	P value
Demographics				
Age, in years (SD)	70.0 (9.8)	69.1 (10.0)	71.3 (9.3)	0.435
Male gender (%)	41 (74.5)	25 (71.4)	16 (80.0)	0.482
Clinical characteristics				
Type of neuropathy				
Sensorimotor axonal PN (%)	38 (69.1)	25 (71.4)	13 (65.0)	
Sensory ganglionopathy (%)	16 (29.1)	10 (28.6)	6 (30.0)	0.400
Mononeuritis multiplex (%)	1 (1.8)	0 (0.0)	1 (5.0)	
Neuropathy severity				
ONLS Arm score (SD)	1.3 (0.9)	1.3 (0.9)	1.3 (1.0)	0.955
ONLS Leg score (SD)	1.9 (1.2)	2.0 (1.2)	1.8 (1.2)	0.617
Total ONLS score (SD)	3.2 (1.8)	3.3 (1.8)	3.1 (1.9)	0.717
Strict gluten-free diet (%)	34 (52.7)	15 (42.9)	14 (70.0)	0.052
MHI-5 score (SD)	79.9 (13.0)	76.6 (13.6)	85.8 (9.6)	**0.010***

Table. Characteristics of patients with gluten neuropathy.

SD, Standard deviation
PN, Peripheral neuropathy
ONLS, Overall Neuropathy Limitations Scale
MHI-5, Mental Health Inventory - 5

Discussion

Pain is very prevalent in PN associated with gluten sensitivity and has a significant effect in patients' mental health status. Screening for PN and evaluation of pain in patients with gluten sensitivity is highly recommended. Gluten free diet is likely to protect from pain in gluten neuropathy

The Coeliac Disease Assessment Questionnaire (CDAQ): responsiveness to change

Helen Crocker, Crispin Jenkinson, Jill Dawson, Michele Peters

Nuffield Department of Population Health, University of Oxford

Introduction

The Coeliac Disease Assessment Questionnaire (CDAQ) is a 32-item patient-reported outcome measure (PROM) developed to assess quality of life in adults with coeliac disease. It is suitable for use in research, including clinical trials, and clinical practice. The CDAQ is a reliable and valid measure, but its ability to detect change over time is yet to be assessed. Therefore, the aim of this study was to assess the CDAQ's responsiveness to change.

The CDAQ

- 32-item questionnaire addressing 5 dimensions:
  - Stigma
  - Dietary burden
  - Symptoms
  - Social isolation
  - Worries and concerns
- Dimension scores and an overall summary score can be calculated.
- Scores range from 0 to 100, with a higher score indicating a better quality of life.

Methods

Responsiveness to change was assessed by conducting a survey of Coeliac UK members (n=1443). As the impact of coeliac disease most predictably changes following diagnosis (and the introduction of a gluten-free diet), only recently-diagnosed members were invited to participate. Members were asked to complete a postal (n=500) or online (n=943) survey, answering the CDAQ at two points in time, four months apart. A four month time period between completions was considered appropriate to allow changes in health, particularly symptoms, to occur.

Baseline, follow-up, and change scores for each of the CDAQ's five dimensions, and Overall index score were calculated. The following distribution-based indicators of responsiveness to change were calculated: effect size (ES), standardized response mean (SRM), and minimal detectable change (MDC).

Paired t-tests were used to assess the change between baseline and follow-up scores. Statistical significance was set at $p<0.05$ with a 95% confidence interval.

Ethics approval was granted by the University of Oxford's Central University Research Ethics Committee (Reference no: MS-IDREC-C1-2015-177).

Results

In total, 277 respondents completed both questionnaires and were included in the analysis. The mean interval between completing the first and second questionnaires was 130 days ± 11.47 days (range: 68-205). The mean time since diagnosis at baseline was 5.21 months (SD 2.99). The majority of respondents were female (59.2%, n=164), married or in a civil partnership (63.3%, n=171), White British (92.1%, n=255), working (including full-time, part-time and self-employed work) (62.9%, n=166), and had never consumed gluten since their diagnosis (71.6%, n=207).

The results of the distribution-based analysis are shown in Table 1. Small to moderate effect sizes (ES) for the CDAQ Overall index score (0.19), Symptoms (0.27), and Worries and concerns (0.19) domains were found. Small to moderate standardized response means (SRM) for the Overall index score (0.37) and dimension scores (0.22-0.39), except Stigma (0.03), were found. The minimal detectable change (MDC) is estimated as 2.06 for the overall index score, and between 14.08 and 18.99 for the dimension scores.

Table 1. Baseline, follow-up and change scores (mean and standard deviation) for the CDAQ Overall index score and dimension scores, and distribution-based analyses (ES, SRM, SEM and MDC)

CDAQ dimension	n	Baseline m (SD)	Follow-up m (SD)	Change m (SD)	95% CI	p	ES	SRM	ICC	SEM_{ICC}	MDC_{ICC} 90%
Overall index score	252	51.77 (18.20)	55.15 (17.39)	3.37 (9.12)	2.24 – 4.50	<0.001	0.19	0.37	0.89	1.10	2.06
Stigma	273	52.78 (22.63)	53.13 (21.34)	0.34 (13.29)	-1.24 – 1.93	0.67	0.02	0.03	0.85	7.64	14.26
Dietary burden	268	37.50 (17.79)	40.04 (17.68)	2.54 (10.86)	1.24 – 3.85	<0.001	0.14	0.23	0.82	7.54	14.08
Symptoms	272	58.89 (22.73)	65.04 (20.62)	6.14 (15.77)	4.25 – 8.02	<0.001	0.27	0.39	0.8	10.17	18.99
Social isolation	269	64.09 (24.64)	67.51 (22.73)	3.42 (15.46)	1.56 – 5.27	<0.001	0.14	0.22	0.86	9.22	17.22
Worries and concerns	269	46.75 (21.53)	50.82 (22.40)	4.07 (13.22)	2.49 – 5.66	<0.001	0.19	0.31	0.78	8.08	18.86

Typical effect size (ES) values: 0.2 (small), 0.5 (medium), and 0.8 (large)

Discussion

In a sample of people with recently-diagnosed coeliac disease, the Overall index, Symptoms, and Worries and concerns scores have been found to be responsive to change. The remaining dimensions (Stigma, Dietary burden, and Social isolation) were less responsive. This study highlights the challenges faced assessing responsiveness in coeliac disease, where much of the impact on quality of life is as a result of following a gluten-free diet. Although the study aimed to include people with newly-diagnosed coeliac disease, the mean time since diagnosis at the time of the baseline survey was approximately 5 months. Therefore, in this sample, some changes (e.g. improvement in symptoms) would have occurred prior to the respondent's enrolment in the study, whereas other changes (e.g. reduced stigma or dietary burden) may take longer to occur or may not occur in a sample that continues to follow a gluten-free diet. The study also lacked a specific intervention. To overcome this, the CDAQ's responsiveness should be assessed in clinical trials of therapeutic treatments which aim to supplement or replace the gluten-free diet. An analysis using anchor-based indicators of responsiveness is underway.

Acknowledgements and funding

We would like to thank Coeliac UK for their recruitment support and the respondents for taking part in the study. The study was funded by Coeliac UK. Michele Peters is a senior researcher of the Department of Health funded Policy Research Unit on Quality and Outcomes of Person-centred care (QORU), a collaboration between the London School of Economics and Political Science (LSE) and the Universities of Kent and Oxford.

Estimating the quality of life impact of Coeliac Disease diagnosis using retrospective population self-reports

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Introduction and Aims

Despite a general improvement in pathways to diagnosis, Coeliac Disease (CD) may still be diagnosed only after a long period of sometimes severe symptoms. These symptoms may cause significant discomfort and anxiety to the sufferers and their families by negatively impacting on:

quality of life 

relationships 

social lives 

work opportunities 

Aims: to quantify the quality of life impact of CD, before and after diagnosis, for patients and their carers, and explore its variation over time, across geographical areas of the UK and by socioeconomic groups of the population

Methods

Study design: A retrospective postal survey, similar to one we conducted in 2006 was carried out at the end of 2015.

Participants: A representative, geographically stratified, sample of 4000 individuals diagnosed with Coeliac Disease, drawn from the membership list of Coeliac UK, with the expectation of obtaining a response rate of 40% (~1,600 responses), which was successfully achieved.

Collected data: data on socio-demographic characteristics of respondents, time to and since diagnosis, type and duration of symptoms, quality of life before and after diagnosis of both patients and their families, NHS services used and other costs.

Statistical analysis: descriptive and regression-based methods used to tease out the key drivers of differences in quality of life before and after diagnosis among different socioeconomic strata of the population over time.

How was Quality of Life measured?

Using the **EuroQol EQ-5D** questionnaire. It contains 5 simple questions each concerned with a different area or "domain" of everyday life: ***mobility***, ***self care***, ***usual activities*** such as work, study, housework and leisure activities, ***pain/discomfort*** and ***anxiety/depression***.

For each of these questions, respondents said whether they had ***no problems***, ***some problems***, or ***extreme problems***. The answers to these questions provided a description or profile of the respondent's quality of life. Using these answers and applying a well-validated algorithm (formula)[1], an overall **measure of quality of life** was estimated, which ***ranges from 1= full health to 0 = death***.

Selected Results

Table 1 - Socio-demographic characteristics of the participants in the 2015 survey

Characteristics	*No. of patients (%)*
Current (2015) age of respondent	55.7 (20.1)†
Age of respondent at diagnosis (years)	44.2 (19.5)†
Gender	
Male	432 (27.3%)
Female	1151 (72.7%)
Annual family income (gross)	
Less than £10,000	115 (7.7%)
£10,000 - £20,000	319 (20.4%)
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UK Region of residency	
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Northern Ireland	41 (2.9%)
Not reported	162(10.2%)

† Mean and standard deviation

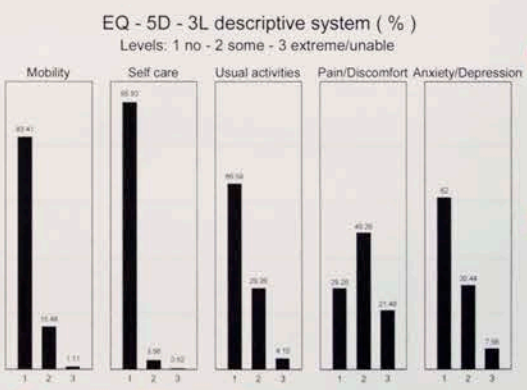

Figure 1A – EQ-5D Before Diagnosis

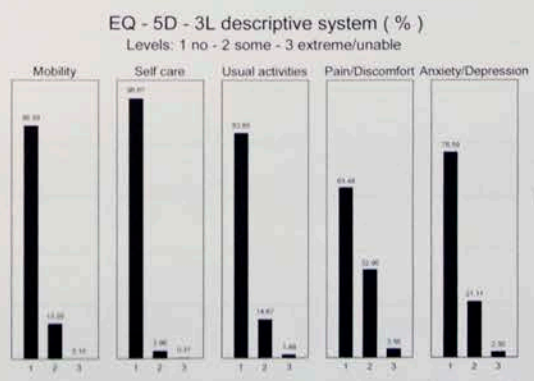

Figure 1B- EQ-5D After Diagnosis (time of survey)

Figures 1A and **1B** report the percentage of respondents at different levels of each of the 5 questions comprising the EQ-5D.

In all 5 dimensions of the EQ-5D, the proportion of respondents reporting no problems was significantly higher at the time of the survey compared to before diagnosis: this was particularly pronounced in the pain dimension, with 63.5% reporting to have no problems at the time of the survey, compared to only 29.3% prior to diagnosis of Coeliac Disease.

The distribution across the three levels of the five dimension of the EQ-5D observed in the 2015 Survey data was similar to the one observed in the 2006 Survey.

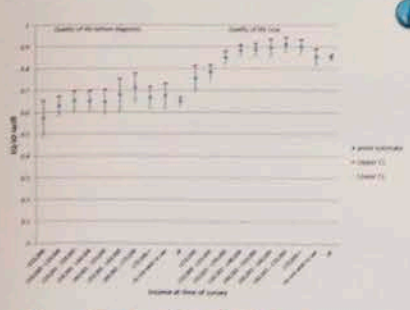

Figure 2 – Quality of Life by income

Figure 2 displays the Quality of Life (QoL) reported by respondents, by income. **Before diagnosis**, QoL rises from 0.57 (95% CI: 0.49, 0.65) among those with an annual family income lower than £10,000 to 0.67 (95% CI: 0.62, 0.72) among those with an annual family income larger than £70,000.

At the time of the survey, QoL rises from 0.75 (95% CI: 0.69, 0.81) for those with an annual family income less than £10,000 to 0.90 (95% CI: 0.87, 0.93) for those with an annual family income larger than £70,000.

Placing valuations on the EQ-5D health states using the British "tariff" (algorithm/formula) [1], the mean Quality of Life **before diagnosis** was **0.65**, (where 0 = death and 1 = full health), and **0.85** at the **time of the survey**, indicating a highly statistically significant improvement of 0.20 (95% CI: 0.18, 0.22). By comparison, the average quality of life in the general population has been reported as 0.80 when age-standardised to age of respondents at time of survey response, or 0.85 when age-standardised to age of respondents at diagnosis.

Results not shown, indicate that Quality of Life (QoL) was clearly related to age before diagnosis, rising from 0.58 (95% CI: 0.53, 0.63) amongst those aged 18-34 when diagnosed to 0.76 (95% CI: 0.73, 0.80) amongst those aged 65 and over at diagnosis. No differences by age in reported QoL was noted at the time of the survey (after diagnosis).

Discussion

- Quality of life of people with undiagnosed symptomatic Coeliac Disease is substantially reduced compared to the general population (by 0.65)
- Quality of life of coeliac people increases markedly after diagnosis (by 0.20)
- Our survey data indicated that the disease is diagnosed only after, on average, 12 years and 9 months, of sometimes severe symptoms. The 2006 survey found that the disease was diagnosed after, on average, 13 years. Therefore in the last 9 years time to diagnosis has not substantially improved.
- Our results underscore the importance of further improving early detection of the disease to better the quality of life of people affected by it, especially among people living in deprivation.

[1] Dolan et al. The time trade-off method: results from a general population. *Health Economics* 1996;5(2):141-54

Acknowledgements: this research was funded by Coeliac UK

Significance of different access routes for gluten free bread and implications for people with coeliac disease

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INTRODUCTION

In the UK, 1 in 100 people has coeliac disease[1], a lifelong autoimmune condition treated by a strict gluten free (GF) diet for life. Non-adherence to the diet can result in long term complications including anaemia, osteoporosis and in rare cases, small bowel cancer[2]. This research examines access to GF bread, a key staple in the diet, in three areas of deprivation in Aylesbury, Buckinghamshire.

METHODOLOGY

A street by street survey identifying locations where food could be accessed was carried out to collect data on the availability of gluten-containing (GC) and GF bread in food shops and pharmacies in three Lower Level Super Output Areas (LLSOAs) in Aylesbury (Gatehouse, Quarrendon and Southcourt)[3], classified as being in the second most deprived decile of deprivation, Index of Multiple Deprivation (IMD level 2)[4]. These data were mapped using Geographical Information System[5] software to model access to bread.

In each of the three areas the following information was collected; locations of pharmacies, locations and types of all retail outlets selling groceries (food shops), and information on the stocking of bread:

a. Did the food shop sell a standard loaf of bread? Any brand of packaged bread loaf counted, e.g. small, large, sliced or unsliced, white, brown, wholemeal or seeded. If yes, how many varieties were available?
b. Did the food shop sell a GF loaf of bread? Any brand of packaged GF bread loaf counted, e.g. large, sliced or unsliced, white, brown, wholemeal or seeded. If yes, how many varieties were available?

RESULTS

A total of 21 stores sold groceries across the three areas, see Table 1.

Table 1. Number of shops stocking GC and GF bread in the three LLSOA areas.

	Gatehouse	Quarrendon	Southcourt	Total
Total number of shops	11	2	8	21
Shops selling GC bread (%)	11 (100%)	2 (100%)	8 (100%)	21 (100%)
Shops selling GF bread (%)	2 (18%)	1 (50%)	1 (12.5%)	4 (19%)

Of the 21 stores surveyed, all stocked a standard loaf of GC bread. Only four (19%) of the 21 stores surveyed stocked GF bread. Figures 1 and 2 show the distribution of shops selling GC and GF loaves of bread.

The number of varieties of GC bread loaves available varied from 1 to 63 with an average of 12 different types. The number of varieties of GF bread loaves available in these stores varied from 1 to 13 with an average of 5 different types.

The stores which stocked GF bread were the major supermarkets and supermarket 'local' stores. GF bread was not available in any of the small chain/franchise convenience stores, independent convenience stores, newsagents or petrol station shops.

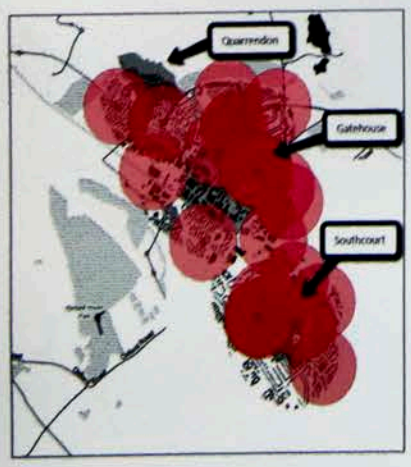

Figure 1. Distribution of shops selling standard GC bread. Map shows location with 400 metre (m) walking distance shown as red circular isochrones.

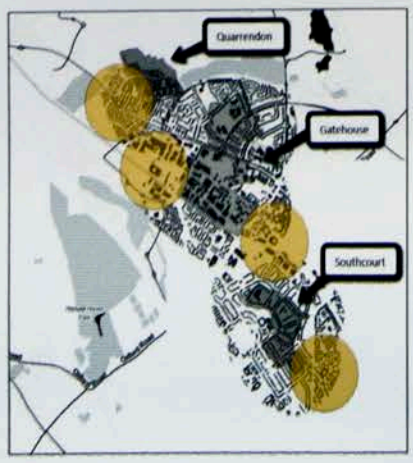

Figure 2. Distribution of shops selling GF bread. Map shows locations with 400 m walking distance shown as yellow circular isochrones.

Pharmacy locations

There were a total of six pharmacies within the three study areas, which doubled the locations where GF bread was available, see Figures 3 and 4.

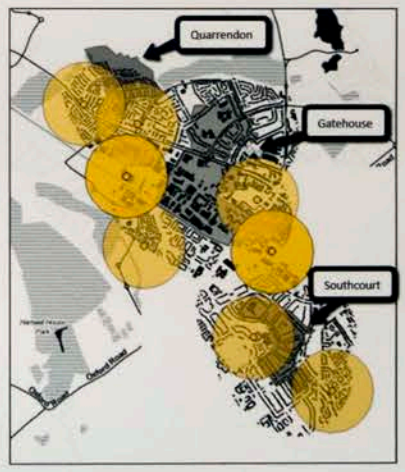

Figure 3. Distribution of outlets (shops and pharmacies) providing access to GF bread. Map shows locations with 400 m walking distance isochrones.

Figure 4. Distribution of outlets (shops only) selling GF bread. Map shows locations with 400 m walking distance isochrones.

CONCLUSION

Access to GF bread was very limited in the areas studied. Whilst 100% of stores stocked a loaf of gluten-containing bread only 19% of stores stocked gluten free bread.

Gluten free bread was not available in any of the small chain/franchise convenience stores, independent convenience stores, newsagents or petrol station shops.

Access to gluten free bread via community pharmacies provided an important access route in the areas investigated where limited availability existed in shops.

REFERENCES

[1]West et al. 2003
[2]NICE, 2015
[3]Office for National Statistics, 2015
[4]Buckinghamshire Business First, 2015
[5]QGIS, 2015

A comparison of the nutritional content of a range of commercial and prescription gluten free bread products.

By M. Barne & N. Powell, Addenbrooke's Hospital, Cambridge

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Introduction

Prescription gluten free (GF) food is restricted or no longer available in many areas across the UK. Therefore people with coeliac disease are increasingly reliant on commercially available products. In a gluten-containing diet 30% of calcium and 44% of iron intake is derived from cereals and cereal products (Henderson et al, 2003), but in the past GF substitute products have often been shown to be not naturally rich or fortified with iron (Thompson 2000).

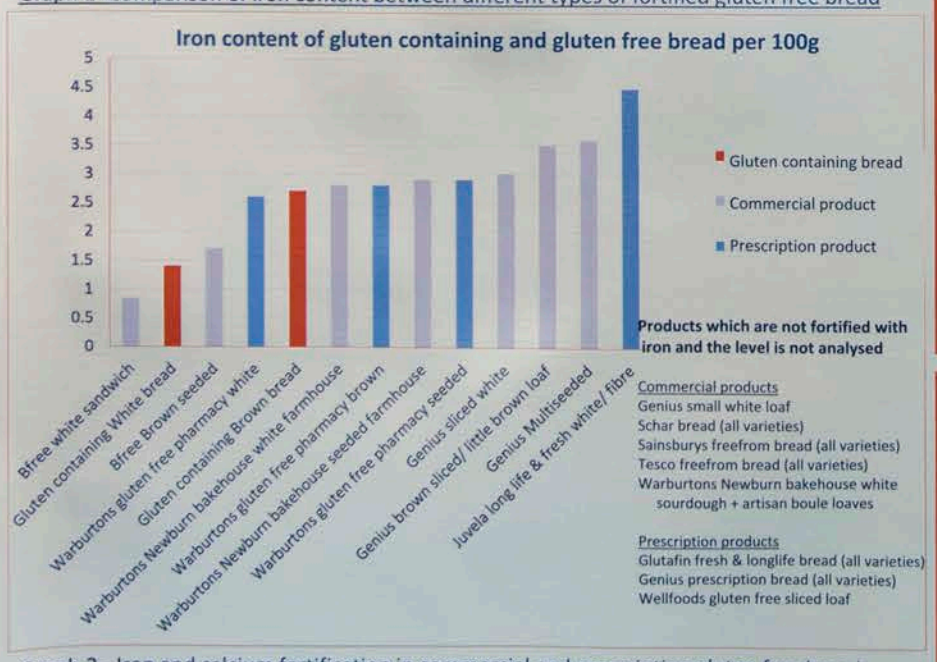
Table 1 -Comparison of calorie and fat content of GF and gluten containing breads

	Average portion size (g)	Kcal per 100g	Fat (g) content per 100g	Iron (mg) per 100g in fortified products	Calcium (mg) content per 100g in fortified products
GF bread (n=26)					
White	32	254	6.1	2.2 (n=3)	280 (n=3)
Brown/seeded	34	265	8.2	3.0 (n=5)	248 (n=5)
Average	33	260	7.3	2.7	260
Range	25-50	190-338	1.1-12.7	0.84-3.6	39-639
Prescription GF bread (n=17)					
White	36	244	5.7	1.9 (n=3)	222 (n=5)
Brown/seeded	34	254	6.9	1.5 (n=4)	220 (n=8)
Average	35	251	6.5	1.6	221
Range	29-50	203-316	2.5-14.1	2.6-4.5	120-630
Gluten containing bread					
White (n=5)	40	236	2.1	1.5	155
Brown/seeded/wholemeal (n=26)	40	231	4	2.3	147
Average	40	234	3.1	1.9	151

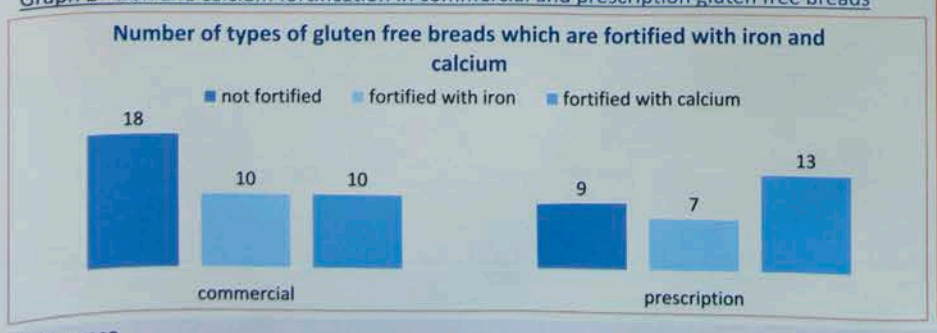
Method

Nutritional content data for GF bread was collected directly from manufacturers, food labels or supermarket websites (Sep 2016-Jan 2017). Information on kcal, fat, iron and calcium was obtained from 6 commercial and 5 prescription only manufacturers. This was compared with the nutritional composition of gluten containing bread (Public Health England, 2015).

Graph 1 -Comparison of iron content between different types of fortified gluten free bread



Graph 2 - Iron and calcium fortification in commercial and prescription gluten free breads



Results

Data was collected for 43 GF breads; nutrient content varied greatly between manufacturers (*shown in table 1*). Compared with gluten containing bread, GF substitute breads were typically higher in kcals and fat (up to 11% increase in kcals and 135% increase in fat); the majority (95%) of GF breads had higher fat content. Where GF breads were fortified they contained equivalent or higher content of calcium and iron (*shown in graph 1*). However many companies do not fortify or analyse the iron and calcium content; only 8/26 (31%) commercial GF breads and 13/17 (76%) prescription GF breads surveyed were fortified with iron and/or calcium (*shown in graph 2*). Some GF breads not fortified do contain calcium based preservatives or mineral rich seeds but as the levels are not analysed nutrient contribution is uncertain.

Discussion

Nutritional content of GF substitute breads varies greatly between manufacturers and products; the majority of GF breads are higher in fat then the gluten containing breads. GF products that are fortified with iron and calcium typically have equivalent or higher iron and calcium content, however in the GF breads not fortified the content of these nutrients was often uncertain. From the survey, a higher proportion of the prescription GF breads were fortified than commercial GF breads. Products should be considered on an individual basis but as it is not compulsory to report micronutrient content on packaging it can be difficult to compare products.

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