Should we be diagnosing coeliac disease in the elderly?

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Introduction

Coeliac disease (CD) is common, but is underdiagnosed in the elderly due to lack of physician awareness and heterogeneity of presentation. We aimed to establish whether there has been a change in the diagnosis of CD in the elderly (over 65 years old) from 1990 until present day, as well as the clinical and histopathological features of CD in old versus young adults.

Methods

Newly diagnosed CD patients were prospectively recruited from the Coeliac Specialist Clinic at the Royal Hallamshire Hospital, Sheffield, between 2008 and 2017. All patients had villous atrophy (VA) on biopsy, positive coeliac serology (IgA-tissue transglutaminase and / or IgA-endomysial antibodies) and compatible Human Leukocyte Antigen (HLA) typing. Additionally, patients were retrospectively identified from 1990 to 2008 to determine the trend in elderly CD diagnostic frequency over time.

Results

1605 patients with CD were recruited (n=644 prospectively, n=961 retrospectively). Of these, 208 patients (13.0%) were diagnosed over the age of 65 years between 1990 and 2017. The proportion of elderly CD diagnoses increased from 0% (n=0/11) in 1990-1991 to 18.7% (n=41/232) in 2016-2017 (p<0.001). The male to female ratio decreased with increasing diagnostic age from 1.71:1 in the 18-34 age group to 1.02:1 in the over 65 age group (p<0.001). Younger patients more commonly presented with fatigue (p<0.001) and gastrointestinal symptoms including diarrhoea (p=0.005), abdominal pain (p=0.019), and IBS-type symptoms (p=0.008), as seen in Table 1. Older individuals most commonly presented with iron deficiency anaemia, followed by folate deficiency and B12 deficiency. Older people more frequently presented with B12 deficiency (p=0.037) and had milder degrees of VA than younger patients (p=0.005) (see figure 2).

Table 1 - Association between clinical features at presentation and age at coeliac disease diagnosis

Presenting feature	Prevalence in overall prospective cohort (n=644)	Age (years) 18-34 (n=258)	35-64 (n=287)	≥65 (n=99)	p-value
Fatigue	24.9% (160)	31.8% (82)	23.0% (66)	12.1% (12)	**<0.001**
Diarrhoea	30.4% (196)	35.7% (92)	30.0% (86)	18.2% (18)	**0.005**
Abdominal pain	23.2% (149)	29.1% (75)	20.2% (58)	16.2% (16)	**0.019**
IBS-type symptoms	18.0% (116)	24.4% (63)	15.0% (43)	10.1% (10)	**0.008**
Iron-deficiency anaemia	30.4% (225)	34.5% (89)	37.3% (107)	29.3% (29)	0.312
Folate deficiency	24.4% (157)	20.2% (52)	28.6% (82)	23.2% (23)	0.071
B12 deficiency	12.1% (78)	10.5% (27)	10.8% (31)	20.2% (20)	**0.037**

Figure 2 - Association between marsh grade at presentation and age at coeliac disease diagnosis (n=626)

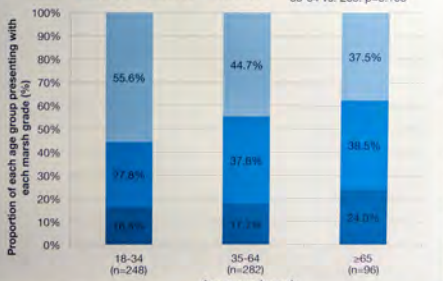
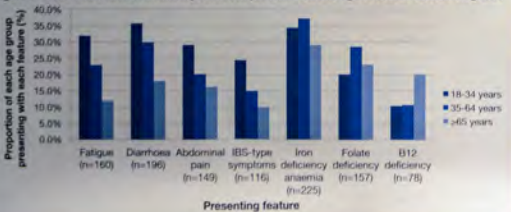


Figure 1 - Association between clinical features at presentation and age at coeliac disease diagnosis



DISCUSSION

Coeliac disease is common in elderly patients but gastrointestinal symptoms occur less frequently than in younger individuals. Elderly patients tend to present with a milder degree of VA. This questions the utility of active case finding in this age group, as a gluten-free diet may not be the most appropriate management in this cohort.

Coeliac disease - Older patients have the most extensive small bowel involvement on capsule endoscopy.

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Introduction

The relationship between symptomatology, serology and findings on small bowel capsule endoscopy (SBCE) in patients with coeliac disease (CD) remains unclear. Clarifying such associations will help determine if symptoms and serology can predict severity and extent of disease on SBCE.

Methods

Patients with newly diagnosed CD (villous atrophy on duodenal histology and positive CD serology) were recruited. Patients underwent a SBCE at the time of diagnosis. Information on SBCE was recorded. Signs and symptoms at presentation, serological markers, histological classification of disease in the duodenum were noted.

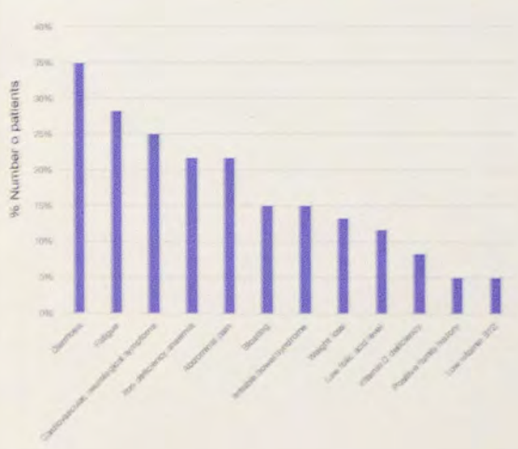

Figure 1: Signs and symptoms of patients at presentation.

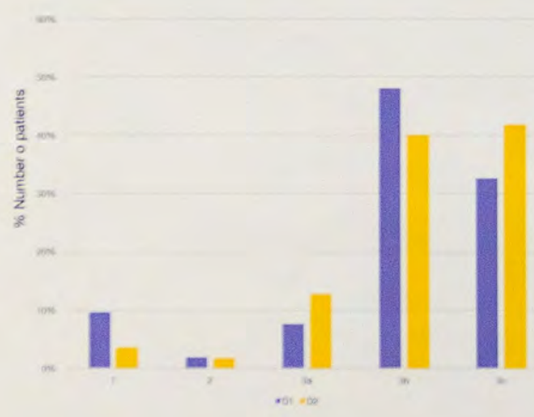

Figure 2: Marsh classification of disease

Figure 3: Scalloping of mucosal folds in the duodenum on (a) gastroduodenoscopy, (b) on small bowel capsule endoscopy;

Results

Sixty patients with newly diagnosed CD (mean age 44.9 years SD□17.4, 17 - 76) were included in this study. Older patients (p=0.025) and patients presenting with iron deficiency anaemia had more extensive small bowel (SB) involvement (p=0.026). Patients presenting with weight loss were more likely to have SB involvement beyond the duodenum (p=0.027). Patients presenting with iron deficiency anaemia (p=0.038) and weight loss (p=0.009) were significantly older at diagnosis. Serum albumin was lower in those patients diagnosed later on in life (p=0.007).

There was no significant association between anti-tissue transglutaminase antibody (p=0.396) and extent of affected SB mucosa.

Patients with more severe Marsh classification of disease on histology from the duodenal bulb had more extensive SB involvement (p=0.017).

CONCLUSION

This is the largest study on newly diagnosed CD and SBCE. Older patients are likely to have more extensive disease on SBCE at diagnosis. Symptoms and serology had no impact on the findings on SBCE apart from weight loss and iron deficiency anaemia.

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Capsule endoscopy in coeliac disease: The role of Flexible Spectral Imaging Colour Enhancement.

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Introduction

Flexible spectral imaging colour enhancement (FICE) is a form of virtual chromoendoscopy that is incorporated in the capsule reading software and that can be used by reviewers to enhance the delineation of lesions in the small bowel. This has been shown to be useful in the detection of pigmented (ulcers, angioectasias) lesions. However, its application to coeliac disease (CD) images from small bowel capsule endoscopies (SBCEs) has rarely been studied.

Methods

This was a European, multicentre study that included 5 expert capsule reviewers who were asked to evaluate a number of normal and abnormal deidentified images from SBCEs of patients with CD to determine whether the use of FICE and blue light can improve the detection of CD related changes.

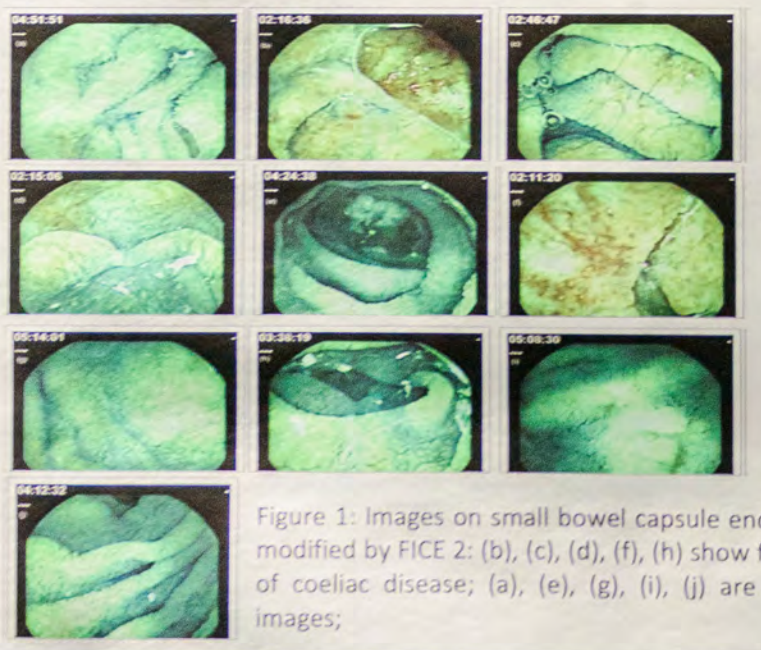

Figure 1: Images on small bowel capsule endoscopy modified by FICE 2: (b), (c), (d), (f), (h) show features of coeliac disease; (a), (e), (g), (i), (j) are normal images;

Table 1: Favoured modality of conventional white light or different FICE settings by all the 5 reviewers;

	Normal white light	Fice 1	Fice 2	Fice 3	Blue light
Mean sensitivity	100%	80%	76%	60%	48%
Mean specificity	100%	100%	96%	92%	96%

Table 2: Fleiss' Kappa co-efficient for normal light and FICE settings;

	Total	Conventional white light	FICE 1	FICE 2
K	0.107	-0.122	0.189	0.149
Standard error	0.073	0.095	0.129	0.129
Z	1.451	-1.284	1.447	1.151
P	0.147	1.801	0.148	0.250
Lower	-0.037	-0.309	0.066	-0.104
Upper	0.250	0.064	0.440	0.402

Results

There was no difference between conventional white light, FICE and blue light for the identification of CD related changes. There was a low agreement (Fleiss Kappa 0.107; p=0.147) between expert reviewers in selecting the best image modification that detected CD related changes.

Figure 2: Fissuring of mucosa in a patient with coeliac disease on small bowel capsule endoscopy: (a) conventional white light; (b) FICE 1; (c) FICE 2; (d) FICE 3; (e) blue light;

CONCLUSION

FICE and blue light were not found to be superior to conventional white light in the delineation of macroscopic changes related to CD on SBCEs.

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The association of Small Capsule Endoscopy and Bone Mineral Density in Patients with Coeliac Disease.

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Introduction

Osteoporosis is an established complication of coeliac disease (CD). Adherence to a gluten free diet is important for the small bowel (SB) to heal and to improve calcium and vitamin D absorption, both of which are important in bone formation and repair.

Methods

Patients with histologically proven CD were recruited. Small bowel capsule endoscopy (SBCE) was carried out within 2 months of obtaining duodenal histology. BMD was carried out within 12 months of SBCE.

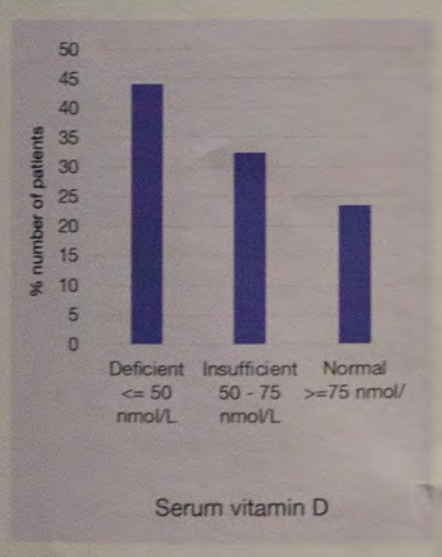

Figure 1 Serum vitamin D in patients with coeliac disease;

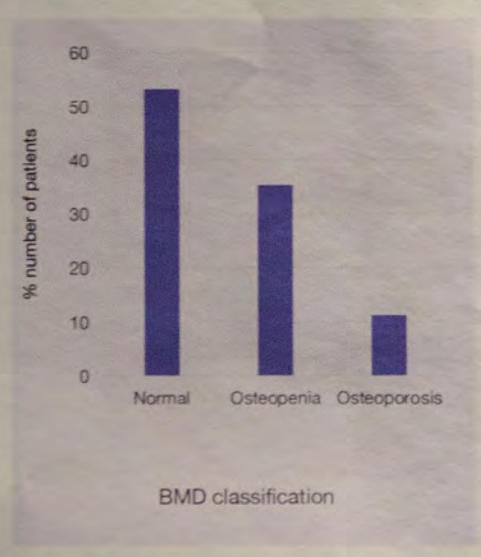

Figure 2 BMD classification in the cohort studied;

Table 1: Correlation of BMD with extent of disease in patients with CD (univariate analysis);

All CD	Time with abnormality (Pearson correlation co-efficient, p value)	Time without villi (Pearson correlation co-efficient, p value)	Total small bowel transit (Pearson correlation co-efficient, p value)	% length of abnormal small bowel (Pearson correlation co-efficient, p value)	% time without villi (Pearson correlation co-efficient, p value)
BMD g/cm2 lumbar spine	-0.253, 0.032	-0.158, 0.212	0.150, 0.214	-0.239, 0.044	/, 0.0001
BMD g/cm2 total hip	-0.238, 0.036	-0.090, 0.467	-0.155, 0.183	-0.202, 0.080	-0.168, 0.226
T score lumbar spine	-0.277, 0.020	-0.183, 0.155	0.150, 0.223	-0.254, 0.035	/, 0.0001
T score total hip	-0.244, 0.034	-0.118, 0.351	-0.186, 0.115	-0.197, 0.093	-0.169, 0.237

Table 2: Correlation of BMD with extent of disease in patients with CD (multivariate analysis);

	BMD g/cm² Lumbar spine (B co-efficient / p value)		BMD g/cm² Total hip (B co-efficient / p value)		T score lumbar spine (B co-efficient / p value)		T score total hip (B co-efficient / p value)	
Smoking (Non-smokers / Ex-smokers / Smokers)	-0.08	0.03	-0.09	0.01	-0.82	0.02	-0.73	0.01
Age at SBCE (years)	-0.01	0.016	-0.01	0.01	-0.03	0.01	-0.03	0.01
% length of abnormal small bowel mucosa on SBCE	-0.01	0.038	-0.01	0.05	-0.02	0.03	-0.01	0.13
Gender	-0.01	0.86	-0.07	0.07	0.17	0.67	-0.05	0.86
EMA	0.09	0.058	0.05	0.28	0.84	0.04	0.30	0.35
Anti-TTG	0.01	0.401	0.01	0.55	-0.01	0.13	-0.01	0.28

Results

A total of 80 patients (68.8% females, 56.3% newly diagnosed) with CD were included.

- Mean age - 48.3 years 17.3.
- Mean anti-TTG - 53.9 65.4 U/ml
- EMA - positive in 49 patients (61.3%)
- Mean calcium - 2.35 0.079 mmol/l (2.20 - 2.60)

In patients with newly diagnosed CD, age at SBCE correlated inversely with BMD (T score lumbar spine p=0.022, T score total hip p=0.0004, overall score p=0.0001). This was also true in patients with established CD (T score lumbar spine p=0.013, T score total hip p=0.048, overall score p=0.019).

CONCLUSION

This is the first study that demonstrates that extent of SB involvement on SBCE corresponds to increased severity of BMD particularly in the elderly. They should be treated aggressively to improve BMD and should be monitored closely with regular repeat BMDs.

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Capsule Endoscopy in Established Coeliac Disease: Clinical symptoms, extent of disease and small bowel transit.

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Introduction

Patients with established coeliac disease (CD) can present with recurrent symptoms requiring further investigations including small bowel capsule endoscopy (SBCE). There is paucity of data on the relationship between the extent, severity of disease and small bowel transit (SBT) on capsule endoscopy in relation to histology, clinical and serological parameters.

Methods

Hundred patients with CD and 200 controls were recruited. All of these patients underwent a SBCE because of symptoms, abnormal serology or a suspicion of complications. Extent of disease SBCE and SBT were studied in relation to symptomatology, serology and severity of histology from the duodenum.

Figure 1: Small bowel transit in patients with coeliac disease vs controls (minutes);

Table 1: Correlation of factors with percentage of affected small bowel mucosa;

	Univariate analysis		Multiple regression analysis	
Factor	Spearman's rho / Mean	Significance (P value)	Unstandardized Coefficients	Significance (P value)
Age at the time of SBCE	Spearman's rho 0.283	0.006	0.057	0.854
Age at diagnosis of CD	Spearman's rho 0.171	0.106	0.018	0.941
Presence of symptoms	No symptoms 19.1% vs symptoms 15.9%	0.613	-3.475	0.543
EMA at SBCE	Spearman's rho 0.0001	0.140	5.645	0.512
Anti-TTG at SBCE	Spearman's rho 0.131	0.245	-0.001	0.986
Albumin at SBCE	Spearman's rho -0.312	0.004	-1.623	0.036
Vitamin B12 at SBCE	Spearman's rho -0.061	0.587	-0.034	0.001
Folic acid level at SBCE	Spearman's rho 0.001	0.992	-1.475	0.008
Haemoglobin level at SBCE	Spearman's rho -0.382	0.0001	-0.302	0.117
Marsh score of D1 biopsies	Spearman's rho 0.558	0.0001	10.494	0.018
Marsh score of D2 biopsies	Spearman's rho 0.558	0.0001	-5.835	0.174
Refractory coeliac disease (RCD)	No RCD 11.6% vs RCD I 24.5% vs RCD II 41.5%	0.007	5.552	0.212

Figure 2: Features of coeliac disease on small bowel capsule endoscopy: (a) villous atrophy, (b) scalloping, (c) ulcers, (d) nodularity, (e) mosaic pattern, (f) fissuring of folds;

Results

In patients with CD, 30 (30.0%) had a normal SBCE, 56 patients (56.0%) had proximal small bowel (SB) involvement, 7 patients (7.0%) had proximal and mid SB involvement and 7 patients (7.0%) had diffuse disease.

SBT was shortest in controls (275.0; range 60.0 – 981.0 minutes), followed by those with established CD but a normal SBCE (260.0; range 104.0 – 467.0 minutes) and those with established CD and macroscopic evidence of CD on SBCE (286.0; range 60.0 - 981.0 minutes) (p=0.0001).

CONCLUSION

Patients with CD have a persistently prolonged SB transit even if there is no evidence of disease on SBCE. This is the first study showing correlation between extent of disease and severity of duodenal histology according to the Marsh classification.

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Type 1 Diabetes: Screening for Coeliac Disease and Quality Standards Audit

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Background

People with Type 1 Diabetes Mellitus (T1DM) are at increased risk of other autoimmune conditions such as Coeliac Disease (CD). NICE published CD guidelines (Sep 2015) recommending that all T1DM patients are screened for CD at diagnosis. NICE also released CD quality standards (Oct 2016). There are also several other CD guidelines from specialist societies which vary in the detail of their recommendations. However, all recommend that screening for CD is carried out in patients with Type 1 Diabetes.

This audit focuses on how well: (a) the NICE CD guideline (Sept 2015) to screen all T1DMs for CD at diagnosis and (b) NICE quality standards (Oct 2015) are being met within the East and North Herts Trust (ENHT) hospital T1DM population.

Aims

1) To review the total population of current T1DM patients (defined as having attended the acute MDT DM clinic in the last 18 months) registered on the East and North Herts hospital diabetes database (CIPTS) and to identify how many had received CD serological testing (IgA tissue transglutaminase tTG test).
2) To look at 2 further T1DM sub groups and identify how many had received CD serological testing. These were:
- Current 19-50 year olds, diagnosed with T1DM for up to 10 years
- Newly diagnosed with T1DM between 2015 – 2016

3) To assess whether the NICE CD Quality Standards (QS) (Oct 2016) – had been met in those newly diagnosed with T1DM and had positive CD serological screening between 2015 – 2016. The NICE CD Quality Standards (Oct 2016) recommend:
QS1) People at increased risk e.g. T1DM or with symptoms of coeliac disease are offered a serological test for CD.
QS2) People with positive serological tests are referred to a specialist.
QS3) People referred to a specialist who need an endoscopic intestinal biopsy to diagnose CD, have it within 6 weeks of referral.
QS4) People newly diagnosed with CD discuss how to follow a gluten free (GF) diet with a healthcare professional with specialist knowledge of CD.
QS5) People with CD are offered an annual review.

Methods

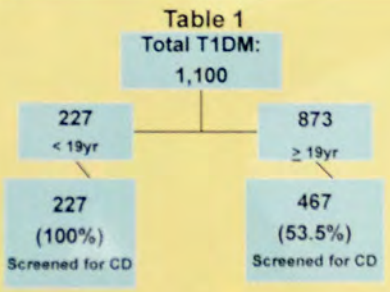
Interrogation of CIPTS (acute diabetes clinical database), completed in February 2017. Subsequent interrogation of ICE (pathology reporting system), completed in July 2017 for adults diagnosed with T1DM between 2015 – 2016. Analysis of paper and electronic clinical notes for T1DMs with raised tTG levels for the CD quality standards.

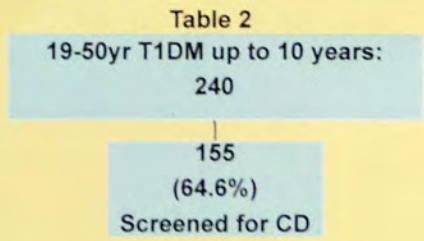
Results

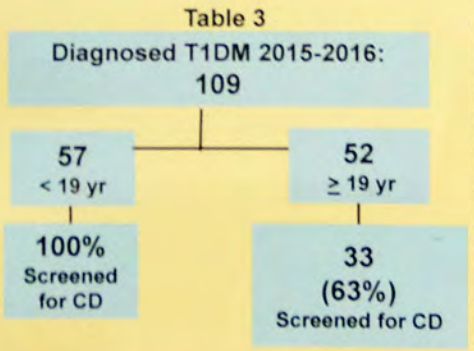
Table 1
Table 1 shows the current total T1DM population in ENHT.
This identified that 53.5% of T1DM adults had received serological testing for CD. The figure was 100% in children and young people (CYP).

Table 2
Table 2 shows that 64.6% of adults (19 - 50 year old, diagnosed with T1DM for up to 10 years) had received serological testing for CD.

Table 3
Table 3 shows that 100% of CYP and 63% (33) adults diagnosed with T1DM between 2015 - 2016, had received serological testing for CD.







Meeting the 5 CD Quality Standards (QS)
- Between 2015-2016, there were 4 paediatric and 1 adult newly diagnosed T1s screened for CD (QS1) that had raised IgA TTG >7 u/ml.
- Based on their clinical note and CIPTS entries, there was no reference to them being referred to a Gastroenterologist (QS2) nor of having biopsies (QS3) (Biopsies are not always indicated for paediatric patients [5,6]).
- All 4 paediatric patients had documentation of receiving specialist GF dietary advice (QS4). However, there was nothing mentioned for the T1 adult.
- Annual review (QS5) was pending.

Limitations of the audit

1. Lack of consistent recording of T1 diagnosis date and CD diagnosis on CIPTS.
2. Incomplete data transfer of serological data from ICE to CIPTS.
3. Possible inclusion of records from out of area patients.

Conclusions

The audit showed that the NICE guidelines (2015) for screening T1 patients is being met in the children and young persons population. However, screening in adults needs to be improved.
The 5 quality standards for CD have not been fully met in those diagnosed with T1DM in 2015 – 2016.

Recommendations

1. To improve serological testing for adults with T1DM by introducing a 'care bundle' i.e. a standardised blood request form including CD tTG test for those newly diagnosed. This is currently being actioned.
2. Implement screening for CD once every three years (as recommended by Coeliac UK and BSPGHAN) within ENHIDE and community Diabetes care. Discussion on how to achieve this needs further exploration.
3. For those T1DMs with CD, to continue to offer an initial consultation with a dietitian and refer for a review as appropriate.
4. Improved recording of data within the CIPTS diabetes database especially for T1DM and CD diagnosis dates.
5. CYP Services to liaise with Paediatric Gastroenterologist regarding quality standard 2 and 3. ENHIDE also to liaise with adult gastroenterologists to review the pathway for referral. These have been initiated.
6. To send tTG blood test forms to the 19 adult patients diagnosed with T1 between 2015-2016 that had not been screened for CD.
7. To re-audit in 2018 - 2019.

References

1. Type 1 Diabetes in Adults: Diagnosis and Management (NICE guideline 28 August 2015)
2. Coeliac Disease: Recognition, Assessment and Management (NICE guideline 2 September 2015)
3. Coeliac Disease: Quality Standard (19 October 2016)
4. Diagnosis and Management of adult Coeliac Disease: Guidelines from the British Society of Gastroenterology (15 June 2014)
5. European Society for Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Diagnosis of Coeliac Disease. JPGN 54(1), Number1, January 2012
6. and ESPGHAN and Coeliac UK guidelines for the diagnosis and management of coeliac disease in children. Munich, Jenkins, Auth et al Arch Dis Child 2013 98: 806-811 2013
7. Measures for Children and Young People's Diabetes 2013. DH England
8. Screening for Coeliac Disease in adult patients with Type 1 Diabetes mellitus-implications and controversies. Sakhar et al. Diabetol Metab Syndr (2016) 8:51
9. Coeliac Disease screening in children with type 1 diabetes mellitus: is it time for a risk approach. Sodnkorth, Patel, Makaya. Practical Diabetes Vol 33 No.8 377-380

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Phenotypic and genetic characteristics of those following a gluten free diet in UK Biobank

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Background

Following a gluten free (GF) diet has increased in popularity in recent years amongst those who do not have a diagnosis of coeliac disease.

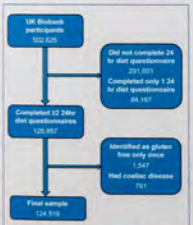
In the US, GF diets amongst those without coeliac disease increased from 0.52% in 2009 to 1.69% in 2013-14 (Hyun-seok et al., 2016).

Aim – In the current study we aimed to investigate the phenotypic and genetic characteristics of those who follow a GF diet, an area that has been underexplored to date.

Methods

Participants were selected from UK Biobank, a cohort of women and men aged 40-69 years recruited between 2006-2010.

All participants attended one of 22 baseline assessment centres located in England, Scotland and Wales.



Flow chart demonstrating selection of final sample

At baseline participants completed:

- Touchscreen questionnaire on demographics, lifestyles & health
- Verbal interview on health
- Physical measures
- 24 hour dietary questionnaire (~71,000)

During follow-up, participants:

- Completed up to four online 24 hour dietary questionnaires
- Record linkage to hospital inpatient data (1996 to 2016), which provided diagnoses of coeliac disease.

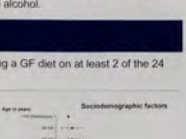
Logistic regression was used to investigate the association between a range of characteristics and following a GF diet.

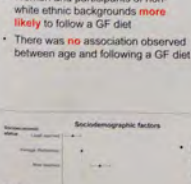
The analyses were adjusted for age, sex, ethnicity, socioeconomic status, education, body mass index, smoking and alcohol.

Results

1,789 (1.4%) participants reported following a GF diet on at least 2 of the 24 hour dietary questionnaires

- Women and participants of non-white ethnic backgrounds **more likely** to follow a GF diet
- There was **no** association observed between age and following a GF diet

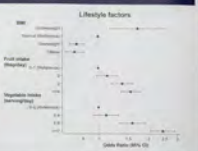


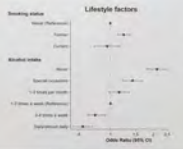


- Participants who lived in the least socio-economically deprived areas were **less likely** to follow a GF diet, whereas those from the most deprived areas were **more likely** to follow a GF diet
- Participants with a higher education were **more likely** to follow a GF diet

Results

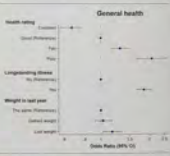
- Participants who were underweight were **more likely** to follow a GF diet, whereas those who were overweight or obese were **less likely** to follow a GF diet
- Participants who had a higher fruit and vegetable intake were **more likely** to follow a GF diet

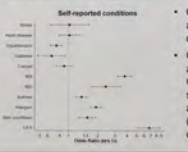




- Former smokers were **more likely** to follow a GF diet. There was **no** association with current smoking
- Participants who drank less alcohol were **more likely** to follow a GF diet

- Participants who rated their health as excellent were **less likely** to follow a GF diet
- Those who rated their health as fair or poor and reported having a longstanding illness were **more likely** to follow a GF diet
- Participants who lost weight in the last year were **more likely** to follow a GF diet

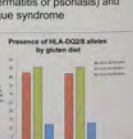




- Certain conditions were associated with a **reduced** likelihood of following a GF diet, such as hypertension and diabetes
- Other conditions were associated with an **increased** likelihood of following a GF diet, including irritable bowel syndrome, inflammatory bowel disorder, asthma, allergies, skin conditions (eczema, dermatitis or psoriasis) and chronic fatigue syndrome

There was little difference in the presence of HLA DQ2/8 haplotypes, which predispose individuals to coeliac disease, between those who follow a GF diet and those who do not

- **41.8%** GF vs **42.4%** non GF had 0 alleles
- **45.6%** GF vs **45.6%** non GF had 1 allele
- **12.6%** GF vs **12%** non GF had 2 alleles



Summary

- Following a GF diet is associated with a range of healthy characteristics, such as a lower BMI, eating more fruit and vegetables, being a former smoker and having a lower alcohol intake.
- Despite this, following a GF diet is also associated with a poorer perception of health and a range of non-cardiovascular conditions.
- These findings raise the possibility that some people choose to follow a GF diet in order to manage a range of health conditions and are not more likely to be genetically predisposed to coeliac disease.

Acknowledgements

This research was conducted using the UK Biobank resource under Application Number 18532. We are grateful to the participants for dedicating a substantial amount of time to take part in the UK Biobank study as well as the staff who make it possible.

Nuffield Department of POPULATION HEALTH

No Association Between HLA-DQA1*05 and -DQB1*02 Gene Dosage and Clinical Phenotype of Coeliac Disease

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Introduction

Coeliac disease is a common gluten-sensitive enteropathy. Disease susceptibility is strongly associated with specific Human Leukocyte Antigen (HLA)-DQA1 and -DQB1 loci. Individuals with the HLA-DQA1*05:HLA-DQB1*02 heterodimer (referred to as HLA-DQ2.5) have the highest risk of developing coeliac disease, particularly if two copies of HLA-DQB1*02 are present[1]. Understanding whether differences in the frequency of DQA1*05 and DQB1*02 accounts for differences in the clinical phenotype of coeliac disease is important for the development of personalised medicine for patients and was addressed in the following study.

Methods

Demographic, clinical and laboratory data was retrospectively collected from adult patients attending the specialist coeliac disease clinic, Royal Hallamshire Hospital between 2008 to 2016 and correlated with the number of DQA1*05:DQB1*02 combinations forming the DQ2.5 heterodimer, as well as the frequency of DQB1*02.

Results

Four hundred and ninety patients had serology and biopsy-proven coeliac disease and complete HLA genotype information. Patients were categorised according to the four possible DQA1-DQB1 allele combinations forming a functional DQ2.5 heterodimer (DQ2.5 heterodimer gene dose) – detailed in Table 1.

Table 1	0% DQ2.5 (n=45)	25% DQ2.5 (n=233)	50% DQ2.5 (n=130)	100% DQ2.5 (n=82)
HLA Genotype	DQ2.2/2.2; DQ2.2/X; DQ2.2/8; DQ8/X; DQ8/8; DQ8/8, A*05; DQ7.5/X	DQ2.5/X; DQ2.5/8; DQ2.2/7.5	DQ2.2/2.5; DQ2.5/7.5	DQ2.5/2.5

Individuals positive for the DQ2.5 heterodimer were more likely to be EMA positive than those who were DQ2.5 negative (p=0.0132). There were no clear linear associations between the DQ2.5 gene dosage and clinical or laboratory parameters assessed (Table 2).

Table 2	0% DQ2.5	25% DQ2.5	50% DQ2.5	100% DQ2.5	sig.*
Gender; female (n)	76% (34)	69% (161)	64% (83)	63% (52)	ns
Age at diagnosis; years (IQR)	42 (22-53)	43 (29-56)	39 (25-54)	34 (24-52)	ns
Villous atrophy; % Marsh 3c (n)	56% (25)	46% (106)	52% (68)	52% (43)	ns
EMA status; % positive (n)	78% (35)	93% (216)	83% (108)	87% (71)	ns
Weight loss (n)	16% (7)	9% (20)	7% (9)	12% (10)	ns
Diarrhoea (n)	36% (16)	36% (83)	33% (42)	42% (34)	ns
Hb; g/L (SD)	129.7 (15.5)	134.5 (18.4)^	128.2 (19.7)^	133.1 (18.4)	ns
Ferritin; ug/L (IQR)	24 (14-74)	35 (17-81)	26 (9-54)	29 (15-61)	ns
Folate (IQR)	7.4 (5.2-9.0)	7.0 (5.4-9.8)^	5.8 (4.0-7.8)^	6 (4.2-8.9)	ns
B12; ng/L (IQR)	317 (252-490)	323 (256-427)	323 (231-422)	322 (252-409)	ns
Albumin; g/L (SD)	44 (6)	44 (4)	44 (4)	44 (5)	ns

*Bonferroni correction for multiple comparisons was applied.

^ Significant difference in folate and Hb levels between 25% and 50% DQ2.5 group (p=0.001).

Results

Patients were also categorised according to the number of DQB1*02 alleles present; detailed in Table 3.

Table 3	DQB1*02 negative (n=22)	DQB1*02 Single (n=278)	DQB1*02 Double (n=190)
HLA type	DQ8/X; DQ8/8; DQ8/8 A*05; DQ7.5/X	DQ2.5/X; DQ2.2/7.5; DQ2.5/7.5; DQ2.2/X; DQ2.5/8; DQ2.2/8	DQ2.5/2.5; DQ2.2/2.5; DQ2.2/2.2

The prevalence of folate deficiency was higher and serum folate and haemoglobin levels lower, in individuals carrying two copies of DQB1*02 than those with a single copy of DQB1*02 (p=0.0031, p=0.0007 and p=0.0272, respectively), but neither were different in DQB1*02 negative individuals (p>0.05) (Figure 1).

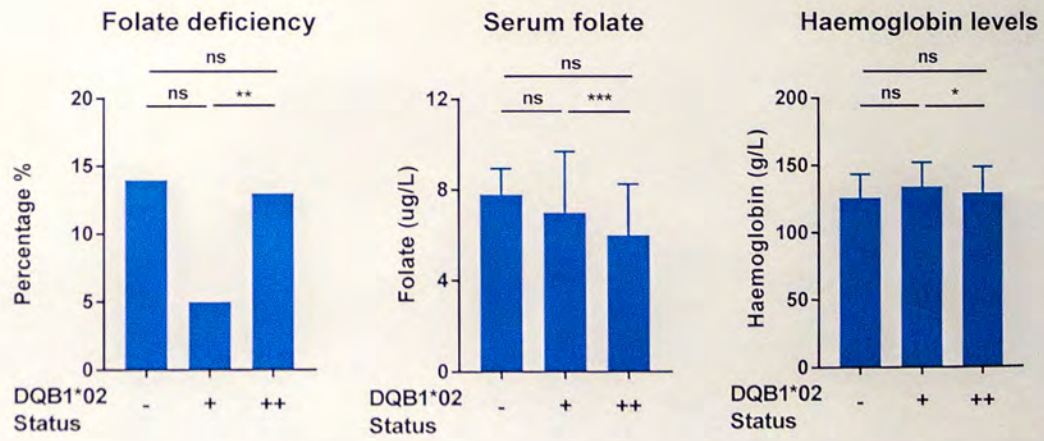

Figure 1. Percentage folate deficiency and serum folate (median; IQR) and haemoglobin levels (mean, +/-SD) in patients with coeliac disease, grouped according to HLA-DQB1*02 status.

The carriage of two copies of DQB1*02 did not correlate with any other demographic or clinical parameters (Table 4).

Table 4	DQB1*02 Negative	DQB1*02 Single	DQB1*02 Double	sig.
Gender; female (n)	82% (18)	69% (192)	64% (122)	ns
Age at diagnosis; years (IQR)	36 (16-65)	43 (29-56)	35 (24-53)	ns
Villous atrophy; % Marsh 3c (n)	59% (13)	45% (125)	55 (104)	ns
EMA status; % positive (n)	82% (18)	90% (250)	86% (163)	ns
Weight loss (n)	5% (1)	9% (26)	10 (19)	ns
Diarrhoea (n)	36% (8)	35% (96)	37% (71)	ns
Ferritin; ug/L (IQR)	42 (11-99)	31 (17-78)	27 (10-55)	ns
B12; ng/L (IQR)	290 (241-572)	324 (256-431)	322 (240-420)	ns
Albumin; g/L (SD)	43 (7)	44 (4)	44 (5)	ns

Conclusions

- **Our results suggest that there is no association between homozygosity / heterozygosity for DQA1*05 and DQB1*02 and the clinical phenotype of coeliac disease.**
- **These results provide an important insight into the interpretation of HLA-DQ data in the setting of coeliac disease.**

1. Ploski R, et al. *Tissue Antigens* 1993;4 (4):173-177.

Use of T cell-specific RNA in situ hybridisation as a novel test to distinguish malignant (lymphomatous) and benign (inflammatory) T cell infiltrates: A possible new approach in the diagnosis of **refractory coeliac disease**.

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1. Department of Pathology, University of Cambridge, 2. Radcliffe Department of Medicine, University of Oxford
3. Roche Tissue Diagnostics, Tucson, Arizona, 4. Weatherall Institute of Molecular Medicine, University of Oxford

Principles: A small proportion of people with coeliac disease develop refractory coeliac disease (RCD), with type I RCD showing features akin to active coeliac disease and type II RCD showing features similar to an early T-cell lymphoma (figure 1). Differentiating between these two types of RCD is very clinically important, but is difficult with common histopathological, flow cytometric and PCR-based clonality testing (figure 2). We present here our recently developed approach to distinguishing between T-cell lymphoma and benign T-cell lymphoid infiltrates, which we believe could provide a clear distinction between RCD types I and II. Our approach to T-cell infiltrates is similar to that used for B cell infiltrates, which relies on kappa/lambda light chain staining (figure 3). If all the lymphoid cells are of the same light chain type, they are malignant (lymphomatous), while a mixture indicates they are benign (inflammatory). For T-cells, using the same principles, we have identified two T cell-specific, mutually exclusively expressed, RNA sequences (TRBC1 and TRBC2), corresponding to the two, alternatively employed, T-cell receptor beta constant regions (figures 4 – 7), for which skewing away from a 1:1 ratio indicates likely lymphoma.

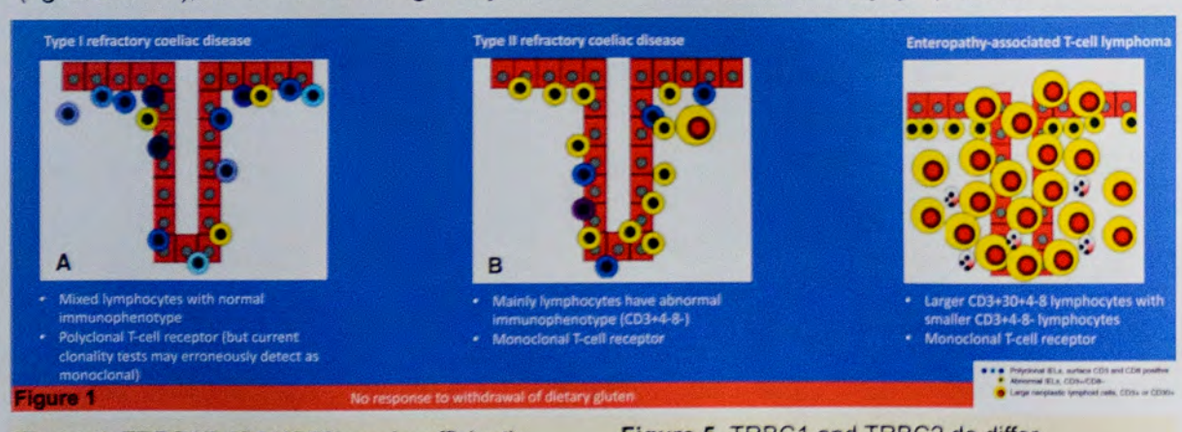
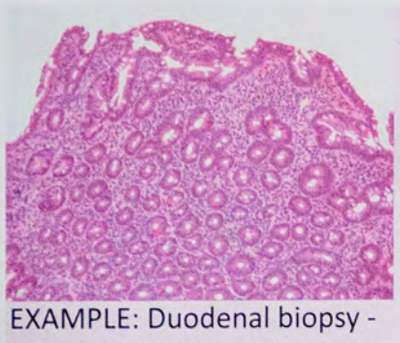


Figure 1



EXAMPLE: Duodenal biopsy - active coeliac disease vs type II refractory coeliac disease.

- Expensive
- Slow
- Not always definitive
- Specialist centres only

Figure 2

Figure 4. TRBC1/2 (Cβ1/Cβ2) are insufficiently different to distinguish at amino acid level (below) by immunostaining, due to difficulties making Cβ1/Cβ2 specific monoclonal antibodies.

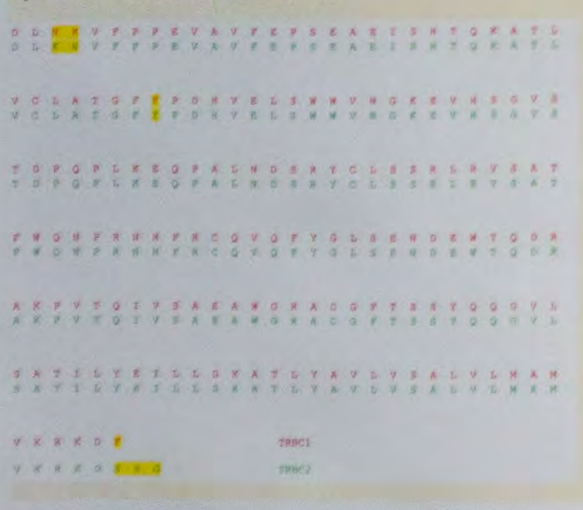
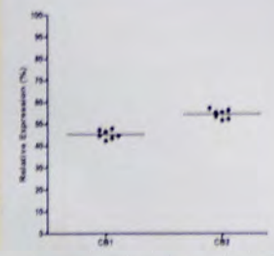


Figure 5. TRBC1 and TRBC2 do differ substantially at RNA level in the 3' untranslated region indicating the need to detect TRBC1/2 at RNA level by in situ hybridisation

TRBC1:
GTCAAGAGAAAGGATTTCTGAAGGCAGCCCTGGAAGTGGAGTTAGGAGCTTCTAACCCGTCA
TGGTTTCAATACACATTCTTCTTTTGCCAGCGCTTCTGAAGAGCTGCTCTCACCTCTCTGCATCC
CAATAGATATCCCCCTATGTGCATGCACACCTGCACACTCACGGCTGAAATCTCCCTAACCCAG
GGGGACCTTAGCATGCCTAAGTGACTAAACCAATAAA

TRBC2:
GTCAAGAGAAAGGATTCCAGAGGCTAGCTCCAAAACCATCCCAGGTCATTCTTCATCCTCACC
CAGGATTCTCCTGTACCTGCTCCCAATCTGTGTTCCTAAAAGTGATTCTCACTCTGCTTCTCATCT
CCTACTTACATGAATACTTCTCTCTTTTTTCTGTTTCCCTGAAGATTGAGCTCCCAACCCCCAAG
TACGAAATAGGCTAAACCAATAAA

Figure 6. Q-PCR to investigate relative expression levels shows an approximate TRBC1:TRBC2 ratio of 1:1 in peripheral blood mononuclear cells, indicating a likely 1:1 ratio in normal tissues.



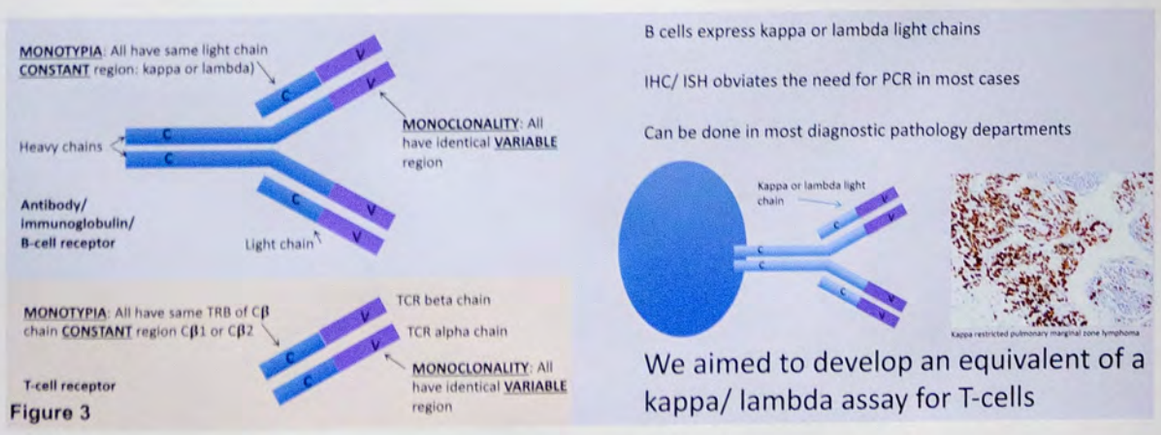
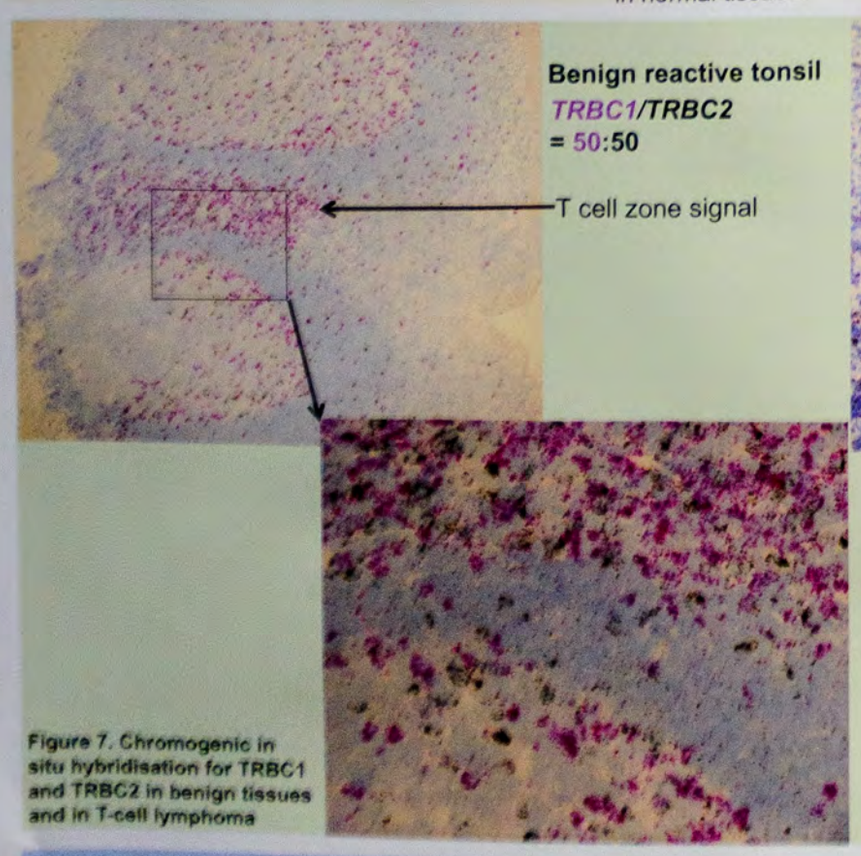
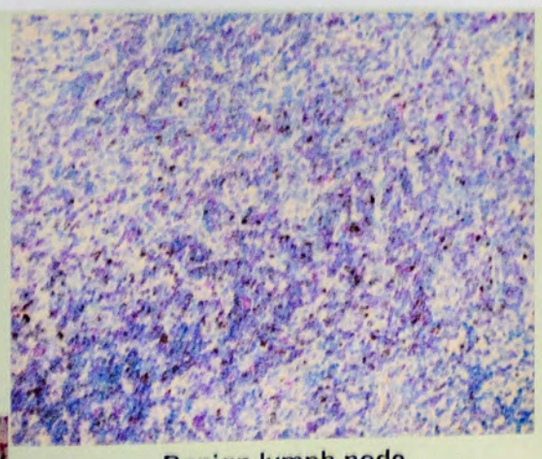
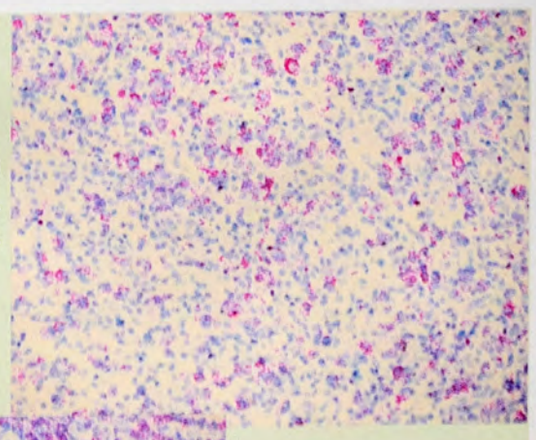


Figure 3

We developed TRBC1/TRC2 segment-specific probes for single and duplex chromogenic in situ hybridisation (CISH), which we validated on FFPE sections of T-cell lymphoma/ leukaemia lines, T-cell lymphoma (n=100) and corresponding benign tissue (n=100). Below we show their utility in separating benign and lymphomatous infiltrates of T-lymphocytes.







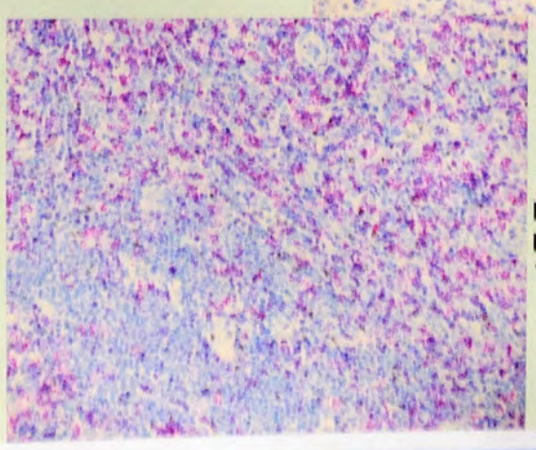


Figure 7. Chromogenic in situ hybridisation for TRBC1 and TRBC2 in benign tissues and in T-cell lymphoma

Conclusion: This is the basis of a novel diagnostic test for T-cell lymphoma, applicable to FFPE sections. In a manner analogous to the transformation in B-cell lymphoma diagnosis contributed by kappa/ lambda staining, we believe that our TRBC1/2 CISH test has the potential to transform both the diagnosis of T-cell lymphoma and the distinction between type I and type II RCD. We wish to build a collaborative consortium to collect RCD cases for further validation of T-cell testing strategy.

References: 1. Malamut, G. et al. Refractory celiac disease: From bench to bedside (2012) Seminars in Immunopathology 34(4):601-13 2. Ho-Yen, C,. et al. Recent advances in refractory coeliac disease: a review (2009) Histopathology 54, 783–795. 3. Van Dongen, J.J.M. et al., Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: Report of the BIOMED-2 Concerted Action BMH4-CT98-3936 (2003) Leukemia volume17, pages2257–2317 4. Ogg, G., et al. T-cell Monotypia and Clonality. UK Patent Application No. 1417498.1 (2014)

Non-Responsive and Refractory Coeliac Disease: The largest UK experience from the NHS England Rare Diseases Collaborative Network.

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[1]Academic Unit of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, UK

Introduction

Non-responsive coeliac disease (NRCD) is defined by persisting symptoms or laboratory abnormalities in patients with coeliac disease (CD) despite a gluten-free diet (GFD). Causes of NRCD are heterogeneous, with refractory CD (RCD) being associated with poor prognosis.[1]

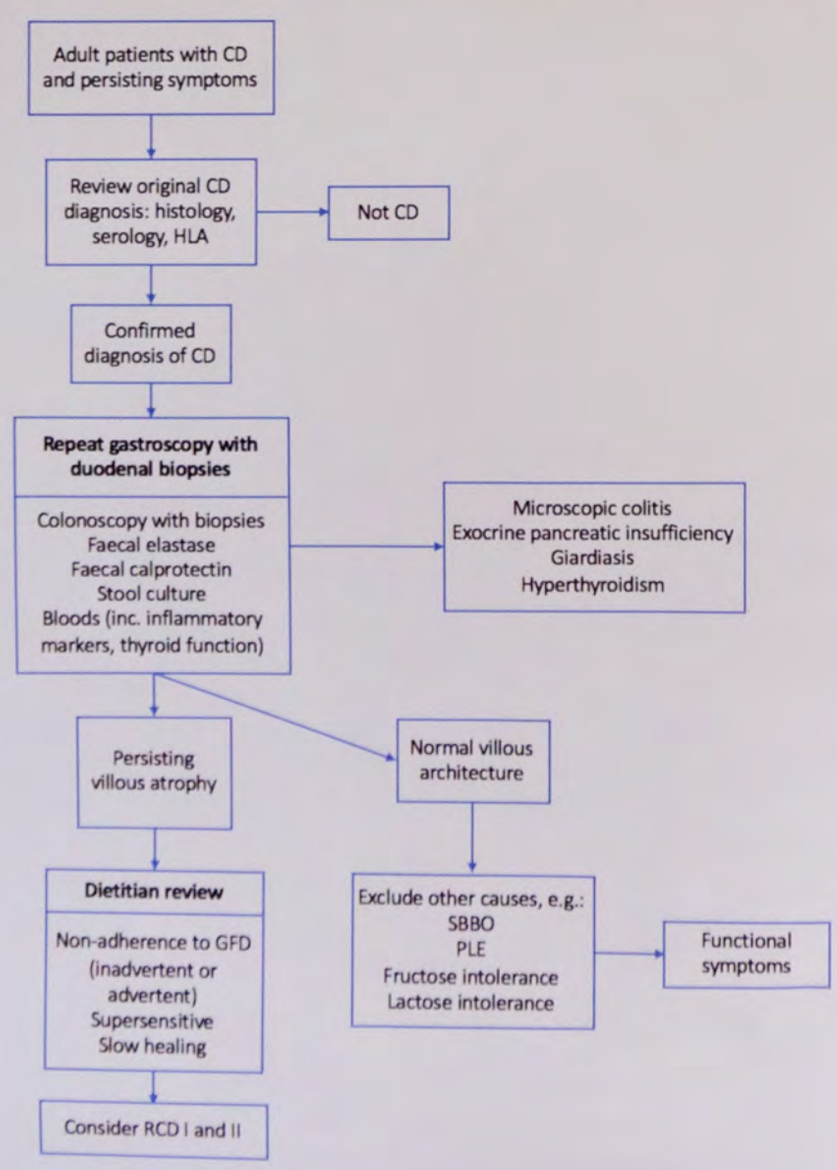
Aims

1) To identify the aetiologies for persisting symptoms in patients with NRCD referred to a national UK centre for CD.
2) To assess mortality rates in RCD I and RCD II groups.

Methods

Data on all CD patients, including those with persisting symptoms and tertiary referrals, was collected prospectively from 1998-2018. Patients were systematically investigated to establish the aetiology of their continued symptoms (figure 1). They were also referred to a specialist coeliac dietitian to identify any lapses in GFD adherence or gluten cross-contamination. A repeat duodenal biopsy was performed and compared to previous biopsies where possible to check for histological remission. Colonoscopy, lactose hydrogen breath test, glucose hydrogen breath test, SeHCAT scan, CLO testing, faecal elastase, immunohistochemistry and γ-TCR clonality were performed.

Figure 1 | Algorithm for investigating persisting symptoms in CD.



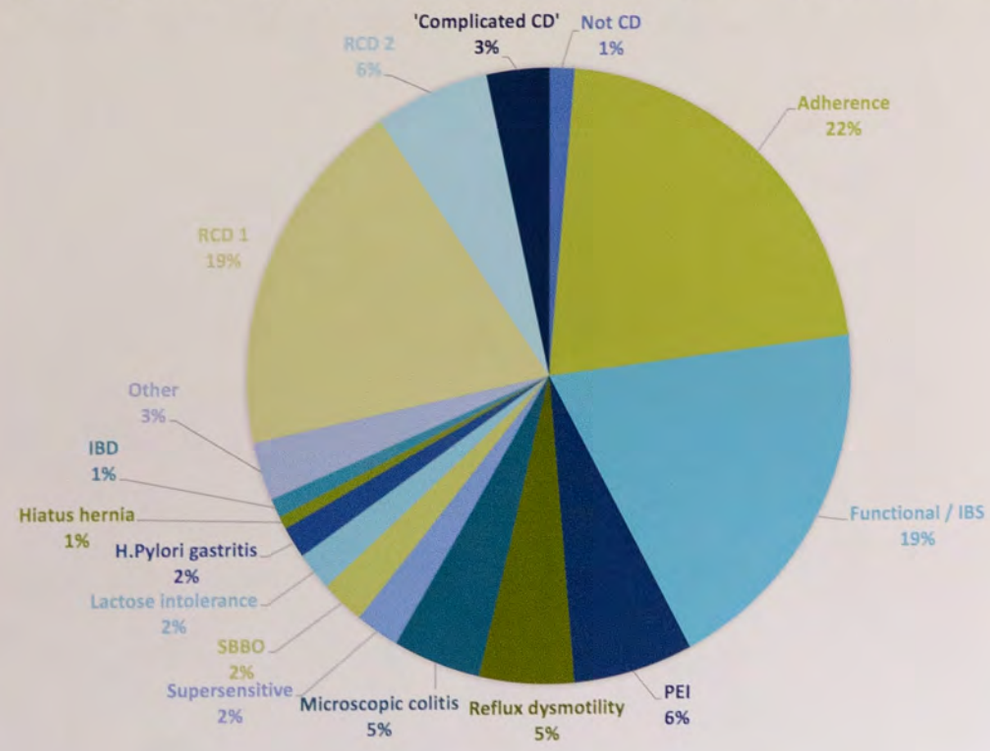
Results

Patients with confirmed CD

2,356 patients with suspected CD were seen in this time period (121 were tertiary referrals). 157 were excluded from analysis due to unconfirmed diagnosis. Of the remaining 2,199 patients with confirmed CD, 2,123 had both villous atrophy and positive IgA-EMA/TTG, and 76 had seronegative CD. Of the 2,199 patients with CD (67% female, mean age at diagnosis 42.8 ± 18.5), 292 (13%) had persisting symptoms.

Aetiologies for Persisting Symptoms

Figure 2 | Aetiologies found for persisting symptoms in patients with CD.

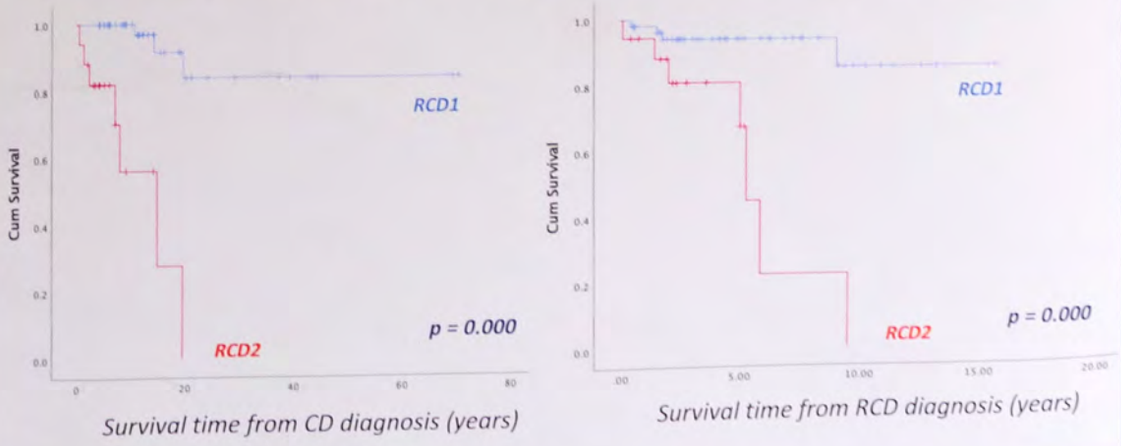


Outcomes for RCD I Vs. RCD II

Table 1 | Characteristics and outcomes of RCD I vs. RCD II.

	RCD I (n = 57)	RCD II (n = 18)	P value
Mean age at CD diagnosis (SD)	41.8 (± 19.0)	55.4 (± 13.3)	0.003
Median delay between CD and RCD diagnosis, years (IQR)	5.5 (2.0-11.0)	1.0 (1.0-3.0)	0.002
Gender (n = female)	41 (71.9%)	6 (33.3%)	0.006
Mean survival from CD diagnosis (years) [95% CI]	61.6 [95% CI 52.1-71.1]	11.9 [95% CI 41.3-62.7]	0.000
Mean survival from RCD diagnosis (years) [95% CI]	14.1 [95% CI 12.8-15.6]	5.53 [95% CI 3.56-7.51]	0.000

Figure 3 | Kaplan Meier curves displaying survival in RCD 1 vs. RCD II.



Discussion

This is the largest ever study of NRCD and RCD, and the largest study of RCD in the UK, providing insight into outcomes in RCD. The contemporary mortality data in RCD II remains poor. Patients with suspected RCD should be referred to the National Centre for consideration of novel therapies such as IL-15 and Stem Cell Transplant.

References: (1) Evans, K., & Sanders, D. (2009). Symposium 1: Joint BAPEN and British Society of Gastroenterology Symposium on 'Coeliac disease: Basics and controversies' Coeliac disease: Optimising the management of patients with persisting symptoms?: Conference on 'Malnutrition matters'. *Proceedings of the Nutrition Society*, *68*(3), 242-248. doi:10.1017/S0029665109001360