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# **Long-term care for patients with Coeliac Disease in the UK: A review of the literature and future directions.**

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## **Abstract**

Coeliac disease is a common digestive disorder that affects 1% of adults. It is characterised by mucosal damage of the small intestine caused by dietary gluten. The main treatment for coeliac disease is a lifelong gluten-free diet, which can reduce morbidity and mortality and also improve quality of life. Despite the benefits, adhering to this diet is often challenging, with patients often struggling to sustain dietary restriction. Structured follow-up for coeliac disease is recommended in international guidelines for improving adherence and for detecting complications, however uncertainty exists as to exactly who should be administering this follow-up care. Here we undertake a review of the current approaches described in the literature to follow-up patients with coeliac disease, and assess the efficacy of these differing models. We also explore future directions for the care of these patients in the context of the UK National Health Service (a publicly funded healthcare system). Although the focus of this review pertains to follow-up within the UK healthcare system, these problems are recognised to be international, so findings are likely to be of interest to all healthcare professionals seeing and managing patients with coeliac disease.

**Keywords:** Coeliac Disease, Follow-up, Efficacy, Adherence

## **Introduction**

Adult coeliac disease (CD) is an immune mediated small bowel enteropathy, which affects 1 in 100 people <sup>(1)</sup>. It occurs in genetically susceptible individuals and is triggered by gluten, which is a protein found in wheat, barley and rye. The commonest age for diagnosis is between 40 and 60 years old, however it can occur at any age, with women 1.5 to 2 times more likely to develop the condition than men <sup>(2)</sup>. Undiagnosed CD significantly impacts on health related quality of life (HRQoL), with HRQoL described previously as being comparable to stroke patients <sup>(3; 4)</sup>.

Adult coeliac disease is protean and patients may present with gastrointestinal symptoms, weight loss, anaemia, reduced bone mineral density, or in association with other autoimmune diseases (for example, Type 1 Diabetes or autoimmune thyroid disease) <sup>(1)</sup>. The detection rates for CD have increased from 1 in 8 in 1999 to 1 in 5 to 2011 <sup>(5; 6)</sup>. Therefore provision of aftercare is essential. Currently, the only accepted treatment for CD is lifelong adherence to a gluten-free diet (GFD). This allows restoration of the structure and function of the small intestinal mucosa. The amount of gluten shown to prevent histological recovery has been reported to be as small as 1 mg per day, thus strict adherence is of utmost importance <sup>(7)</sup>. Adherence to a GFD has also been shown to improve morbidity, quality of life and potentially mortality <sup>(3; 8; 9; 10; 11; 12)</sup>. This benefit in mortality may be confined to symptomatic patients, with recent studies from the UK and Finland showing no increased mortality in those undetected and subsequently untreated. <sup>(13; 14)</sup>

Specifically relating to malignancy, historical work demonstrated that patients with untreated CD had higher rates of malignancy than the general population (oropharyngeal and oesophageal cancer relative risk (RR) 22.7,  $P < 0.001$ ; lymphoma RR 77.8  $P < 0.001$ ; and small bowel carcinoma standardized incidence ratio of 25) <sup>(15; 16; 17)</sup>. However, more recent studies have downgraded this risk. <sup>(18; 19)</sup> The relationship between persisting histological changes and small bowel lymphoma is well described <sup>(20)</sup>. Strict adherence has been reported to correlate with histological remission, and patients on a GFD for more than 5 years have the same overall risk of malignancy as the general population <sup>(15; 16)</sup>.

Although lifelong careful GFD adherence is advocated, often patients find this difficult, with reported strict adherence rates ranging between 42% and 91% <sup>(21; 22)</sup>. This adherence is strongly associated with cognitive, emotional and socio-cultural influences, membership of an advocacy group and on having regular dietetic follow-up <sup>(22)</sup>. Given the difficulties, national and international guidelines advocate long-term follow-up for CD, to help control any ongoing symptoms, facilitate adherence to a GFD, and avoidance or early detection of complications <sup>(1; 23; 24; 25)</sup>. This is supported by a recent systematic review on long-term management of CD <sup>(26)</sup>. Despite being advocated, uncertainty currently exists about who, when and how exactly follow-up care should be provided for patients with CD <sup>(27)</sup>.

The aim of this narrative review is to evaluate the different types of follow-up that have been described in the medical literature, and also evaluate the differing tools used to assess dietary adherence to a GFD. Findings will be of interest and potential relevance to healthcare professionals who see and manage patients with CD.

## **Methods**

An electronic search of the literature was conducted using the online databases PubMed and Web of Science entering the query terms ‘Coeliac Disease’, ‘Celiac disease’, ‘adherence’, ‘compliance’, ‘follow-up’, ‘service provision’, ‘gluten free diet, using and/or Boolean connectors. Studies retrieved were limited to the English language and had no time limitations applied. Approximately 400 identified articles were screened, and all articles discussing the subject matter of this review were thoroughly reviewed. Articles from alternative sources were also thoroughly assessed and incorporated into this review if deemed relevant to the subject matter of this review.

## **Different methods of follow up**

### **Hospital Outpatient Follow-up**

Follow-up in hospital outpatients is one way that follow-up care may be provided for patients with coeliac disease <sup>(28)</sup>. This may involve reviews with gastroenterologists, dietitians or assessments in a dedicated coeliac specialist clinic, encompassing a multidisciplinary team. Currently, uncertainty exists as to the exact number of patients who actually receive this care and a paucity of evidence demonstrating that improvements in long-term outcomes are achieved. A previous historical study suggested that a dedicated doctor-led coeliac follow-up clinic could improve adherence to a GFD (97.5% adherence in doctor-led clinic vs. 40.4% for those no longer under follow-up) <sup>(29)</sup>. This work has limitations however in being an observational study with potential biases and also being from a single centre. Supporting the merits of hospital follow-up is a small survey of patients with coeliac disease (n=126), where hospital follow-up ranked highly with patients as to the way they wanted follow-up care to be delivered <sup>(30)</sup>.

### **Primary Care follow-up**

The Primary Care Society for Gastroenterology (PCSG) from the United Kingdom advised in their guideline from 2006 that following diagnosis patients with CD should be reviewed at 3 and 6 months in the gastroenterology department, and then following satisfactory progress and management of their diet reviewed annually in primary care <sup>(24)</sup>. This method of follow-up has potential advantages in delineating those individuals requiring specialist support in secondary care due to persisting symptoms, whilst also reducing the burden on hospital gastrointestinal services to deliver follow-up care for all CD patients. In a nationwide study from Finland, the decentralisation of coeliac disease follow-up from tertiary centers to primary health care providers was not associated with a detriment in dietary adherence <sup>(31)</sup>. Although these findings provide reassurances about this model of care, follow-up care for CD within primary care in the United Kingdom remains highly variable. This approach could be supported by further research establishing patients' satisfaction with such a service. Furthermore, ascertaining whether general practitioners felt able and competent to deliver comprehensive follow-up services for CD would be valuable.

## Community Pharmacy Follow-up

Other healthcare professionals could potentially help reduce the burden of delivering follow-up care. Currently, research is ongoing looking at how pharmacists could be utilised in the care of patients with CD <sup>(32; 33)</sup>. In Scotland a gluten free food service (GFFS) was introduced to the community pharmacy contract in April 2014 as a pilot service, and then subsequently fully introduced across the country in October 2015. This service aimed to support the provision of direct NHS pharmaceutical care to patients with coeliac disease or DH, by providing a national pharmacy-led consistent service. In addition, the GFFS service aimed to provide appropriate clinical monitoring for patients including dietetic intervention and annual pharmacy health checks. A review of this service undertaken in September 2015 from major stakeholders (1571 patients, 357 community pharmacists and 516 General practitioners) demonstrated strong support for this service and for its continuation, however the report concluded that the annual coeliac pharmacy health check required further monitoring over upcoming years to thoroughly assess its effect and value <sup>(34)</sup>.

## Other types of follow-up

Other approaches to follow-up that have been described in the medical literature include an Internet based online intervention tool, which demonstrated improvements in dietary adherence over a period of 3 months <sup>(35)</sup>. In ulcerative colitis a strategy empowering patients using guided self-management helped to reduce doctor visits and was not associated with an increased morbidity. As a chronic illness like CD, this model of self-guided management could potentially be applicable to patients with CD, thereby reducing the need for regular follow-up appointments.

## **Do all patients with CD require follow up care?**

Mucosal healing is often considered the outcome measure of choice to assess adherence in CD, as the absence of healing increases the risk of lymphoma, bone disease, and refractory CD.<sup>(23)</sup> Based on symptoms and histology, patients with CD could be classified into 4 main groups at follow-up (Figure 1), which could help

delineate individuals with the highest risk of developing complications. This could have potential merits in ensuring individuals with the highest risk receive the greatest level of support and follow-up care. Rationalising services in this way could have potential cost saving benefits, however a limitation to this approach is that follow-up biopsies to obtain histology are not mandated in the UK.<sup>(1)</sup> Given this problem alternative markers to assess adherence have been advocated, which are discussed in more detail below. Further work is now required to help establish which is the most effective non-invasive marker to assess GFD adherence, and whether this is acceptable to people with CD attending follow-up services.

### **Tools to assess adherence to a GFD**

Currently, there are a number of different surrogate markers, which have been used to assess GFD adherence. These include dietitian evaluation, patient-reported outcomes, coeliac serology, histological response and adherence scores<sup>(36; 37; 38; 39)</sup>. Further descriptions and limitations of each of these tools are described below.

#### **Dietitian Evaluation**

An evaluation by a skilled dietitian or a nutritionist has been shown to be a highly effective method of assessing GFD adherence, compared to patients' self-report of adherence and serological markers<sup>(23; 36; 40)</sup>. Their methods of assessment include the use of food diaries, food ingredient quizzes and by dynamic clinical interview. Unfortunately, there is no standard or quality control for dietetic review, making standardisation in both a clinical trial and beyond into clinical practice problematic<sup>(1)</sup>. Furthermore, there is no evidence that this can be substituted for a biopsy to predict mucosal damage<sup>(1)</sup>.

#### **Patient reported outcomes**

Patient's self-reported outcomes on adherence and symptoms are unreliable measures of adherence<sup>(1; 36; 41)</sup>. Villous atrophy has been shown to often persist in CD patients, despite clinical improvement in symptoms on a GFD<sup>(26)</sup>. Consequently, using patients reported outcome measures has not been widely used for assessment of dietary adherence.



## Coeliac Serology

Using coeliac serology for assessment of adherence has benefits both with regards to costs and tolerability. However, concerns have been raised about both endomysial antibodies (EMA) and IgA anti-tissue transglutaminase antibodies as surrogate markers of adherence, with normalisation often occurring well before normalisation of the villous atrophy <sup>(1; 26)</sup>. Despite their limitations, coeliac serology is frequently checked at follow-up appointments, with positive antibody titres informing as to whether there may be inadvertent gluten ingestion as opposed to whether strict adherence is being achieved <sup>(1)</sup>.

## Histology

Historically, the diagnosis of CD required three intestinal biopsies: a biopsy on a gluten-containing diet (diagnosis), a biopsy after a period of a GFD, and a biopsy after a gluten challenge <sup>(23)</sup>. Diagnostic pathways have since evolved, but small bowel histological assessment remains the only definitive way of determining healing of the mucosa, which can inform long-term outcomes <sup>(42)</sup>. Recent work has shown that despite being advocated, only two in three adults with CD, who were adhering to a gluten-free diet (GFD) had complete histological recovery after 1 year <sup>(43)</sup>. These findings were supported by work from Cambridge (one of the recruiting centres for this trial), where re-biopsy assessments performed between 12 and 24 months, demonstrated that 47% of CD patients (182/391) had on-going villous atrophy despite maintaining a GFD <sup>(39)</sup>.

International guidelines currently recommend a re-biopsy strategy for monitoring CD <sup>(23)</sup>. Recent British Society of Gastroenterology guidelines however do not mandate this, with guidance to limit follow-up biopsies to selected high-risk individuals <sup>(1)</sup>. This restricted strategy is based on insufficient evidence and cost-benefit analysis to support a re-biopsy strategy for every CD patient. Another significant problem is that oesophogastroduodenoscopy (OGD) is often poorly tolerated, which derives problems if all patients are mandated to undergo this intervention for follow-up biopsies <sup>(44; 45)</sup>.

## Adherence Scores

Novel adherence scoring systems have been devised, to help overcome the limitations of accuracy, costs and ease of use identified in other tools <sup>(37; 38)</sup>. These scoring

systems have predominantly been used in the research setting, as simple means of assessing adherence, and to allow comparisons between differing studies. Currently, the Celiac Dietary Assessment tool (CDAT) is the most widely used scoring system. The CDAT is a seven-item questionnaire, which has been used and validated in 6 studies to date, involving 1,855 patients <sup>(35; 37; 46; 47; 48; 49)</sup>. CDAT has yet to be compared to histology for adherence, but correlated highly with dietetic evaluations, for assessing adherence <sup>(37)</sup>. The score proposed by Biagi et al. has only been used in 141 patients to date. Furthermore, in a recent pilot study by our group in 94 patients, this score fared poorly compared to serology in predicting villous atrophy, with a sensitivity and specificity of 30.6% and 79.3% respectively <sup>(50)</sup>.

### Novel Adherence Markers

Measuring gluten immunogenic peptides (GIP) in either urine or faeces could be a future way of assessing GFD adherence. Work from Spain evaluating these novel peptides has shown real promise, with these non-invasive markers correlating well with the amount of gluten ingested and with mucosal damage.<sup>(51; 52)</sup> Urine collection may hold advantages over faecal assessment due to lower costs, ease of collection, transport, storage and its relative homogeneity. Further work is now needed to validate these promising findings in other centres.

### **Follow up care for CD – is it feasible to standardise care?**

Although CD is increasing in its frequency, there are variations in prevalence in differing international populations <sup>(53)</sup>. Providing uniform care internationally for all patients with CD is likely to be problematic due to differences in healthcare models employed in different countries. Healthcare within the UK is a devolved matter, which means England, Northern Ireland, Scotland and Wales each have their own systems of publicly funded healthcare, which is funded through general taxation. This gives rise to different policies and priorities within the different regions. This model differs to other countries where fee paying and national health insurance models exist to support health care costs.

Like other healthcare systems, the financial pressures facing the National Health Service (NHS) in the United Kingdom are well documented. Over recent years local clinical commissioning groups (CCGs) overseen by NHS England have had the capacity and capability to successfully commission services for their local population. This has seen several changes in local policies, with a reported 27% of CCGs restricting or removing all support for patients with coeliac disease <sup>(54)</sup>.

Consequently, this has led to significant variations in care for CD patients across England, leading to a postcode lottery regarding care and support following diagnosis. Given that poor adherence to gluten free diet is associated with complications and comorbidities, restricting GFD prescriptions and access to adequate follow-up CD services is likely to be a false economy for the NHS, resulting in increased treatment costs and poorer long-term health outcomes <sup>(54)</sup>. In Scotland, attempts to remove this health inequality have been addressed with the implementation of the Gluten-free Food Additional Pharmaceutical Service <sup>(34)</sup>. Further work is now needed to help establish which model of follow-up care is best applied within the constraints of the NHS, ensuring high quality and equitable care for all CD patients in the UK. This could help inform best practice and have application to other healthcare settings, where resources are increasingly being restricted. Understanding and maximising the effectiveness of dietitians is another key research area identified by the National Institute for Health and Care Excellence (NICE), which could also help advance long-term care. <sup>(25)</sup>

## **Conclusions**

An increasing number of patients are being diagnosed with CD in the UK. Gastroenterology services are currently inadequately funded to provide equitable follow-up care for all these CD patients. This review has highlighted the differing strategies currently available to manage follow-up care for CD patients, and how assessment of dietary adherence to a GFD can be undertaken. Work is now required moving forward to help establish the most cost effective way of delivering CD follow-up care, which is both acceptable to patients and their caregivers, within the constraints of the NHS.

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**Figure 1:** Stratifying CD patients at follow-up as to future risk of complications

