Current perspectives on returning gluten to the diet to test for coeliac disease; how much, how long?

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Abstract

The diagnosis of coeliac disease can be straight forward if the patient presents on a gluten containing diet; the process becomes more complex if gluten has been removed. How much gluten, what type of gluten and for how long should gluten be returned to the diet? These are questions that in Australia and internationally evoke a mixed bag of answers. Doctors need to develop an understanding of the gluten content of the patients diet as not all gluten is equal in provoking disease. Wheat flour products are best used as a gluten challenge. Oats, wheat starch, malt, beer, wheat thickeners and wheat glucose syrups do not contain the quantities of gluten desired in a gluten challenge food. If insufficient gluten is in the diet, serogenetic tests to exclude coeliac disease can narrow down the group requiring gluten provocation. No one guideline can cover the spectrum of patient interpersonal sensitivities to returning gluten to the diet. To optimize the diagnosis of coeliac disease, Leffler's shorter two week ingestion of two slices of bread each day, followed by coeliac specific serology taken at week four, may be utilised in a symptomatic wheat-sensitive subgroup of patients. The conventional challenge of 4 slices of bread each day for 6 weeks could also be reduced to *at least 2 slices* of bread each day for 6 weeks, for those who could push through symptoms for this time frame. Since the interpretation of the results is dependent on the presence of gluten, doctors should consider including gluten consumption information in the test outcome reports.

Key Words

Coeliac disease; Gluten; diagnose; challenge

Section 1. Introduction

Self-reported wheat intolerance is on the rise with a greater number of patients attributing decreased quality of life to gluten or wheat induced intestinal and extra-intestinal symptoms. Hence many patients have removed wheat/gluten from their diet before a diagnostic cause has been investigated. Coeliac Disease (CD), Irritable Bowel Syndrome (IBS) and Non Coeliac Gluten Sensitivity (NCGS) can present clinically with very similar symptoms. Since they are managed quite differently, it is essential to distinguish between the conditions as undiagnosed CD carries along with it potential for future medical complications.

It is thought that 80% of Australians who have CD remain undiagnosed,[1] leading to a poorer quality of life[2] and the implication of future medical issues. An accurate diagnosis of CD should be established before commencing a life-long gluten free diet. Coeliac-specific serology and mucosal villous damage need to be evidenced. Symptom response to a gluten free diet alone should not be used to diagnose CD, as this does not differentiate from IBS or NCGS, nor does it drive home to the patient the significance of CD and the importance of the gluten free diet.

Irritable Bowel Syndrome is classified as a functional, chronic, lower gastrointestinal disorder where diagnosis is based on varying presentations of gut pain and altered bowel motions, after exemption of other disease. While IBS can be painful and decrease quality of life, it does not display any structural, physiological or biochemical abnormalities of the gastrointestinal tract[3], but recent research hints that possible organic causes may yet be found[4]. Symptoms of IBS in Australia are experienced by about 1 in 10 people, but this is thought to be under reported.[5] Symptoms often emerge in early childhood and affect twice as many females as males.

Non Coeliac Gluten Sensitivity refers to the occurrence of a range of both intestinal and extra-intestinal symptoms in response to the ingestion of wheat and gluten-containing cereals, yet lacks the diagnostic indicators of wheat allergy or coeliac disease.[6] Currently the aetiology of reported symptoms is largely unknown and no biomarkers have been identified.[7]

Coeliac disease is a small intestinal inflammatory disease triggered by the ingestion of the gluten portion of grain proteins found in wheat, spelt, triticale, rye, barley and controversially, oats. While traditionally recognized by its nutritional malabsorption outcomes and gastrointestinal symptoms, today its wide range of presentations see it classified as a multi-organ autoimmune disease that is on the radar of doctors of many specialities. CD can be diagnosed across a lifespan of ages and occurs in genetically susceptible individuals. Karell et al[8] has determined that 99.6% of people with coeliac disease carry one or more of the Human Leukocyte Antigens (HLA)- DQ2 or HLA-DQ8 genotypes. Although roughly 30% of the world has these genes only about 3% of that group, go on to develop CD.[9] It has been reported that 56% of Australians have one or both genes.[1] It is estimated that 1 in 80 males and 1 in 60 females in Australia have CD.[1] One negative test for coeliac disease does not mean negative for life.[1] Over time, repeat tests in the same individual may be required.[10]

Approximately 20% of those with CD are classified asymptomatic at diagnosis[11] and a great many more present with extra-

intestinal manifestations. It is thought that less than 50% may present with classic gastrointestinal symptoms[11] and it is this group who would be most likely to self-diagnose a food intolerance and remove gluten from their diet before seeking medical advice.

Currently the sole treatment for CD is a lifelong gluten free diet which requires significant patient education from a specialist dietitian, motivation from the patient and follow up.[12] Adherence to this is expected to improve not only symptoms, nutritional status and small bowel villous damage, but also to prevent long term medical complications that could include infertility, osteoporosis, anaemia, gastrointestinal cancers and reduced life expectancy.[13] For these reasons strict adherence to the gluten free diet is essential for those with coeliac disease, while only gluten reduction to control symptoms is required for the majority of those with and IBS-wheat/gluten sensitivity.

Section 2. Who to test

International recommendations suggest that screening for coeliac disease should take place in all those who present with IBS-like symptoms.[12,14] The pooled prevalence from a recent meta-analysis suggests that 3.3% and maybe up to 5% of people with IBS have biopsy proven coeliac disease.[13] The National Institute for Health and Care Excellence (NICE) guidelines also suggest screening for CD in patient presentations listed in table 1 below.[15] However, the outcome of screening tests cannot be interpreted if performed while the patient has been excluding gluten from the diet.

Table 1: The National Institute for Health and Care Excellence guidelines suggest testing for CD in these patient groups[15] (p54)

Offer serological testing for CD to these	**Consider serological testing in these groups**
First degree relatives of people with CD People with any of the following • persistent or unexplained abdominal or gastrointestinal symptoms • prolonged fatigue • faltering growth • unexpected weight loss • severe or persistent mouth ulcers • unexplained iron, vitamin B12 or folate deficiency • type 1 diabetes, at diagnosis • autoimmune thyroid disease, at diagnosis • IBS (in adults)	• metabolic bone disorder (reduced bone mineral density or osteomalacia) • unexplained neurological symptoms (particularly peripheral neuropathy or ataxia) • unexplained subfertility or recurrent miscarriage • persistently raised liver enzymes with unknown cause • dental enamel defects • Down's syndrome • Turners syndrome

Section 3. Wheat exclusion

In recent years there has been greater public and medical awareness of the role that diet may play in triggering gastrointestinal and other symptoms, with the result that many people have removed gluten containing foods completely or almost completely from their diet.[11,16] Hischenhuber et al[17] report wheat sensitivity in both children and adults has increased in the last decade to levels of approximately 15-20% of the human population. Even consumers lacking wheat-provoked symptoms perceive gluten free products as healthier than wheat containing products, adding to the patient group who may be excluding gluten.[18] It is unclear what proportion of the Australian population limit gluten but Anderson et al[1] report survey data suggesting that 28% of adults monitor their dietary gluten intake, with 4% avoiding it altogether, 5% strictly controlling intake, and a further 18% loosely controlling consumption.

The return of symptoms due to a gluten challenge is no indicator of CD[19], as patients with NCGS also show exacerbation of symptoms during a gluten challenge.[21,22] Biesiekiersk et al[22] suggests that symptoms in wheat sensitive patients are due to fructans in the carbohydrate portion of wheat and not gluten protein, leading to the suggestion that pure gluten flour may be a better challenge food than bread, to investigate CD in this group. However, Di Sabitini et al[21] provoked symptoms in patients with NCGS, in a blinded trial, using 4.3g pure gluten/day in capsules.

Tests can reveal that many individuals whose symptoms improve following gluten withdrawal have no genetic, serological or mucosal markers of CD.[23] While this group can eat reduced quantities of gluten and do no harm, those with coeliac disease cannot. It is thought that the longer gluten is exposed to the mucosa of those with CD, the more detrimental will be its effects, impacting healing and recovery.[24] Ideally a diagnosis of CD should not be delayed or falsely attributed, given the degree of difficulty in adhering to a life-long gluten free diet.[25]

Section 4. Diagnosing coeliac disease

The diagnosis of coeliac disease is continuously evolving with the duodenal biopsy remaining the gold standard for adults and the majority of paediatric patients.[12,14,26] The recommended diagnostic process involves three steps[12] and it is essential that significant levels of gluten are in the diet for the first two. First; coeliac-specific antibody serology may suggest CD is present. Second; those with positive CD-serology undergo a small bowel biopsy to show villous damage. Third; later while on a gluten free diet, a follow up biopsy showing the bowel is recovering completes the diagnosis.[12]

4.1 Gluten-containing ingredients

Claims for serological testing for CD, reimbursed by Medicare Australia, are on the rise.[1] To ensure efficacy of test requests, if coeliac disease is suspected, the doctor must first enquire whether the patient is eating gluten. Most members of the public are uninformed about the intricate details of gluten and don't realise that the residual gluten in a wheat derived thickener in a salad dressing, is significantly different in quantity and effect to the gluten in a slice of bread. If simply asked if they are eating gluten, they may well respond positively, even if the salad dressing is the only gluten-containing food in their diet.

Doctors need to ask probing questions that require some knowledge of gluten ingredients, to estimate whether enough gluten is being eaten, before ordering coeliac-specific tests. Wheat flour products (bread, pasta, biscuits, cake, pizza), is the preferable form of gluten to have in the diet before testing. Spelt, rye and barley products in theory could be utilized, but their effect on CD diagnostic parameters is far less studied.[19] Oats should not be used as a pre-test gluten source because avenin poorly activates the disease process and it is thought, controversially, that only 5% of people with CD will react to oats.[27] It is for these reasons that pure oats have been accepted into a gluten free diet in Canada, Europe and the United States,[12,28,29] but discouraged in the diet of Australians with CD. The residual gluten alone, in beer,[30] wheat starch, wheat thickeners or malt will not reach the required levels of gluten to stimulate changes in most.[31] Wheat derived glucose syrup and dextrose can be safely consumed by those with CD,[32] so cannot be considered to contribute to pre-test gluten loads.

4.2 Role of serogenetic tests

If the patient has already removed gluten from the diet, they cannot be tested for CD. The main role of serogenetic data is to exclude CD, since the absence of HLA-DQ2 and HLA-DQ8 virtually excludes it.[8] This test alone cannot diagnose CD.[26] The ESPGHAN guidelines suggest a negative HLA genotype forestalls further investigations.[26] Testing for these genetic alleles, in those on self-imposed gluten free diets, allows doctors to more accurately define which patients will be required to load gluten back to the diet to undergo usual coeliac specific tests and which do not.

4.3 Gluten challenge

The conundrum facing the medical world is how much gluten and for how long should gluten be returned to the diet to trust, when tested, that sufficient antibody production and villi damage has been stimulated.

There is no one study with an authorative formulae that can guarantee the diagnosis of CD. Guidelines for gluten loading vary around the world and with the on-line publication of Leffler et als' research in 2012[33], guidelines are again in flux.

Many of the initial gluten challenges were done in children from the 1970's-1990's, with only a small range of trials in adults. Gluten varied in quantity and form from eating wheat flour, gluten powder, a regular gluten-containing diet or gluten-containing food products, generally wheat bread.[19] Doses varied from 0.2-30 g gluten/day and ingestion duration varied from 1 day to 8 years.[19] Many tests fell in the range of 10-20g gluten a day for 6 weeks to 3 months.[19] Bruins' review group concluded that a 3-month high-dose gluten challenge should be suitable to diagnose the majority of paediatric and adult CD patients,[19] but clinical response time to gluten shows great inter-individual variability.[34]

4.3.1 Australian gluten challenge

From these experiences, conventional protocols have been adopted in the range of 4 slices of bread, equating to 10g gluten, each day for 6 weeks.[12,33,35] In the 1990's, the Gastroenterological Society of Australia's (GESA) pamphlet guideline was to eat 2-3 slices of bread each day for 3-6

weeks before testing for CD. Although 6 weeks was encouraged, symptoms were so great in some that tests were performed at the earlier date. Currently GESA has no formal recommendation other than to advise that "patients must continue to consume gluten in the diet at the time of investigations.[36]"

The current recommendation from the Medical Advisory Board to Coeliac Australia is for children and adults to eat 2 and 4 slices of bread respectively each day for 6 weeks before CD-specific serology tests should be done[37]. Many patients baulk at this directive[1] and decline to be tested as they fear the pain and disability their returned symptoms will impose on them.

4.3.2 Recent challenge information

The ideal test for CD that requires no gluten ingestion is still a future hope. In the meantime, there is a growing number of patients removing gluten from their diet before investigations occur, and the statistical probability is that most will have NCGS and not CD. Discovering those with CD is important. Addressing the issues of returning symptoms, Leffler's group[33] tested two gluten quantities in adults with CD. For 2 weeks only, each group ate either 3g or 7.5g of gluten each day and then stopped. At the end of the second and fourth week, symptoms, serology and mucosal outcomes were measured. Their study reported that over 75% of adults met the diagnostic criteria for CD after a 2 week gluten challenge, with just 3g of gluten per day (2 slices of bread) inducing Marsh 3 villous atrophy in 68% in that time frame.[33] It is not practical nor cost effective to biopsy at 2 weeks, each person undergoing a gluten challenge. To narrow down the patients for mucosal biopsy, CD-specific antibodies need to be induced from the gluten challenge. An interesting feature of Leffler's study showed that coeliac serology titres continued to rise significantly when gluten ingestion stopped. Antibody titres increased slightly from baseline to day 14 in both groups, but they markedly increased by day 28. At the end of 4 weeks, 65% had IgA-TTG or IgA/IgG-DGP titres above the upper limit of normal in both gluten groups, a measure that can be used to distinguish those requiring a diagnostic biopsy from those who do not.

Table 2: Challenge guidelines for different patient groups

Patient group	Challenge	Serology test	Comments
Current Australian guidelines for all	Children 2 slices and adults 4 slices of bread each day for 6 weeks	At 6 weeks	Difficult for the symptomatic subset of patients to start or complete
Highly symptomatic	May still be too difficult to do a gluten challenge		
Patients willing to push through symptoms for 2 weeks	*2 slices of bread each day for 2 weeks, (spread intake out over the day) Stop eating bread and wait 2 weeks	4 weeks after initial bread ingestion	May capture positive IgA-TTG or IgA/IgG-DGP titres in ~65% of those with CD
Those willing to push symptoms for 6 weeks and those without symptoms	**At least 2 slices* of bread each day for 6 weeks	At 6 weeks	2 slices of bread each day instead of 4, may allow more patients to complete this longer test. More bread can be eaten if tolerated
Negative serology from above, but strong indications of CD	May require prolonged individual challenge		Refer to a Gastroenterologist

*Modifications suggested from Leffler's results[33]

4.3.3 Personalized gluten challenge for symptomatic patients

In both the 3g and 7.5g gluten/day test groups, no differences were seen in each gluten loads ability to stimulate antibody production and mucosal damage. Both groups did experience an exacerbation of symptoms, which peaked by day 3, but importantly the group eating 3g gluten/day experienced less symptom return. In those who struggle to consume 4 slices of bread each day for 6 weeks, this 2 week challenge of 2 slices of bread each day, with serology taken at 4 weeks, may ease the burden of the gluten challenge for a subset of symptomatic patients.[12,14,38] See suggestions in table 2.

However, 35% of people with CD may be missed by this method. Bruins[19] review certainly concludes a longer consumption of gluten, due to inter-person sensitivities, would diagnose a greater number of people. Leffler's works suggests that the conventional recommendation of 4 slices of bread daily could be modified to the consumption of *at least 2 slices* of bread each day for 6 weeks in those whose returning symptoms may be endured for the longer 6 week challenge. Because considerable variation between patients exists in the time to serological relapse on gluten,[34] if these methods reveal negative outcomes but the indices of suspicion are great for coeliac disease, other individual challenge recommendations may need to be

suggested on a case by case basis (refer to Table 2). All those with positive serology should be referred to a Gastroenterologist for mucosal biopsy.[12,14,24]

Section 5. Conclusion

Doctors must first recognise the patient groups in whom CD testing is recommended. Detailed diet questions focusing on gluten containing foods, should be asked of the patients to ascertain their current gluten intake. If current dietary gluten comes only from trace ingredients or is avoided altogether, serogenetic tests can confirm which patients need to load gluten back to their diets before testing for CD.

Considerable inter-personal variability exists in stimulating clinically measurable CD parameters from an oral gluten challenge. An optimal duration and dose to diagnose all people, has not been established. Patients on self-imposed gluten free diets do not bare up well to the conventional gluten challenge approach. For the very symptomatic, personalization might involve a shorter 2 week gluten ingestion followed by serological tests at 4 weeks as suggested by Leffler. Others who may push themselves to cope with the longer challenge may better tolerate at least 2 slices of bread each day for 6 weeks, instead of 4 slices each day for this time period. Other prolonged challenges need to be judged individually and referred on to a Gastroenterologist. The interpretation of the test results is dependent on gluten being in the diet, so doctors should consider reporting patient gluten intake on all test reports associated with CD investigations

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