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Systematic review: the evidence base for long-term management of coeliac disease

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SUMMARY

Background
While gluten-free diet is an effective treatment for coeliac disease, the need for and goals of long-term management of patients are poorly defined.

Aim
To review systematically the complications and associations of coeliac disease, to identify potential risk factors, to define ways of assessing risk factors and to provide a strategy for management.

Methods
Review of medical literature from 1975.

Results
There is an increasing list of potential complications and/or conditions associated with coeliac disease, in particular, autoimmune disease, malignancy and bone disease. Risk factors that may predict or influence long-term outcomes include genetic susceptibility, environmental factors predominantly gluten ingestion, persistent small intestinal inflammation/injury and nutritional deficiencies. Genotyping of patients is yet to have an established clinical role in long-term management. Assessment of adherence to the gluten-free diet largely relies upon skilled dietary history, but the ultimate test is duodenal histopathology, which is the only currently established means of assessing healing. Symptoms, serology or other non-invasive means are poor predictors of healing and the likelihood of complications.

Conclusion
Evidence (albeit limited) that adherence to a gluten-free diet and mucosal healing prevent and/or ameliorate complications indicates that a planned long-term strategy for follow-up is essential.

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INTRODUCTION

The introduction of serological tests with good specificity for coeliac disease (CD) has led to the realization that this condition is common. In fact, the rate of diagnosis has markedly increased in recent years.[1, 2] Treatment with a gluten-free diet (GFD) is successful in improving quality of life and in healing the small intestine in a majority of patients and recent detailed guidelines on the diet relevant to Australia and New Zealand have been published.[3] However, it is becoming increasingly recognized that patients with CD are at increased risk of developing long-term complications and other autoimmune conditions. Can these be prevented and outcomes improved?

It is commonly argued by experienced clinicians that once the diagnosis is made, GFD instituted and symptoms improved, a majority of patients do not require repeat duodenal biopsy and medical follow-up is needed only where the symptoms attributed to the CD recur. While such an approach may be adequate for majority of patients, it may disadvantage the minority. On the other hand, those who claim that intense lifelong follow-up with repeat duodenal biopsies, blood tests and other investigations may be accused of overservicing a patient group and inducing a culture of the 'worried well'. To decide rationally where the ideal viewpoint rests, several issues require addressing. These include definition of the complications and consequences of CD; whether the risk of these relates to strict adherence to the GFD and/or healing of the small intestine or to neither; the best methods for assessing adherence to GFD and healing of the small intestine and the practical issue of the optimal way patients should be followed in routine clinical practice.

COMPLICATIONS AND CONSEQUENCES OF CD

There is a large body of literature describing conditions and complications associated with CD. These, in addition to the strength of the associations, are shown in Table 1.

RISK FACTORS FOR COMPLICATIONS

If risk factors for outcomes can be identified, then patients could be more rationally stratified in terms of the monitoring schedule applied and the use of preventive interventions. While there is a paucity of definitive information, considerable data do exist and these are summarized in Table 2. Risk factors have been categorized into four potential areas: genetic, gluten exposure, intestinal inflammation and nutritional deficiency.

Genetic

Susceptibility to CD is determined to a significant extent by genetic factors. Approximately 88% of CD patients carry the HLA DQ2 heterodimer encoded by alleles DQA1*05 and DQB1*02.[4, 5] The remainder possess either HLA DQA1*05 or HLA DQB1*02, or express HLA DQ8 encoded by alleles DQA1*03 and DQB1*0302.[5, 6] HLA DQ2 and DQ8 are within haplotypes that are also associated with other autoimmune conditions, such as type-1 diabetes mellitus,[7–9] autoimmune thyroid disease,[10–12] primary biliary cirrhosis,[13] Addison's disease, Sjogren's syndrome and autoimmune hepatitis,[14] although such an association has not always been found.[15, 16]

A genome wide association study identified non-HLA genes associated with CD. After testing 310 605 single-nucleotide polymorphisms for association in 778 CD cases and 1422 controls, a linkage disequilibrium block encompassing the IL2 and IL21 genes was identified as a novel susceptibility factor.[17] Additional genotyping recently identified seven previously unknown risk regions. Type-1 diabetes mellitus and CD shared several of these regions including HLA-DQ, IL2–IL21, CCR_3 and SH_2B_3.[18] While these genetic associations will help understand pathogenic mechanism, they are not yet useful as predictors of the risk of developing severe complications of CD.

Of more potential use would be associations of particular HLA molecules with outcomes. HLA-DQ2 homozygosity has been associated with severe complications of CD; 26% of patients with refractory CD without aberrant T cells (RCD 1), 44% with refractory CD with aberrant T cells (RCD 2) and 54% with enteropathy-associated T-cell lymphoma (EATL) were homozygous for DQ2, compared with 21% with uncomplicated CD.[19] The MYO9B gene on chromosome 19 also increases the risk for RCD 2 and EATL.[20] Homozygosity for the HLA-DQB1*0201 allele has been associated with a more severe clinical phenotype at presentation. In one report, it was associated with more marked villous atrophy, younger age, severe diarrhoea, a lower level of blood haemoglobin at diagnosis and a slower recovery of villous atrophy after a GFD.[21] In another, HLA-DQB1*0201 homozygosity

Table 1. Prevalence of complications of and diseases associated with coeliac disease

Complication/ consequence	Details	Prevalence			Evidence for association (reference)		
		Disease in general population	Disease in CD	CD in disease	Probable	Possible	No
Autoimmune disease	Thyroid disease	10–20% women, 1–2% men[156]	0.3% (subclinical CD)[157] 1.2%[34] 13%[158] 14%[159] 14%[160] 26%[161] 41% (anti-thyroid antibodies)[162]	1.86%[163] 4.3%[164] 5.4%[165] 5.9%[166]	158–162, 164–166	167, 168	
	Type-1 diabetes mellitus	0.17%[169] 0.5–1%[170]	4%[34] 6%[171] 7% (subclinical disease)[157]	4.4%[172] 4.6%[173] 4.9%[174] 5.7%[175]	34, 157, 170–172, 174–176		
	Type-2 diabetes mellitus	7.2%–9% [177]	Unknown	Unknown			178
	Latent autoimmune diabetes in adults (LADA)	0.3%[179] 7–10% of adults with type-2 diabetes mellitus[179–181]	Unknown	Unknown			178
	Autoimmune hepatitis		1.1%[34] 4%[182]	6.4%[183] 16%[184]	8, 34, 182, 183, 185		
	Sjogren's syndrome	1.56% women[186] 3–4%[187] 13.3%[188]		4.5%[189]	189	168	
	Glomerulonephritis					190	
	Microscopic colitis			15%[191]	191	192, 193	
	Addison's disease	0.09%[194]	0.1%[34]	5.9%[195]	195, 196	34, 197, 198	
	Systemic lupus erythematosis	0.033%[199] 0.071%[200] 0.159%[201]	1.3%[34]			34, 202	
	Alopecia areata	0.1%[203]	1.3%[34]			10, 34	
Liver abnormalities	Hypertransamin asaemia	0.5%[204] 7.3%[205]	25%[206] 32%[207] 39%[208] 42%[209] 44%[210]	9%[211] 9.15%[80] 9.3%[212]	80, 207–210		

Table 1. (Continued)

Complication/ consequence	Details	Prevalence			Evidence for association (reference)		
		Disease in general population	Disease in CD	CD in disease	Probable	Possible	No
	Primary biliary cirrhosis	0.012%[213] 0.34%[214]	2.6%[210] 3.7%[215]	0%[210, 216] 2%[217] 2.7%[218] 3.4%[215] 3.5%[219]	215, 217, 219, 220	168	210, 216, 221
	Cryptogenic liver disease			1.5%[222]		222, 223	
	Primary sclerosing cholangitis	0.014%[224]		1.6%[219]		219, 220	
	Non-alcoholic fatty liver disease	10–24%[225]		3.3%[226] 3.4%[227]		220, 227	
Pancreatic disease	Elevated pancreatic enzymes		25%[206]			206	
	Pancreatitis	0.004–0.2%[228] 11.5%[229]		7%[230]		230, 231	
Neuropsychiatric disease	Neurological abnormalities		6–10%[134] 10%[232] 12%[65]		65	65, 134, 232–241	Ataxia [242] Epilepsy [243]
	Psychosis	0.006% (adolescents)[244] 1%[66] 0.2–2.2%[245]	0.5%[246]			246, 247	248, 249
	Depression	7.06%[250] 9.5%[251] 15.2%[252] 22%[253]	57%[254]		254–257		
	Anxiety	4.8–6%[258] 10.6%[259] 18.1%[251] 19.5%[260]	71%[254]		254		
Reproductive function: male	Sexual dysfunction	31%[261] 52%[262]			263, 264		
	Hypogonadism		7%[263]		25, 263		

Table 1. (Continued)

Complication/ consequence	Details	Prevalence			Evidence for association (reference)		
		Disease in general population	Disease in CD	CD in disease	Probable	Possible	No
Reproductive function: female	Sexual dysfunction	43%[261]			264		
	Menstrual abnormalities	5% (early menopause)[265] 3–7.6% (secondary amenorrhoea)[266]	39% (amenorrhoea)[267]		267, 268	269	
	Infertility and obstetric problems	7.4% (infertility)[270] 10% (small for gestational age)[271]	9%[267]	4.1%[272] 8%[273]	267, 268, 273–280		281--284
Bone disease	Reduced bone mass	27.3%[285] 28–47% (men), 15–33% (women)[286]	31–35%[86] 75%[50]	1.9%[287]	50, 86, 287–290		
	Osteoporosis	3–6% (men), 1–4% (women)[286] 4.1%[285] 0.9–87%[291]	7–14%[140] 26%[86] 47% (women), 50% (men)[87]	9.4%[292]	86, 87, 140, 292		
	Fractures	8%[293] 33%[294] 34%[295]	9%[296] 25%[293] 35%[294] 44%[295] 20–47%[297]		295–299		294, 300
Hyposplenism	Functional hyposplenism and splenic atrophy		16%[301] 32.8%[302] 77%[303]		301, 303, 304	305	
Infection	Urinary tract infection					306, 307	
	Bacterial sepsis					308	
	Tuberculosis	5%[309]	17%[309]		310	311	
Immune deficiency	IgA deficiency	0.11%[312]	2.3%[313] 2.6%[314]		313, 314		
Cardiac disease	Pericarditis, myocarditis, cardiomyopathy			2.1%–5.8% [315–317] 4.4%[318]		315–318	319
Venous thromboembolism	Venous	1.4%[320]	2.6%[320]			320	
Nutritional deficiencies	Iron deficiency	1–11%[321]	46%[157]	2.3–20%[322–326]	157, 322, 324–327		
	Low folate		37%				
	Low vitamin B6		20%[127]				
	Hyper-homocysteinaemia		20%[85]				

Table 1. (Continued)

Complication/ consequence	Details	Prevalence			Evidence for association (reference)		
		Disease in general population	Disease in CD	CD in disease	Probable	Possible	No
Malignancy	Lymphoma		SIR 2.2–51[8, 31, 327–337] RR 42.7[29, 30]	0.92%[335]	8, 327–337		
	Other		RR 9.7–12.3[29, 30]		29–31, 328, 338, 339		
Impaired QOL					340–343		

The strength of association was judged as 'probable' for reasonable case series where a clear association was found and judged as 'possible' for case reports of for case series in which only a weak association was found.
CD, coeliac disease; SIR, standardized incidence ratio; RR, relative risk.

was associated with severe intestinal damage (Marsh 3c) in a dose-dependent manner, but not with the clinical presentation of the disease.[22] In contrast, the zygosity of the DQA1*0501 allele does not have a significant impact on the severity of CD.[21] Thus, identification of DQB1*02 homozygous patients may help identify CD patients at risk for developing these severe complications.

Environmental

The major environmental factor associated with the risk of developing coeliac-related complications is persistent exposure to dietary gluten and this is discussed in detail below. It is reasonable to assume that known risk factors for those complications in the general population would also apply to patients with CD, but the validity of that extrapolation has not been formally tested. Examples include smoking as a risk factor for Graves' ophthalmology[23] and osteoporosis;[24] alcohol excess for early menopause in women and loss of gonadal function in men[25] resulting in osteoporosis[26] and transient postpartum thyroiditis for chronic thyroiditis.[27, 28]

Gluten

Gluten provides the antigenic drive to maintain intestinal disease and its removal from the diet not only results in symptomatic improvement but also allows a reduction in small intestinal inflammation and permits mucosal healing with improved absorptive function. It is anticipated, therefore, that gluten exposure would be associated with increased risk and/or a worse course of complications. Two key questions arise.

The first is whether GFD alters the course of associated illnesses. When complications or associated conditions are already present at the initiation of a GFD, there is abundant evidence of improved course of many, but not all conditions. The published data are outlined in Table 3.

The second key question is whether compliance to a GFD reduces the risk of developing complications or associated illnesses. Acquiring such data is extraordinarily difficult. The strongest evidence for a preventive effect of GFD is on malignancy, particularly lymphoma. Patients with untreated CD have higher rates of malignancy than the general population [oropharyngeal and oesophageal cancer relative risk (RR) 22.7, $P < 0.001$; lymphoma RR 77.8,

Table 2. The reported contribution of ongoing gluten exposure, intestinal inflammation and injury and nutritional deficiency to the risk of complications in patients with coeliac disease

	Risk factor		
Complication	Gluten exposure	Intestinal inflammation – mucosal injury	Nutritional deficiency
Autoimmune thyroid disease	Yes[34, 158] No[35, 36, 161]	Yes[39] Possible[77, 78]	Possible[88, 89]
Type-1 diabetes mellitus	Yes[34] No[35, 36, 344–347]	Possible[77, 78]	
Liver disease	Yes[34, 207–209, 218, 223, 227, 348] No[35]	Possible[77, 78, 82]	
Neurological disease	Yes[241] No[349]	Possible[65, 350]	Possible[83, 90]
Psychiatric disease	Yes[68, 254, 256] No (depression)[254]	Possible[67]	
Impaired reproduction and fertility	Yes[263, 264, 268, 269, 274–279, 283, 351]		Possible[85, 274]
Bone disease	Yes[47, 53, 56–60, 86, 87, 293, 352] No[140, 289]	Yes[50–52, 86]	Yes[47, 85–87] No[57]
Hyposplenism	Yes – functional[353] No – atrophy[354]	Yes[73]	
Infection		Yes[63]	
Cardiac disease	Yes[318, 355, 356]		
Thromboses		Yes[320]	Yes[85]
Nutritional deficiencies	Yes[7, 51] No[127]		
Refractory coeliac disease	Possible[39]	Yes[72, 73]	
Malignancy	Yes[29–31, 337]	Yes[73]	

$P < 0.001$;[29, 30] and small bowel carcinoma standardized incidence ratio 25].[31] In comparison, CD patients on a GFD for >5 years have the same overall risk of malignancy as the general population.[29, 30] The mean age at diagnosis of CD for patients diagnosed with cancer was significantly higher than the age at diagnosis of CD in patients who did not develop a malignancy.[31] Assuming that the patients diagnosed with CD at an older age had a longer duration of untreated CD, the results further support that the GFD is protective against the development of malignancy.

In a cohort of 4633 individuals, an increase in mortality, particularly because of cancer, was associated with the presence of elevated IgA tissue transglutaminase (tTG) antibodies.[32] It was unclear whether this was because of undiagnosed and, therefore, untreated CD, or whether the tTG antibodies were a marker of serious diseases such as cancer or heart failure. Analysis of blood samples obtained from US military recruits between 1948 and 1954 reveal that 0.2% were seropositive for tTG and endomysial (EM) antibodies.[33] These cases with unrecognized serologically detected CD had a nearly fourfold increased risk of death compared with seronegative subjects.

There is currently conflicting evidence regarding GFD altering the risk of developing autoimmune disease. One study showed that the duration of exposure to gluten may predispose to autoimmune disorders,[34] whilst others have been unable to demonstrate this association.[35, 36] One of the proposed mechanisms by which autoimmunity might develop, molecular mimicry, does implicate continuing exposure to gluten. Gliadin may activate T cells and allow for expansion of the B cells specific for autoantigens complexed with gliadin peptides and for subsequent autoantibody production. Such inflammatory responses may have the capacity to exist in genetically susceptible hosts and lead to chronic organ-specific autoimmune disease via epitope spreading.[37] More recently, however, it has been demonstrated that tTG knockout mice immunized with transglutaminase do not develop any pathology, whereas immunized wild type did develop periductal lymphocytic infiltrates in

Table 3. Effect of gluten-free diet on the course of associated illnesses

System	Evidence
Endocrine disorders	Normalization of subclinical hypothyroidism[158] Improved glycaemic control and increased body mass index in children with type-1 diabetes mellitus[357] No differences in height, BMI, HbA1C, insulin dose and haemoglobin between type-1 diabetes mellitus with or without CD at diagnosis of CD[347]
Liver disease	Normalization of isolated mild elevations in transaminase activity and nonspecific hepatic histological changes[34, 207, 209] Prevention of progression to hepatic failure in severe liver disease (n = 5)[223, 348]
Neurological disease	No improvement in peripheral neuropathy and/or autonomic dysfunction (n = 32)[349] Significant improvements in muscle strength and neurophysiological abnormalities in motor neuropathy (n = 2)[241]
Psychiatric disorders	Reduced proportion with anxiety from 74% vs. 26% ($P < 0.001$)[254] No change in the proportion of patients with depression (57% vs. 48%) – higher than in controls[254] Improvement in depressive symptoms 2–5 months after the commencement of a GFD – case reports[256] Increase in major serotonin and dopamine metabolite concentrations in brain – in parallel with improvements in symptoms[358]
Fertility and reproduction	Increased sexual activity and satisfaction[263, 264, 268, 274, 275, 277–279, 283, 351] Reduced rates of infertility, miscarriage, intrauterine growth restriction and low birth weight[263, 264, 268, 274, 275, 277–279, 283, 351] Undiagnosed CD may be a risk factor for unfavourable foetal outcome[276]
Cardiac disease	Improvement in myocarditis and dilated cardiomyopathy[318, 355, 356]
Hyposplenism	Functional hyposplenism may be reversible[353] Splenic atrophy usually irreversible[354]
Malignancy	Remission in some patients with type-1 RCD[39] Increased overall mortality and rate of malignancy with ongoing gluten ingestion[338].
Bone disease	Improvement in bone mineral density[53–60], including postmenopausal women and those without complete duodenal mucosal recovery[53] Normal bone mineralization long term in children and adults[59, 352]
Nutritional status	Increase in body weight, body mass index, fat mass, bone mass and triceps skin fold thickness[359] Improved in fat mass but not indices of lean body mass[84] Improved nutrition and height velocity in Asian children[360] Prevention of nutrient deficiencies, in particular, iron deficiency anaemia[7, 51] Improved calcium absorption from the gut[361] though not to normal values[47] Parathyroid hormone levels return to normal[47, 59].
Quality of life	Improvement (limited data)[340–343] Benefit in 'silent' CD, with improvements in fatigue and general well-being[341]

GFD, gluten-free diet; RCD, refractory coeliac disease; CD, coeliac disease.

lacrimal glands.[38] This observation suggests that the development of autoimmunity against tTG can be a pathological event which may lead to organ damage.

Prevention of many of the other complications that are a direct result of intestinal and systemic inflammation and/or nutritional deficiencies, such as bone disease, is assumed as GFD is able to attenuate and, in many cases, correct such pathogenic mechanisms. However, it is unknown whether adherence to a GFD reduces the chance of subsequently developing conditions in which the pathogenic mechanisms is uncertain (such as autoimmune disease, infertility, neuropsychiatric disorders and liver disease). Patients with CD must be considered as having an ongoing risk.

Ongoing mucosal inflammation and injury

If ongoing inflammation and injury in the intestinal mucosa are pathogenically involved in complications and associated conditions, then ensuring healing of the intestinal lesion becomes a key target in their prevention. The clearest evidence of the pathogenic importance of ongoing inflammation in the development of complications of CD derives from observations in patients with type-1 RCD, where intestinal inflammation persists independently of gluten ingestion. These patients are at increased risk of concomitant autoimmune diseases and infectious and thromboembolic complications.[39, 40] In fact, despite clinical improvement on the GFD, many histologically nonresponsive CD patients develop severe complications, such as gastrointestinal cancer and lymphoma, within a relatively short follow-up.[40]

Several mechanisms by which intestinal immune and inflammatory events may contribute to systemic symptoms and development of other conditions have been implicated. First, the production of cytokines and other inflammatory mediators as an integral part of immune activation at the mucosal level is associated with systemic exposure to such factors. Circulating levels of proinflammatory cytokines are increased in patients with untreated CD including IL-1β, IL-2, IL-2 receptor, IL-6, IL-10, IL-18, IFN-γ, TNF-β/α indicative of T-cell activation,[41–45] and reduction in levels of anti-inflammatory cytokines, such as IL-1 receptor antagonist, has also been observed.[41] Of importance, circulating levels of proinflammatory and anti-inflammatory cytokines significantly decrease and increase, respectively, on effective treatment of CD with a GFD.[41, 42] These manifestations of 'systemic inflammation' are likely to contribute to major symptoms and signs of untreated CD, such as fatigue and weight loss. Cytokines increase bone turnover and induce cortical bone loss via direct effects on osteoclastogenesis and osteoblast activity and these have been demonstrated in patients with CD.[46–50] Such a mechanism probably underlies the greater reduction in BMD in patients with villous atrophy compared with those with less histologic severity.[51, 52] Treatment with GFD and the subsequent reduction in systemic inflammation are associated with improved BMD[53–60] as outlined above.

Secondly, systemic cellular changes occur and these may be responsible for the increased risk of infection. Untreated patients have significantly reduced levels of leucocytes, total lymphocytes, and CD3+, CD4+ and CD8+ lymphocytes compared to those with treated CD and to the general population.[61–63] Hyposplenism/splenic sequestration (see Table 1) is one mechanism. The proportion of natural killer and cytotoxic T cells is lower in untreated and treated coeliac patients than in healthy populations, postulated to be because of sequestration of lymphocytes within the intestinal mucosa and/or because of their loss into the gut lumen.[63] Furthermore, excessive apoptosis of T cells has been reported in CD and this may contribute to the observed lymphopenia.[64]

Thirdly, shared immunological abnormalities suggest a common underlying vulnerability between active CD and neuropsychiatric disorders.[65, 66] It has been postulated that gluten may exert its pathogenic effect on processes in the brain through cell-mediated immune mechanisms and lymphocyte stimulation.[67] Impaired availability of tryptophan and disturbances in central serotonergic function may play a role in the development of anxiety, headaches/migraines, behavioural symptoms and depression in CD.[68, 69] These disturbances may be caused by interferon-γ, the predominant cytokine produced by gluten-specific T cells in active CD.[70] Interferon-γ can suppress serotonin function both directly and indirectly by enhancing serotonin turnover.[71]

Fourthly, immunological events can lead to local intestinal complications. In patients with type-2 RCD, clonal expansion of intraepithelial lymphocytes appears to be driven by IL-15 secreted by epithelial cells. This causes proliferation of intraepithelial lymphocytes independent of gluten stimulation. This results in the secretion of interferon-γ, which is cytotoxic to intestinal epithelial cells.[72] Patients with this type of RCD are at high risk of developing ulcerative jejunitis, mesenteric lymph node cavitation, hyposplenism and small intestinal lymphoma[73] and have a poor prognosis.[74]

Finally, mucosal inflammation is associated with increased intestinal permeability, because of epithelial injury[75] and possibly altered zonulin signalling.[76] Such increased leakiness of the epithelium has been implicated in several aspects of the symptomatology and complications of CD. It may predispose to other autoimmune disorders by facilitating further external antigens such as food proteins, bacterial products and endotoxins to enter the intestinal lamina propria, thus leading to the activation of autoimmune phenomena.[77–79] Entry of these molecules into the portal circulation has been postulated to cause

hypertransaminasaemia[80, 81], which is significantly associated with increased intestinal permeability in patients with CD.[82] Likewise, systemic exposure to xenobiotics may contribute to tiredness and other nonspecific symptoms. It has also been implicated in the pathogenesis of acquired neurological disorders,[83] but the nature of the putative toxins remains unknown.

Nutritional deficiencies

It is important to recognize nutritional deficiencies that impact upon the likelihood of complications of CD occurring as these can usually be readily corrected. There is relatively little information of the influence of macronutrient malnutrition, except in children where this is likely to be associated with developmental delay and/or growth failure. In adults, it is unusual for indices of lean body mass to be deficient amongst patients diagnosed with CD today.[84] In contrast, micronutrient deficiencies are well recognized and relatively common, as follows:

Iron deficiency may lead to anaemia, tiredness and cognitive impairment.

Folate deficiency may also contribute to anaemia, but is also with associated elevated homocysteine levels. Hyper-homocysteinaemia is a risk factor for thrombosis, recurrent miscarriages and osteoporosis.[85]

Intestinal malabsorption of *calcium* and *vitamin D* may also contribute to osteoporosis and osteomalacia.[47, 86, 87]

The body content of *selenium* may be low in untreated CD[88] and this may impair the action of thyroid hormones,[89] although there are currently no data on the association between thyroid function and selenium deficiency in patients with untreated CD.

Vitamin E deficiency has been postulated to be one of the causes of neurological abnormalities, in particular, cerebellar disease.[83, 90] Other nutrient deficiencies have been postulated without evidence.[83]

METHODS OF EVALUATING RISK FACTORS

Assessing genetic risk factors

The utility of genetic testing to estimate risk in CD is still in its infancy and should not be applied to routine clinical practice at present. However, there are suggestions that gene dosage, subtypes and zygosity of HLA-DQ2 and DQ8 may be useful predictors of which of the patients should be closely followed in the future.[21, 22, 91] Other genes associated with CD will need to be assessed in this context.

Assessing environmental risk factors

At each review, environmental risk factors independent of gluten and inflammation need addressing. Important factors include smoking, alcohol excess and obesity.

Monitoring adherence to the GFD

Assessment of compliance to the GFD is challenging. There are no clear guidelines as to the optimal method for monitoring adherence to this diet. However, a multidisciplinary assessment approach is needed:

Dietary history. Dietary compliance as assessed by a skilled dietitian trained in GFD at interview is thought to be one of the best markers of dietary adherence because of low cost, non-invasiveness and correlation with intestinal damage.[92] Adherence to the diet requires a focused dietary history and it is essential that dietitians are up-to-date for the current teaching of a GFD.[3]

Clinical assessment. Lack of strict adherence to the GFD is the most common cause of persistent symptoms in CD.[92, 93] However, resolution of symptoms may not be accurate in assessing adherence to the GFD as judged by interview and biopsy.[94] Symptoms may also indicate issues other than gluten ingestion; for example, malabsorption of fructose and lactose is common in untreated CD, irritable bowel symptoms may worsen with the GFD because more fruits or 'naturally' gluten-free foods rich in fructose are consumed[95] and occasionally symptoms represent the development of complications such as RCD or lymphoma.

Coeliac serology. Levels/titres of coeliac-associated antibodies fall with reduction in gluten intake. EM antibody and tTG IgA levels have been shown to normalize in seven out of eight patients within a year on a strict GFD.[96] However, the rate of fall, speed of its normalisation or whether serology normalizes or not are not reliable markers of strict adherence to the GFD[97–99] and cannot replace expert nutritionist assessment.[99]

Likewise, normalization of the levels of, for example, that of EM antibody levels, occurs in 87% of patients after 12 months on a GFD, but this is an unreliable marker of healing of the intestinal lesion[96, 97, 100–102] arguably a good index of strict adherence (see below). After normalization, serological markers can then be used as indicators of ongoing gluten-free dietary compliance.[96, 103, 104] Thus, serial serology has greater utility in predicting non-adherence than strict adherence.

Duodenal biopsy. Small bowel histological assessment is the gold standard for assessing strict compliance, as indicated by healing of the mucosa. To complicate the issue, some patients who have healed their intestinal mucosa can ingest gluten without inducing further histological abnormality.[105, 106] Interpretation of the histopathology with respect to gluten intake must also be made in light of previous biopsy appearances when taking a GFD. This is a strong argument for performing a follow-up biopsy after 12 months or so of apparent strict GFD.

Assessing intestinal inflammation and mucosal injury

The definitive way of assessing the degree of healing and mucosal inflammation is via the assessment of small bowel histology. A repeat biopsy on the GFD will help define mucosal healing and identify persistent mucosal injury, even in the absence of symptoms or positive serology. Despite apparent adherence to the GFD, histological recovery has been demonstrated to take time; for example, 62% of 57 patients had persisting villous atrophy over a median of 13 months[84] and in other cohorts, 40% had incomplete healing after 24 months[107] and 10% after 5 years.[108] The criteria for diagnosis of CD from the European Society of Paediatric Gastroenterology and Nutrition do not demand follow-up biopsy,[109] but, given the high rate of persistent villous atrophy despite the GFD, a repeat biopsy should be considered 1–2 years after its commencement.[108]

A minimum of four endoscopic forceps biopsies of the descending duodenum are known to enhance the value of small bowel histology.[110, 111] Thus, obtaining only two biopsy specimens will lead to a confirmed diagnosis in only 90%, whereas four specimens will lead to 100% confidence in diagnosis.[111] However, because of the patchy nature of villous atrophy, a five-biopsy regimen including one from the duodenal bulb, two from the first part and two from the second part of the duodenum, is required for detection of the most severe lesion.[112] The issue of patchiness of the lesions is also being addressed by techniques such as magnification endoscopy,[113, 114] confocal laser microscopy[115, 116] or capsule endoscopy,[117] although optimal roles for these technologies in clinical practice are yet to be clearly established.

Non-invasive ways of assessing healing and inflammatory activity are desirable so that they can be repeated at more frequent intervals. Potential techniques include the following:

Clinical assessment. Despite clinical improvement on the GFD, villous atrophy may persist.[40, 97, 118, 119] Symptom assessment cannot be advocated as a reliable method for determining absence of persistent small bowel villous atrophy.

Coeliac serology. Normalization of coeliac antibodies does not in itself guarantee that the small intestinal villous structure has improved.[40, 97, 100] For example, in a series of 57 consecutive patients, 53% had normalized tTG IgA, but three out of five of these had ongoing villous atrophy. Conversely, one-third of the patients who still had raised tTG antibody levels at 12 months had normal histology.[84] In a series of 13 patients with persistent villous atrophy and crypt hyperplasia, tTG IgA was normal in 59% and EM antibody normal in 74%.[40] However, persistently positive serology or rising titres may indicate mucosal injury or the development of RCD.[120]

Markers of systemic inflammation. The use of circulating cytokine levels has not progressed from a research tool to clinical practice. The utility of commonly used markers such as the erythrocyte sedimentation rate or levels of C-reactive protein has not been reported.

Markers of absorptive surface area and function. No marker of absorptive function has proven utility in defining small bowel surface area and therefore the degree of villous atrophy. Candidates include the ^{13}C-sucrose breath test, which has been a useful and

sensitive biomarker for defining changes in the severity of mucositis in patients receiving cancer chemotherapy,[121, 122] or plasma citrulline levels, which correlate with small bowel length and xylose absorption.[123]

Intestinal paracellular permeability. Dual sugar permeability studies are frequently abnormal in CD,[124, 125] improve rapidly on the GFD[126] and appear to be sensitive in detecting even small amounts of gluten in the diet.[125] However, their use in longitudinally evaluating patients with CD has not been reported.

Testing for nutritional deficiencies

Fortunately, the key nutritional markers outlined above can be measured in routine laboratories and methods for their correction are readily available. Despite adherence to the GFD, nutritional deficiencies may still exist. A Swedish study showed that despite a GFD for several years, half of adult coeliac patients still showed signs of a poor vitamin status with elevated homocysteine levels, low folate and low vitamin B6 levels.[127] This may be attributed, in part, to reduced dietary intake of nutrients because of the strict GFD. The results suggest that when following up patients with CD, the micronutrient status should be reviewed even in patients who have a good response to the GFD.

RECOMMENDATIONS FOR FOLLOW-UP

There are four key issues that require addressing:

Defining whether follow-up is indicated

Given the high number of complications associated with CD, the discovery of several risk factors, which may cause these or worsen outcome and the development of ways to assess risk, it appears intuitive that follow-up is necessary. Gluten ingestion is one of the key risk factors for developing complications and regular follow-up and improved knowledge in both children and adults have been shown to correlate positively with dietary compliance.[128–131] The concept that the intensity of follow-up can be stratified according to phenotypic characteristics of the individual patients has little supportive evidence. Symptoms and serology are poor guides to the severity of the intestinal lesion and to nutritional and bony status. The prevalence of persistent histological changes on the GFD is high, being up to 60% at a median of 2 years.[119] As this is a clear risk factor for complications,[40] follow-up is indicated for all patients.

Defining who should administer follow-up

There is a lack of evidence on who should follow-up patients with CD, whether a specialist gastroenterologist, general physician, general practitioner or dietitian. Instinctively, someone who has both knowledge and interest in CD would be optimal. When surveyed, patients with CD would prefer to see a dietitian for follow-up with a doctor being available.[132] Provided that the dietitian was trained in assessing and instigating the GFD and that clear guidelines on when to call for medical help are in place, this approach would allow good assessment of dietary compliance[3] and offer opportunities for reinforcement of dietary principles, with less medical input for a majority of coeliac patients who remain well. A doctor trained in the management of CD would be required at initial consultation for those patients who require more intensive management and to monitor laboratory investigations to detect nutritional deficiencies or other complications.

Defining what should be monitored and how often

Recommendations on the frequency of follow-up cannot be made on a solid evidence-base, but derive from what seems reasonable. Following histological diagnosis of CD, the minimum requirements for all patients are an initial consultation 1–2 weeks after endoscopy, review consultation 3–6 months later and subsequent reviews yearly,[133] although this would need to be individually assessed. A suggested plan of management is illustrated in Figure 1.

Follow-up should address several aspects:

Compliance to GFD. The central platform of gaining optimal outcomes in patients with CD is to ensure that they adhere to the GFD. At each review, dietary compliance should be assessed by history and serology. A dietitian is best equipped to evaluate by dietary history and to correct any misconceptions and educate regarding inadvertent gluten ingestion. As

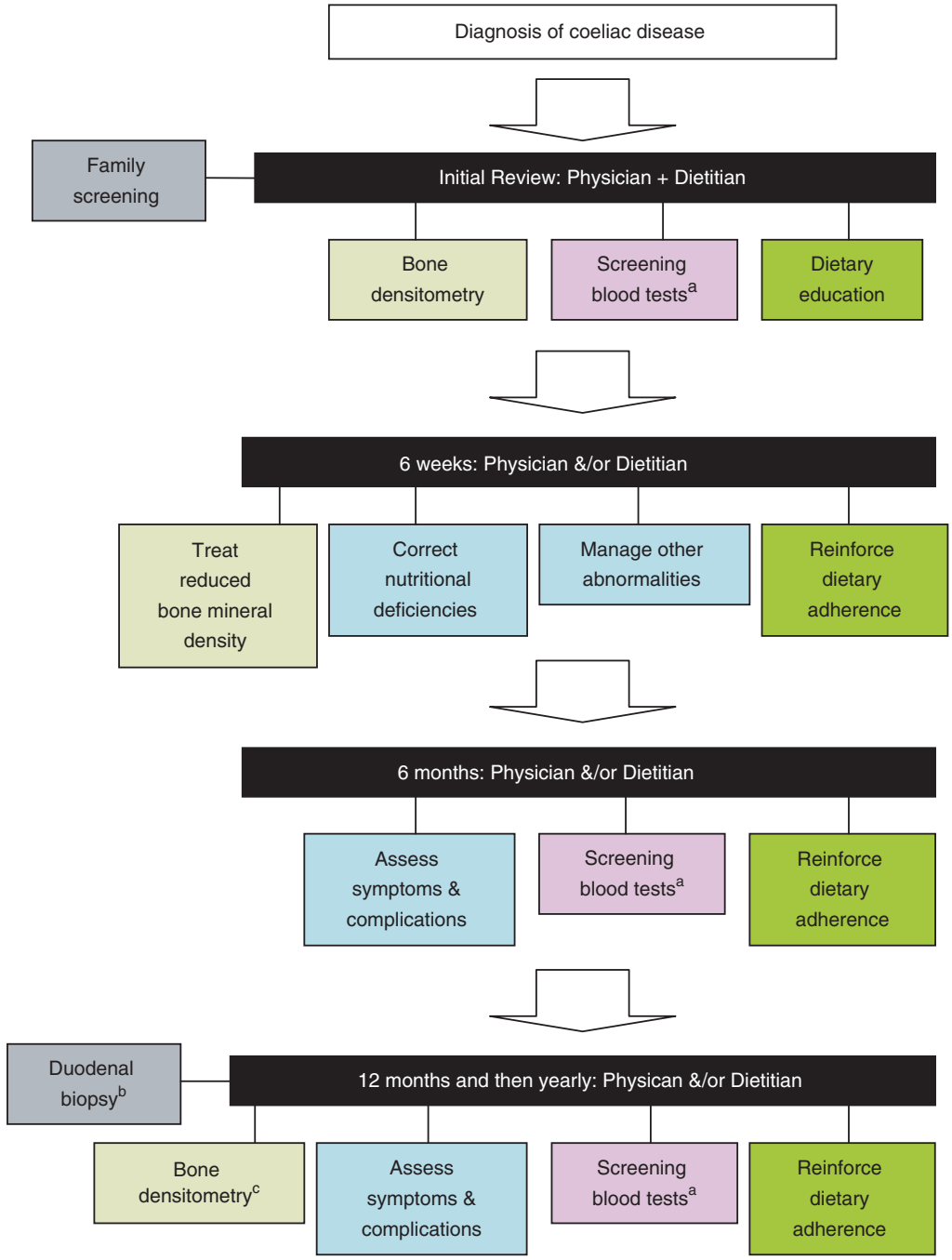

Figure 1. A suggested plan of follow-up management of patients with coeliac disease. [a]Coeliac serology, FBC, electrolytes, LFTs, thyroid function, iron studies, calcium, phosphate, vitamin D, folate, B_{12}, fasting glucose, ± zinc, Mg. [b]At 1–2 years; then as indicated on clinical grounds. [c]3–5 yearly in high-risk groups (noncompliance, refractory coeliac disease, female ≥50 years, fractures, men ≥55 years); yearly if osteoporosis on treatment.

outlined above, the results of serological tests, tTG IgA and EM antibodies, have to be interpreted carefully to avoid false security or inappropriate anxiety in the patient. For the medical practitioner, every review should be an opportunity to promote compliance. Ensuring membership of a patient-led self-help organisation is essential as these organisations provide detailed dietary information, food lists and

educational material in addition to social support.[129] Neuropsychiatric disturbances, such as depression, may adversely affect compliance[134] and must be addressed and managed. Anger can worsen the patient-clinician relationship and has been inversely correlated with dietary compliance.[135]

Symptoms. At each review, a thorough history of gastrointestinal symptoms and other symptoms associated with related conditions and complications such as neuropsychiatric symptoms, fatigue and sexual dysfunction may guide future management.

Duodenal biopsy. The need for repeated assessment of duodenal histopathology has been controversial and practice in this way varies across practitioners. As outlined above, symptom response and serology are poor predictors of healing in the individual patient and accurate non-invasive methods of assessing healing are yet to be validated. Demonstrating that the intestinal lesion has healed provides reinforcement and reward for the patient's efforts, provides important information for the appropriate interpretation of biopsies that may be subsequently performed because of the appearance of gut symptoms or other issues and permits recognition of patients with RCD before serious complications may develop. The main disadvantage of performing follow-up biopsies is the risk of inducing anxiety in patients because of undue expectation of having achieved healing. Thus, appropriate counselling needs to be linked to the revelation of the results.

The appropriate timing of the follow-up biopsy after GFD is initiated has not been established, but the earlier it is, the higher the chance that healing will not have occurred. Re-biopsy no earlier than 1–2 years after commencement of the GFD is recommended.[107, 108] If the mucosa has healed, further biopsies cannot be justified unless indicated on changes in clinical status. If histological improvement is incomplete, biopsies probably should be performed again in another 1–2 years. No improvement requires a different strategy, comprising at least dietary re-evaluation and repeat biopsies in a further 6–12 months. In some clinical scenarios, imaging of the small bowel maybe indicated (see discussion below).

Nutritional assessment. Micronutrient deficiencies are common even in patients who are adherent to the GFD.[127] For this reason, the key markers of nutritional state should be evaluated at each review. Thus, full blood evaluation, iron studies, and the levels of vitamin D, calcium, phosphate, folate and B_{12} should be measured. Other markers that could be considered in selected patients and/or on some occasions include: homocysteine levels, particularly in those patients with a history of venous thromboembolism; parathyroid hormone concentrations as an indicator of secondary hyperparathyroidism[24] as serum calcium, phosphate and alkaline phophatase measurements may be normal despite the presence of osteomalacia; serum magnesium as this was low in 13% one population reported;[136] and serum zinc as this is reduced in up to one in three patients with CD.[136] Assessing the levels of vitamin E and selenium (as discussed above) must be considered optional. Deficiencies should be corrected by specific supplementation and subsequent monitoring schedules adjusted accordingly.

Screening for complications and associated diseases. As the new development of associated diseases/complications is relatively uncommon in patients with CD, any monitoring should be simple and inexpensive. Thyroid function tests, a random or fasting blood glucose, electrolytes, liver function tests and platelet count should be routinely performed at every review. Homocysteine levels should be monitored in the appropriate clinical situation (as discussed above).

Bone densitometry. The timing of bone densitometry is controversial. The British Society of Gastroenterology[24] recommends that all patients have bone densitometry performed at diagnosis and regularly thereafter on the basis of increased fracture risk.[24, 137] This seems reasonable given the fact that reduced bone density cannot be predicted on the basis of symptoms, blood results or duodenal histology.[84] However, the actual risk of fracture in patients with CD is still unclear and the predictive value of bone densitometry is not sufficient to identify accurately individuals who will sustain fractures.[137, 138] The recommended approach to perform densitometry regularly after the initial study is not widely supported and requires further studies on safety, efficacy and cost-effectiveness.[139–141] Follow-up bone density assessment should probably be restricted to high-risk situations that include patients with osteopenia/porosis at diagnosis,

those with RCD, post-menopausal women, patients who have sustained minimal trauma fractures and perhaps men >55 years. The frequency of bone densitometry should be dictated by the scenario; for example, post-menopausal women should be screened every 3–5 years, whereas patients undergoing treatment for osteoporosis may require yearly assessments.[24]

Defining a strategy for 'red flags' for intestinal complications

A schedule of routine monitoring requires strategies for dealing with abnormalities detected. Identification of specific micronutrient deficiencies or associated conditions such as thyroid disease or hyposplenism leads to clear plans of action that are beyond the scope of this review. However, 'red flags' for more serious intestinal complications of CD, namely RCD, ulcerative jejunoileitis and small bowel lymphoma, should be recognized and subsequently addressed.

Such red flags include the following: ongoing, increasing or newly developed gastrointestinal symptoms; the development of associated symptoms such as unexplained fever, weight loss and night sweats; ongoing or new nutritional deficiencies and increasing levels of coeliac antibodies. The strategy should include:

Dietary exposure to gluten should be re-evaluated by a specialist dietitian and more extensive counselling regarding the GFD should be given. There are two additional key issues to consider. First, the style of GFD that was taught should be defined. Guidelines on how gluten-free the diet should be vary throughout the world, with recommendations on permissible gluten ranging from 20 to 200 mg/day. For example, in the UK, the 'limited detectable gluten diet', which permits ingestion of minute amounts of gluten up to the limit recommended by the Codex Alimentarius, is recommended, whereas the 'no-detectable gluten' diet is applied in Australia and the 'zero-tolerance' GFD in Canada. One of the larger studies addressing the safety threshold of prolonged exposure to trace amounts of gluten recommended that ingestion of contaminating gluten should be kept lower than 50 mg/d in the treatment of CD.[142] A recent systematic review of thirteen studies assessing permissible gluten levels found that while many patients tolerated an average of 34–36 mg of gluten per day, others who consumed about 10 mg of gluten per day developed mucosal abnormalities.[143] It is intuitive that patients with incomplete histological recovery must be advised to ensure as close to complete exclusion of gluten from their diet.

Secondly, the consumption of oats must be considered. Whether oats is allowed in the GFD is a contentious issue and opinions are divided on toxicity of oats in CD.[144–147] While oats may be tolerated by most coeliac patients, some patients are sensitive to oats[144] and commercially available oats are often contaminated by wheat, barley and rye.[148] It seems only sensible that patients who do not have their intestinal lesion healed should avoid oats until clinical and histological remission is achieved.[144, 146] Subsequently, up to 50–70 g/day of noncontaminated oats may be added.[145, 146]

Alternative causes should be contemplated. For example, gut symptoms should prompt consideration of the presence of irritable bowel syndrome, itself often amenable to additional dietary changes[149] or other causes of duodenal villous atrophy and malabsorption such as autoimmune enteropathy, inflammatory bowel disease, common variable immune deficiency syndrome, tropical sprue and oeosinophilic gastroenteritis should be reconsidered; recurrent iron deficiency should prompt consideration of colorectal neoplasia in the older patient or excessive menstrual blood loss in young women.

A *repeat duodenal biopsy* should be seriously considered after ensuring adequate dietary compliance. This provides not only useful information for both the patients and the attending doctor but also the key investigation in identifying patients at risk of proceeding to severe clinical manifestations such as RCD, ulcerative jejunoileitis and small bowel lymphoma.[40]

Special investigations may then be necessary, if the duodenal mucosa is atrophic or lymphoma is suspected. Immunophenotyping or immunohistochemistry of the intestinal mucosa can provide important clues. They may demonstrate the characteristic expanded intraepithelial lymphocyte (IEL) population that lacks CD4, CD8 and T-cell receptor β-chain[150] and may be useful in confirming the diagnosis of RCD. Aberrant cells of more than 20% are considered abnormal. Clonality assessment for TCR-γ gene rearrangements is achieved using a TCR–PCR protocol. A clonal T-cell population can be found in RCD and is thought to be predictive of the development of EATL.[39, 151] Increased lactate dehydrogenase or β2-microglobulin is a strong indicator of lymphoma in addition to clonal TCR gene

rearrangements.[152] In patients on a GFD, EATL may not be accompanied by duodenal villous atrophy. If an overt lymphoma is suspected, an extensive work-up is required including gastroscopy with multiple duodenal biopsies, CT chest, abdomen and pelvis.[74] Other potentially useful investigations include CT or MR enteroclysis,[153] PET scanning,[154] video capsule enteroscopy and double balloon enteroscopy.[74, 155] In some cases, laparotomy, intraoperative enteroscopy and full thickness biopsies are necessary.

CONCLUSIONS

The bulk of evidence suggests that CD is not a trivial disease and requires not only early diagnosis but also planned, long-term follow-up. While a vast majority of patients will have an excellent long-term outlook, current understanding does not permit stratification of patients for various levels of intensive review. The presence of symptoms is no guide to the severity of intestinal, bony or nutritional abnormalities and should not be the principal guide to the initial or long-term management strategy. Improved methods to identify those patients at high risk of developing complications and/or associated diseases are needed. Duodenal biopsy remains the best means of checking dietary compliance and detecting ongoing intestinal inflammation and villous atrophy, but it remains an invasive and expensive test that cannot be frequently repeated. Reliable non-invasive methods of assessing the status of the duodenal mucosa will greatly assist in more precise follow-up.

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