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Review article: Systemic consequences of coeliac disease

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Summary

Background: The best-known symptoms of coeliac disease are related to the gastrointestinal tract, but the disease may also present with various systemic manifestations outside the intestine. Some of these consequences may remain permanent in undiagnosed individuals or if the diagnostic delay is prolonged. However, for many of the systemic manifestations, the scientific evidence remains scant and contradictory.

Aims and Methods: We conducted a narrative review of the most thoroughly studied and clinically relevant systemic consequences of coeliac disease, especially those that could be prevented or alleviated by early diagnosis. The review is intended particularly for physicians encountering these patients in daily clinical practice.

Results: The possible systemic consequences of coeliac disease extend to multiple organ systems, the best studied of which are related to skeletal, reproductive, cardiovascular and neurological systems. Furthermore, the disease is associated with an elevated risk of psychiatric comorbidities, non-Hodgkin lymphomas and intestinal adenocarcinoma.

Conclusions: The various systemic consequences of coeliac disease play a significant role in the overall health of patients. Early diagnosis and treatment with a gluten-free diet appear to be beneficial for most, but not all of these conditions. The possible negative metabolic and psychosocial effects of the diet should be acknowledged during follow-up.

1 | INTRODUCTION

During the past few decades, coeliac disease has been seen to affect approximately 1% of the population worldwide.[1] Even though the introduction of modern coeliac disease-specific serological tests has lowered the threshold for active case-finding and risk group screening, the clinically multifaceted disease remains underdiagnosed.[2] The best-known 'classic' symptoms of coeliac disease, such as diarrhoea and weight loss, are directly related to the gastrointestinal tract, which is also the main site at which the disease-associated autoimmunity is considered to occur.[3] However, it is now known that coeliac disease is a systemic disorder which may also present with a variety of extraintestinal manifestations (Figure 1).[4]

The terminology referring to the diverse features of coeliac disease is not straightforward. While many of the symptoms and manifestations are directly associated with the disease and alleviated after commencing a gluten-free diet, others have less evident gluten dependency and treatment response.[5,6] It may also be challenging to

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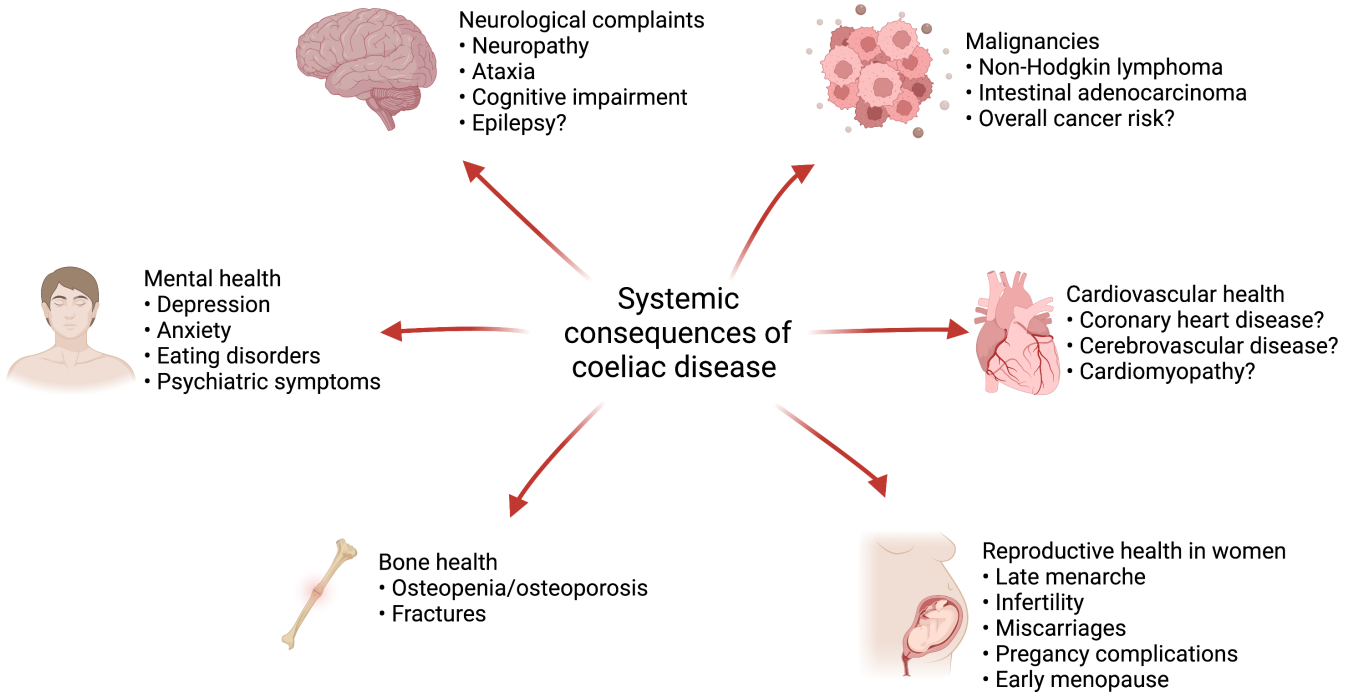

FIGURE 1 Wide range of possible clinical consequences of coeliac disease outside gastrointestinal tract

distinguish persistent symptoms during the diet caused by ongoing gluten intake from those unrelated to coeliac disease. Additionally, several clinical entities, such as autoimmune diseases, have been associated with coeliac disease.[7] Although not actually systemic consequences and probably not preventable by a gluten-free diet,[8,9] these comorbidities may nonetheless increase the overall burden of disease. It should also be noted that the dietary treatment itself may be nutritionally suboptimal and have a detrimental impact on general health.[10,11]

In this review, we discuss the various systemic consequences of coeliac disease, focusing particularly to adult patients and consequences that could possibly be prevented or at least alleviated by a prompt diagnosis and strict gluten-free treatment (Table 1). Unfortunately, for many of these manifestations the scientific evidence remains limited or contradictory. Here we aimed to focus on those consequences that have been studied the most thoroughly, including disturbances of the skeletal, reproductive, cardiovascular and neurological systems, psychiatric comorbidities and malignancies.

2 | BONE HEALTH

Reduced bone mineral density (BMD) is a well-documented finding in untreated coeliac disease.[12–15] According to a recent systematic review, osteoporosis can be found in 4%–20% and osteopenia in 10%–50% of men and premenopausal women with coeliac disease.[16] Likewise, 7%–16% of children have been reported to present with reduced BMD at diagnosis.[17–19] The pathogenetic mechanisms are likely complex, including for example, malabsorption of calcium and vitamin D, inflammatory mediators and autoimmunity,[20–22] which may also partly explain the wide variation in the prevalence figures reported. For example, in some patients decreased BMD can be detected even before the development of significant small-bowel mucosal atrophy.[23] Coeliac disease has also been associated with increased fracture risk compared to that of general population.[24–27]

The current evidence does not support routine screening for osteoporosis of all patients.[28–30] Instead, measurement of BMD could be considered in patients with long diagnostic delay and with clinically or histologically severe disease at diagnosis. Also, other osteoporosis risk factors, such as age, sex, weight and nutritional status, the presence of comorbidities, medications, physical activity and menopausal status in women, affect the risk for osteoporosis.[14,15,29–33] To combine these risk factors to predict the fracture risk in coeliac disease, various clinical tools such as FRAX® score may be useful.[25] The diagnostic workup and evaluation of the severity of osteoporosis follows standard clinical practice.

In most studies, reduced BMD has already improved significantly within 1 year on a gluten-free diet.[17,34,35] However, particularly in adults, recovery may remain partial, while children generally achieve more complete improvement of bone health.[17,34–36] In fact, the early coeliac disease diagnosis might be especially important in paediatric patients, as the peak bone mass is achieved during young adulthood,[37] and thus the bone accrual may remain incomplete if the diagnosis is delayed. Whether the dietary treatment also decreases the fracture risk remains more controversial, as in some studies their frequency has decreased to the level of general population,[27,38,39] whereas in others the risk has remained elevated.[25,26] In a Swedish register-based study,

TABLE 1 Possible systemic consequences of coeliac disease, estimated level of scientific evidence and suggestions considering their screening and treatment

Systemic consequence	Evidence	Proposed clinical approach
Impaired bone health and increased risk for fractures	Confirmed	• Measure BMD especially if severe clinical presentation, long diagnostic delay or poor GFD response, and in patients with additional risk factors for osteoporosis • E.g. FRAX® tool can be used to estimate the fracture risk
Non-Hodgkin lymphoma and intestinal adenocarcinoma	Confirmed	• Repeat duodenal biopsies in non-responsive coeliac disease • Consult experts if malignancy is suspected
Neurological complaints	Probable	• Suspect especially in elderly patients with long diagnostic delay. • Consult specialised unit about the treatment.
Psychiatric symptoms	Probable	• Consult psychiatrist if poor response to strict GFD. • Provide support if high burden of dietary restriction.
Impaired reproductive health	Probable	• Screen coeliac disease in women with unexplained infertility or recurrent miscarriages. • Provide professional dietetic support for coeliac women who are planning pregnancy.
Decreased cardiovascular health	Controversial	• Routine screening due to coeliac disease alone is not recommended. • Possible negative metabolic effects of GFD should be considered in patients with cardiovascular risk factors

Abbreviations: BMD, bone mineral density; FRAX®, Fracture Risk Assessment Tool; GFD, gluten-free diet.

ongoing fracture risk was associated with slow histological recovery, suggesting that this may be attributable to either a more severe duodenal lesion at diagnosis or poor dietary adherence—or both.[40] Recommendations regarding the importance of sufficient intake of calcium and vitamin D and use of specific medications follow general guidelines. Continuous bone loss during gluten-free diet should lead to the evaluation of dietary adherence and consideration of repeat biopsy.[28] In newly diagnosed coeliac disease, patients with documented osteoporosis, intravenous administration of bisphosphonates may be preferable.[29] To conclude, the association between coeliac disease and reduced BMD and increased fracture risk is well-established, and early coeliac disease diagnosis could be assumed to improve bone health significantly.

3 | REPRODUCTIVE HEALTH

Untreated coeliac disease may already affect hormonal balance in childhood, causing, for example, delayed puberty[41] and higher age at menarche.[42] In addition, although the evidence so far is more contradictory, later-in-life women have been suggested to be at increased risk for infertility, miscarriages and pregnancy complications, as well as for early menopause.[42,43] In contrast, the few studies published on reproductive health in men with coeliac disease have reported fertility comparable to that of age-matched controls.[44,45]

Whether there is an association between undiagnosed coeliac disease and infertility, two recent meta-analyses reported contradictory results.[46,47] Although women with a coeliac disease have demonstrated improved fertility rates after initiation of gluten-free diet,[48] neither the presence of untreated coeliac disease nor initiation of the dietary treatment affected reproductive outcomes in women undergoing in vitro fertilisation.[49] The risk for miscarriages has been reported to be increased in untreated coeliac disease, especially a few years before the eventual diagnosis,[50–52] whereas appropriately treated patients do not seem to differ from controls.[50,51] This may be explained, for instance, by the presence of nutrient deficiencies and non-specific inflammation, as well as coeliac autoantibodies interfering endometrial angiogenesis.[53] However, the true causality and benefits of a gluten-free diet remain debatable as shared genetic risk factors between coeliac disease and miscarriages have also been proposed.[54] Although more evidence is needed, at this point, active screening for coeliac disease seems to be justified in women with unexplained infertility or recurrent miscarriages.[29,55]

Other suggested adverse pregnancy outcomes include stillbirth, intrauterine growth retardation and prematurity.[44,56] These complications have been reported in both untreated and treated patients, and initiation of a gluten-free diet has improved some of the results.[56] Interestingly, high levels of serum coeliac autoantibodies have been associated with foetal growth restriction.[57] However, in another study an association was only reported between untreated coeliac seropositivity and small-for-gestational age in boys, but not with other adverse pregnancy outcomes.[58] Notwithstanding these partly controversial results, in addition to dietary counselling in general, specific focus on a strict gluten-free diet could be beneficial for women with coeliac disease who are pregnant or planning pregnancy.

4 | CARDIOVASCULAR HEALTH

Like many other autoimmune diseases,[59] coeliac disease may increase the risk of cardiovascular diseases, for example by chronic inflammation leading to acceleration of atherosclerosis.[60–62] However, the scientific

evidence remains sparse and inconsistent. The risk of coronary heart disease and cerebrovascular disease, for example, appears to be only modest at most,[63–66] but mortality due to cardiovascular events may nevertheless be increased compared with general population.[64] Coeliac disease may also be associated with some non-ischaemic conditions, such as idiopathic dilated cardiomyopathy, but again the results are inconsistent.[67–69] As the scientific evidence remains contradictory, the screening for cardiovascular diseases due to celiac disease alone is not recommended. Of note, the risk can be affected by the presence of comorbidities such as type 1 diabetes.[70]

The principles in the prevention and treatment of cardiovascular diseases in coeliac disease patients follow general recommendations.[71] The effect of a gluten-free diet has been little studied, but there are some indications of a beneficial effect on carotid intima thickness and serum lipid profile,[61,72,73] as well as on cardiac performance in patients with cardiomyopathy.[74] Paradoxically, the diet may also increase the risk of cardiovascular events, as it often has poor fibre and mineral content and high levels of added sugar and fat.[10,11,75,76] This possibly negative effect should be considered both at diagnosis and during the later follow-up, particularly in patients presenting with other cardiovascular risk factors.[10] As a whole, however, the benefits of a gluten-free diet for the general health and cardiovascular risk of coeliac disease patients seem to outweigh the potential disadvantages.

5 | NEUROLOGICAL MANIFESTATIONS

Coeliac disease appears to be associated with certain neurological entities, varying from vague and transient symptoms such as commonly reported headache and 'brain fog' to permanent conditions seriously disturbing daily life.[77] For example, a recent meta-analysis concluded neuropathy and ataxia to be more common among coeliac disease patients than among general population, although there was considerable heterogeneity and increased risk was not seen in all studies.[78] More controversial is the association between coeliac disease and epilepsy,[79,80] except for rare forms of treatment-resistant temporal lobe epilepsy and epilepsy with cerebral calcifications.[81,82] There is also some evidence that untreated coeliac disease may cause cognitive impairment.[83] It is in fact possible that these conditions at least partly belong under the wider umbrella of gluten-related neurological disorders, as there are patients who do not meet the official criteria for coeliac disease but may still benefit from a gluten restriction and express anti-gliadin antibodies or autoantibodies to transglutaminase 6.[84] However, the true association between neurological manifestations of coeliac disease and other gluten-related symptoms, as well as possible shared mechanisms, remain unclear.[85] Given the complex nature of these conditions, low-threshold referral to a specialised centre is recommended.

Gluten-free diet may have at least some beneficial effects on the neurological symptoms, possibly depending on dietary adherence and histological response.[78,79,81,86,87] However, full recovery, for example, from gluten ataxia is infrequent.[88] Similarly, impaired cognitive functions have been reported also to be overrepresented in treated coeliac disease.[83] Of note, Croall and colleagues found coeliac disease patients with neurological findings to present with white matter abnormalities, supporting the permanent nature of these comorbidities.[89] Studies with larger patient cohorts and control groups would be needed to confirm the effect of gluten-free diet on cognitive function.[90] Altogether, while awaiting more evidence, the often incomplete recovery from gluten-dependent neurological complications emphasises the importance of prompt diagnosis of coeliac disease.

6 | MENTAL HEALTH

Establishing the causal associations between coeliac disease and mental health is challenging, as ongoing symptoms may obviously have a negative effect on mood. In any case, many psychiatric illnesses, such as depression, anxiety and eating disorders, seem to be overrepresented at least in untreated patients.[91,92] The biological mechanisms behind this association remains to be ascertained although disturbances in the gut–brain axis and white matter tract changes have been hypothesised.[89,93,94] However, psychiatric comorbidities have been reported to be increased also among treated coeliac disease patients.[92,95,96] The underlying pathogenesis and role of gluten-free diet on psychological symptoms and quality of life are currently unclear due to the paucity of the long-term follow-up studies.[97,98] Altogether, patients' mental health and the presence of psychiatric symptoms require attention when coeliac disease is diagnosed. Low-threshold psychiatric consultation should be provided at the latest when the symptoms persist despite successful treatment or there is a suspicion of concomitant psychiatric disease.

An additional issue to be considered is that a gluten-free diet may be difficult to maintain and socially restrictive and therefore give rise, for example, to increased anxiety and emotional distress.[99] In fact, Shah et al. reported coeliac disease patients to have as high a treatment burden as those dependent on dialysis due to end-stage renal disease.[100] Patients with a psychiatric comorbidity may find the strict dietary restriction particularly burdensome[101] and the often-observed incomplete clinical response may further impair motivation for treatment.[102–104] Conversely, even well-responding patients may be at risk for increased anxiety if their approach towards the diet is hypervigilant.[105,106]

7 | MALIGNANCIES

A well-known although exceptionally rare complication of non-responsive (refractory) coeliac disease is enteropathy-associated T-cell lymphoma (EATL), a subtype of non-Hodgkin lymphoma which is estimated to affect 0.1%–3.2% of all coeliac disease patients.[107–109] An increased risk for other subtypes of non-Hodgkin lymphoma as well as intestinal adenocarcinoma has also

been recognised.[107,109,110] In contrast, the association between coeliac disease and overall cancer risk remains debatable and the prevalence figures for any cancer in coeliac disease have varied between 2.3% and 15.9%.[107–109,111] In fact, the risk for breast cancer may even be reduced.[109,112–114] In some studies, the risk for malignancies has been increased mainly during the first few years after coeliac disease diagnosis.[111,113,115] This may be at least partly because newly diagnosed patients are often also evaluated with lower threshold for malignancies—especially in case of unsatisfactory treatment response. Conversely, symptoms of cancer may lead to extensive investigations, including gastrointestinal endoscopies or serological testing for coeliac disease.

Another factor possibly affecting the reported risk for malignancies in coeliac disease is that the clinically recognised forms of the disease with higher risk for malignant complications have been overrepresented, especially in earlier studies.[1,116] In recent decades, advances in non-invasive diagnostics and active screening have resulted in earlier diagnosis and mitigated clinical features.[117,118] Simultaneously, adherence to a strict dietary treatment has become easier due to better availability of gluten-free products.[119] These timely changes could explain some of the discrepancies in the overall cancer risk between studies.

The increased risk, especially for non-Hodgkin lymphoma and intestinal adenocarcinoma, nevertheless persists and should be kept in mind particularly in elderly patients,[66,111] as well as in those presenting with a long diagnostic delay or severe malabsorption.[120] Naturally, factors affecting cancer risk in general, such as obesity, smoking, alcohol consumption and other lifestyle factors also apply to coeliac disease patients. Of note, the patients seem to be less often smokers[121] and may present more often with favourable BMI than their non-coeliac counterparts.[75,122,123] It is also good to remember that coeliac disease is associated with autoimmune comorbidities and chromosomal abnormalities, which may increase the risk for certain malignancies.[124–126] The overrepresentation of malignancies is likely a major reason for the increased mortality rate in coeliac disease patients.[64,127–129]

8 | CONCLUSIONS

Coeliac disease has traditionally been considered primarily a gastrointestinal disorder, which may result in underestimation of its effects on various extraintestinal organs and malignancy risk. Unfortunately, the current scientific evidence remains scarce and heterogeneous, making it difficult to estimate the effects of coeliac disease screening in preventing these systemic manifestations. These consequences also play a significant role in the overall health and mortality of coeliac disease patients, together with lifestyle factors, the presence of comorbidities and successful adherence to a gluten-free diet.[64,127–129] Early diagnosis and dietary treatment may protect against coeliac-related impaired bone health, neurological symptoms and malignancies, and also at least some of the hormonal complications seem to be reversible on a strict gluten-free diet. The possible negative effects of a strict dietary restriction on cardiovascular health and psychological well-being should also receive special consideration during long-term follow-up.

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AUTHOR CONTRIBUTIONS

Pilvi Laurikka: Conceptualization (equal); writing – original draft (equal). **Laura Kivelä:** Conceptualization (equal); writing – original draft (equal). **Kalle Kurppa:** Conceptualization (equal); writing – review and editing (equal). **Katri Kaukinen:** Conceptualization (equal); project administration (lead); writing – review and editing (equal).

CONFLICT OF INTEREST

None.

AUTHORSHIP

Author contributions: Pilvi Laurikka and Laura Kivelä drafted the manuscript and performed the literature review with equal contribution. Kalle Kurppa and Katri Kaukinen edited and reviewed the manuscript and contributed with additional references. All authors conceptualised the review and approved the final version.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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