Review article: future research on coeliac disease – a position report from the European multistakeholder platform on coeliac disease (CDEUSSA)

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SUMMARY

Background
CDEUSSA is a Specific Support Action project from the Sixth Framework Programme Priority of the European Union (EU). Its aim is to bring together basic and applied research in the area of coeliac disease (CD). This paper reviews the main issues that are a result of the CDEUSSA initiative.

Aim
To identify the major issues in need of investigation in the areas of clinical aspects, treatment, prevention and public health.

Methods
Key stakeholders, representing a wide range of knowledge with crucial importance for CD research and practice, have participated in two workshops aimed at identifying and proposing to the EU, as high priority research, topics in the areas of clinical aspects, treatment, prevention and public health.

Results
In public health, the overall goal should be to improve quality of life of the European population by implementing primary prevention strategies, early diagnosis and improved treatments for CD. New treatment strategies need to be developed. The option of primary prevention should be fully explored, which requires combined epidemiological, clinical and basic scientific research efforts. Such studies should also consider the importance of gene–environment interactions in the development of CD. Increased knowledge is needed on the natural history of CD. Diagnostic criteria need to be revised.

Conclusions
To achieve these goals, a collaboration of the stakeholders is fundamental, including research and patient organizations, as well as industries within both diagnostics and food production.

INTRODUCTION

Coeliac disease (CD) is generally defined as a gluten-dependent enteropathy, but is actually a multiorgan inflammatory disorder with large negative health consequences for many of those affected. It is not, as previously thought, a rare disease of childhood, but can have its onset at any age, and has lately emerged as a worldwide public health problem.

CD has a multifactorial aetiology. With regard to disease development, both genes and the environment and interactions between the two of them influence immunological responses and may confer either increased or reduced CD risk. CD has a genetic basis,[1] illustrated by family clustering with a prevalence of about 10% in first-degree relatives[2] and a 75% concordance in monozygotic twins,[3] a rate higher than in any other condition with a multifactorial basis. The principal determinants of genetic susceptibility are the highly variable human leukocyte antigen (HLA) class II DQA and DQB genes located in the major histocompatibility complex at chromosome 6. The combination of HLA-DQA1*0501 and DQB1*02 alleles encode the HLA-DQ2 class II protein molecule, which presents gluten peptides to CD4 positive cells.[4] However, it is clear that additional factors are critical for the development of CD as up to 30% of persons of North European ancestry, most of whom eat wheat, express HLA-DQ2, but CD develops in only a small proportion of these carriers. Altered processing of gluten by intraluminal enzymes and changes in intestinal permeability precede the activation of innate and adaptive immune responses.

Considerable research has been devoted to CD over the last decades. CDEUSSA is a Specific Support Action project from the Sixth Framework Programme Priority of the European Union. Its aim is to bring together basic and applied research in the area of CD. The CDEUSSA process was initiated by selecting and inviting key stakeholders representing a wide range of knowledge with crucial importance for CD research and practice. Thereafter, the call to join has been open with the aim to expand successively the platform to ensure representation of a wide range of stakeholders and to increase its usefulness also in future exchange of information. CDEUSSA now forms a platform, mobilizing key stakeholders from research, the food industry, the European public health field and patient associations. So far, 103 professionals from 27 countries, representing a large range of organizations and disciplines, have adhered to the CDEUSSA initiative. More information on CDEUSSA is available on the web (http://www.cdeussa.com). As part of the process, two workshops were organized in 2006 and participants identified four CD topics – clinical aspects, treatment, prevention and public health – that need to be investigated during the next few years. These research areas and related topics have been proposed to the European Union as high priority research to improve the health status of the European population. This paper reviews the main issues that emerged during the two workshops, and is thus a result of the CDEUSSA initiative.

CLINICAL ASPECTS

Elucidation of the clinical and histological spectrum

It is now widely accepted that CD represents a wide spectrum of clinical presentations and small intestinal mucosal changes. Typical clinical manifestations of CD include chronic diarrhoea, weight loss and anaemia. However, a significant proportion of patients present with extra-digestive symptoms, including skin lesions, isolated hypertransaminasaemia, bone pains and fractures, infertility, aphthous ulceration, ataxia or polyneuropathia.[5, 6] It is worth noting that there are also subjects with no or negligible symptoms (silent coeliac patients), but still with a small intestinal mucosa with villous atrophy. The suboptimal medical awareness of the very variable clinical presentation of CD is an important factor in the lack of recognition and underdiagnosis of the disease. In Finland, an education campaign among the health care professionals has resulted in 50% of diagnoses among individuals with CD, whereas in most European countries and the US, only 10–20% have been diagnosed.[7] Similar initiatives should be undertaken in other countries to increase the recognition of the disease and to improve the health of the patients by case finding.[8]

The pathomechanisms underlying the different manifestations of the disease remain to be clarified. With the demonstration of deposits of IgA antitransglutaminase in different organs,[9] and with the emerging demonstration of their biological activity,[10] the possibility that some of these clinical manifestations are the result of an autoimmune insult is more than a hypothesis.

The pivotal work of Marsh[11] has shown that gluten-induced pathology can range from very mild (only intraepithelial lymphocyte infiltration) to different degrees of villous atrophy depending on several factors, including the time after challenge and the amount of gluten. Approximately 10% of children with serum antiendomysial antibodies undergoing intestinal biopsy have no villous atrophy (potential coeliac patients). On immunohistochemical analysis of these serologically positive patients, inflammatory signs are mild.[12] It is unclear whether their low inflammatory indices are genetic, perhaps because of lack of non-HLA predisposing gene(s), or if environmental or immunological factors play a role. In this group, there are also patients who become 'seronegative'. The identification of markers predicting if this lesion will proceed to enteropathy would be very relevant.

Autoimmunity

CD can be considered an autoimmune disease because of the presence of autoantibodies in both the serum and the intestinal mucosa.[13] However, the biological consequences of anti-tissue-transglutaminase autoantibodies in the coeliac intestinal lesions are not yet elucidated. Of note, CD is also associated with concomitant autoimmune disease, approximately 5–10 times more than in the general population. The whole spectrum of autoantibodies associated with CD and the mechanisms by which they are induced on a gluten-containing diet and disappear on exclusion diet need clarification. These studies have a general relevance to understand the biological basis of autoimmunity, as CD is a unique model of autoimmunity where the trigger is well identified. The association of CD with a number of other autoimmune conditions is the result of a common genetic background as suggested by HLA (HLA-DQ2/8) and non-HLA genes[14, 15] shared with other autoimmune diseases. Gluten as such may play a role; in fact, emerging clearly is the role of feeding in the first year of life namely, the time and amount of gluten ingestion as risk factor for the development not only of CD but also of other autoimmune diseases, such as type 1 diabetes mellitus.[16]

Definition of the natural history

The definition of the natural history of CD is a crucial issue, which demands active investigation. The identification of the time by which a great majority of susceptible individuals develop CD-associated autoantibodies is important for the definition of the time of possible mass screening strategies. A US study of at-risk, HLA-DR3+ individuals demonstrated a high prevalence (1:100) of CD-associated antibodies at the age of 5 years, suggesting that 'seroconversion' can occur quite early in genetically predisposed individuals.[17] Importantly, Simell et al.[18] demonstrated seroconversion already at the age of 1.3 years with another 1% annual conversion at least until age 6 years, but with half of them normalizing without any dietary manipulation. Such long-term follow-up studies could also be used to find out the environmental and life style factors contributing to the development of the disease and conditioning the severity of the histological and clinical picture. Also, the typical life-course pattern with respect to health-related quality of life (HRQOL) and complications needs to be mapped for CD cases, taking into account differences with respect to the degree of small intestinal mucosal changes. In such long-term follow-up studies, several other factors should also be taken into account, such as if a subject is treated with a gluten-free diet (GFD) or remains untreated, the degree of compliance with the GFD in treated subjects and preferably also the duration between development of gluten hypersensitivity and initiation of treatment, as all these factors might influence development of long-term complications.

Revision of diagnostic criteria

In 1990, ESPGHAN revised its former diagnostic criteria for CD laid down in 1970.[19] Requirements remaining mandatory for the diagnosis are: (i) the finding of villous atrophy with hyperplasia of the crypts and abnormal surface epithelium, while the patient is eating adequate amounts of gluten and (ii) a full clinical remission after withdrawal of gluten from the diet. The finding of circulating IgA antibodies to gliadin, tissue transglutaminase (tTG) or endomysium at the time of diagnosis and their disappearance on a GFD adds weight to the diagnosis. The growing contribution of serology, together with the recognition of a wider spectrum of histological changes and the contribution by genetic tests, demonstrates the necessity to move on to a revised diagnostic approach. For this purpose, we need not only epidemiological studies aimed at assessing the risk related to gluten ingestion in the different groups of

patients (symptomatic, silent, potential) but also more information on the genetic make-up and on the immunological mechanisms leading to the full disease. The complete identification of genes involved is needed so that genetically susceptible individuals can be identified and the risk of developing the disease can be precisely assessed. The involvement in the same patient of the different branches of the immune response to gluten – adaptive and innate – needs to be assessed, as both probably are necessary for a full expression of the disease. This information will have a strong impact on the clinical categorization of patients and even on the definition of CD.

As far as clinical aspects of CD are concerned, major issues in need of investigation are reported in Table 1.

TREATMENT

Who should be treated?

As far as the need for a GFD, it is quite clear that in a vast majority of cases, such a diet leads to disappearance of clinical symptoms, recovery of normal duodenal histology, disappearance of the serological signs of CD and prevention of CD complications, although it should be noted that there are no large RCT evaluating the effect of GFD. Furthermore, the criteria for remission are not clearly defined. A recent Italian study confirms histological normalization in 74.1% of paediatric cases, but only in 17.5% of adults.[20] To assess health improvement after initiation of CD treatment is relatively easy in patients with clinical symptoms of the disease, but difficult in persons with asymptomatic CD identified by screening such as in first degree relatives of CD patients or subjects with Down's syndrome or type 1 diabetes. In addition, it is not known if patients with untreated CD detected after screening have the same long-term risk of complications as patients with clinically diagnosed CD. Moreover, little is known about the health risks of those untreated with minor enteropathy, maybe silent from a clinical point of view. In addition, it seems that some CD patients may develop tolerance for gluten later in life.[18, 21, 22] Thus, more knowledge about the mechanisms involved in the re-gaining of tolerance is necessary to identify those patients that may not need a GFD during their whole life. Well designed follow-up collaborative studies between epidemiologists and clinicians are needed to elucidate all these aspects.

Improving health care in CD patients

Adherence to a GFD may have negative nutritional consequences,[23, 24] but regular dietary controls are reported only by a minority of the CD patients,[24] with large variations between countries. Prospective collaborative studies between dieticians and clinicians are needed to investigate if better dietary support is necessary to achieve an ongoing satisfying management and to prevent long-term complications in this group of patients.

Table 1. Clinical aspects of coeliac disease – major issues in need of investigation	
Elucidation of the clinical and histological spectrum	Increase in awareness of the health professionals in identifying CD by case finding.
	Pathomechanisms underlying the different manifestations such as malabsorption and autoimmunity
	The role of tissue deposited IgA antitransglutaminase antibodies
Exploring the autoimmunity spectrum	Identification of the whole spectrum of gluten-related autoantibodies
	Gluten ingestion and risk of autoimmunity
	Infant feeding patterns and risk of autoimmunity
Definition of the natural history	Timing of appearance of CD-related autoantibodies and progression of intestinal damage
	Environmental factors conditioning the severity of the histological and clinical presentation
Revision of diagnostic criteria	Identification of genes and risk assessment
	Immunological markers of innate and adaptive immunity
	New diagnostic approaches based on immunology and genetics, enabling performing biopsy and histology only in selected cases

CD, coeliac disease.

Gluten threshold for gluten-free food

In 1982, the Codex Alimentarius Committee on Nutrition and Food for Special Dietary Uses (CCNFSDU) set the limit of gluten allowed in raw materials to produce gluten-free food to 0.05 g nitrogen per 100 g dry matter. Recently, an R5 ELISA method for gluten/gliadin determination in food has become available based on a monoclonal antibody reacting with the specific gliadin pentapeptide QQPFP. This method shows a sensitivity and limit of detection (1.5 ppm gliadin), which is superior to older methods.[25] At the moment, provisional levels of (20 ppm gluten) for food gluten-free by nature and (200 ppm) for food rendered gluten-free (wheat starch-based products) have been accepted [Draft Revised Standard for gluten-free foods (ALIN-ORM 04/27/26) CCNFSDU]. The problem is that this standard refers to the amount contained in a food item but not to the amount of food that can be taken by a person who is sensitive to it. Recently, the results of a prospective, double-blind, placebo-controlled trial performed to establish the safe gluten threshold for patients with CD have shown that most patients with CD should ingest less than 50 mg gluten per day.[26] Studies linking the best available analytical detection of gluten to the clinical applications and relevance in the treatment of the patients should be performed. An important aspect in this respect is that it is not known to what extent the threshold of tolerance for gluten ingestion varies between different CD patients. Also, it is not yet clear if it is constant over time in a certain patient, or varies over time merely by a change in age or also by influence of other environmental factors. Collaborative studies should be performed to elucidate these mechanisms and to define the threshold of tolerance for gluten in different CD individuals with different genetic make-up and at different ages.

Oats toxicity

Currently, CD treatment is almost the same as it has been for more than half a century: a life-long strict GFD with exclusion of gluten from wheat, rye and barley. In general, oats are safe both for adults and for children with CD.[27] One concern about oats consumption in a GFD is the frequent contamination of oats with gluten during the harvesting and milling process.[28] In addition, some CD patients have avenin-reactive mucosal T cells, although not all these have concurrent enteropathy.[29] In conclusion, it seems wise to add oats only when the GFD is well established, so that possible adverse reactions can be readily identified by a strict clinical follow-up. Studies directed to obtain commercial uncontaminated oats safe for peoples with CD are needed. Moreover, further studies are necessary to assess immunogenicity and toxicity of different oat cultivars.[30]

Development of new foods for CD patients

Gluten is a complex mixture of proteins that contain a multitude of immunogenic peptides. There are many wheat varieties and not all of which appear to be equally toxic to patients.[31] Recently, first attempts have been made to quantify the toxicity of a range of bread wheat and pasta wheat varieties and of species that contain only one of the three genomes of bread wheat. Using specific T-cell clones and monoclonal antibodies, the results demonstrate that large quantitative differences exist in the presence of toxic gluten peptides, with some cultivars completely lacking particular harmful peptides.[31] Large-scale genomics and proteomics wheat research will elucidate the genetic and allelic diversity of the wheat gluten genes and proteins. Alternative strategies include the application of RNA interference to silence specifically those gluten genes that contain CD-toxic epitopes, as well as the construction of hexaploids from diploid wheat species of proven low CD-toxicity. The main problem will be to eliminate or avoid CD epitopes, while retaining the industrial quality of the material. By linking these data to toxicity data, it will be possible to evaluate the feasibility of marker-assisted breeding to produce or select nontoxic wheat varieties. This offers new opportunities for the generation of safer wheat strains. In addition, other cereals that do not contain harmful gluten or gluten-like molecules such as the Ethiopian cereal tef can be selected.[32] Future projects on selection and cultivation of traditional or biotechnologically modified gluten-free cereal variants, such as tef or oats, provide great promise to coeliac patients, although the economic feasibility and the time horizon of introducing these new variants may have possibly been judged rather optimistically.

New treatments

A GFD is at present the only possible treatment for CD patients, but there are a number of drawbacks to a life-long diet. At present, there are several options that can

be explored. Because of the high proline content, gliadin peptides are highly resistant to digestive processing by pancreatic and brush border proteases.[33] Enzyme supplement therapy using bacterial prolyl endopeptidases has been proposed to promote complete digestion of cereal proteins and destroy T-cell multipotent epitopes.[34–36] The efficacy of this approach needs to be assessed in *in vivo* studies. Other promising areas include modulation of intestinal permeability,[37] preventing gliadin presentation to T cells by blocking HLA-binding sites, use of tTG inhibitors,[38] and assessing the use of interleukines and other immunomodulatory strategies to promote tolerance.[39–41] Evidence that gluten toxicity is not dependent only on T-cell recognition is growing; activation of innate immunity has been demonstrated in CD[42, 43] and antibodies to IL-15 have been proposed to treat refractory CD.[44] Nevertheless, one should realize that usually CD is a benign disease and dietary treatment is safe although strenuous. An immunomodulatory approach will need to have a safety profile equivalent to that of the GFD, but with the advantage of increased compliance.

Moreover, there are not only theoretical problems to solve but it is also crucial to consult the patients for their demands and for their acceptability of medications that may ultimately replace GFD. The cost-effectiveness of treatment alternatives to GFD should be assessed. At the moment, many of the commercial activities to develop new treatments for CD are based outside Europe. To enable also European researchers to translate their results to outcomes for patients, it is important that such commercial activities and investments are increased in Europe and that collaborative studies and alliances between industry and researchers from in and outside Europe are stimulated.

As far as treatment of CD is concerned, major issues in need of investigation are reported in Table 2.

PREVENTION

Infant-feeding practices

As CD has a multifactorial aetiology, it is likely that environmental factors contribute to CD development throughout the life span;[45] however, so far, research has mainly focused on the infancy period and early feeding. Thus, it has been suggested that primary prevention might be attained through favourable infant-feeding practices,[45, 46] thereby increasing the chance for infants to develop oral tolerance to gluten and possibly also promoting the maintenance of tolerance throughout life.

Table 2. Treatment of coeliac disease – major issues in need of investigation.

Decision on treatment criteria	Long-term health risks of silent and potential coeliac disease and the impact of early diagnosis
	Natural development of permanent or transitory gluten tolerance in CD cases
Improvement in health care and quality of life	Nutritional consequences of the gluten-free diet and advantages of a better dietary support
	Food labelling, availability of gluten-free foods and awareness of the disease.
Development of safe and new foods	Oats toxicity
	Threshold of tolerance to gluten
	Genomics and proteomics of different wheat cultivars and implementation of traditional or biotechnologically modified gluten-free cereal variants
Exploring treatment alternatives	Enzyme supplements therapy
	Reestablishment of the intestinal barrier against gluten entry
	Blocking of gliadin presentation by HLA blockers and tTG inhibitors
	Cytokines and anticytokines such as IL10, anti-IFNγ and anti-IL15
	Reestablishment of tolerance (modified gluten peptides, nasal tolerance)
	Development of a relevant animal model
	Explore the cost-effectiveness of alternative treatments
	Assess the demand from patient support group of the nature of alternative treatment to GFD
	Strategies to stimulate collaborative studies and alliances between industry and researchers from in and outside Europe

CD, coeliac disease; HLA, human leukocyte antigen; tTG, tissue transglutaminase; GFD, gluten-free diet.

A recent meta-analysis of observational case-referent studies has concluded that breastfeeding during the introduction of dietary gluten and increasing duration of breastfeeding were associated with reduced risk of developing CD.[47] However, it is not clear from the primary studies whether breastfeeding provides a true protection in a short- or long-term perspective or merely modifies the symptoms with delayed diagnosis as a result. In a recent prospective observational study including only children with a high risk for autoimmune disease, no protective effect of prolonged breastfeeding was observed with respect to CD autoimmunity.[16] The true impact of breastfeeding on the development of CD remains controversial. A possibility is that differences in gut microbiota between breastfed and formula fed infants play a role in the protection given by breast feeding. Long-term prospective cohort studies in high-risk children for CD are required to investigate further the relation between breastfeeding and CD.

There may be an age interval during which humans acquire increased ability to develop oral tolerance to a newly introduced antigen, an option that needs to be explored also with respect to gluten and CD risk. Age of the infant at introduction of dietary gluten did not remain an independent risk factor in a case-referent study adjusting for differences in other exposures, i.e. breastfeeding status and varying amounts of gluten given during introduction, although with the limitation that only the first year of life was evaluated.[48] In one prospective observational study, it was examined whether timing of introduction of gluten to infants diet influences subsequent onset of CD autoimmunity.[16] Among HLA-DR3-positive children, introduction of gluten foods by age 3 months was associated with a fivefold increased risk for CD autoimmunity compared with exposure at age 4–6 months. Exposure at or after age 7 months was also associated with a slightly increased risk for CD autoimmunity compared with exposure at 4–6 months. These data suggest that both early ($\leq$3 months after birth), and late (>7 months after birth), introduction of gluten may increase the risk of CD and should be avoided. The strength of this study is its prospective design; however, it has several limitations as the small number of subjects in whom the outcome measures occurred, the use of CD autoantibodies as a surrogate for biopsy-diagnosed CD and also the amount of gluten during introduction was not assessed and thus remains as a potential confounder.

The dose of dietary antigen ingested during infancy may influence whether or not oral tolerance develops. Interestingly, Sweden has experienced an epidemic of CD in children below 2 years of age, where the abrupt fourfold rise in incidence was preceded by a twofold increase in the average daily consumption of gluten and later, the abrupt fall in incidence coincided with a decreased consumption by one-third.[46, 49] Moreover, a Swedish population-based incident case-referent study demonstrated, for the first time, that introduction of gluten-containing foods in large amounts compared to small or medium amounts was an independent risk factor for CD development (adjusted OR = 1.5, 95% CI: 1.1–2.1).[48] Thereafter, an interaction between HLA-DQ expression and the available number of T-cell stimulatory gluten peptides was also demonstrated, suggesting a quantitative model for CD development.[50] It is, however, not clear whether there is a direct dose-response effect or a threshold effect.

Given the importance of feeding pattern in the first year of life as environmental factors contributing to CD risk, the prevention strategies we can envisage today are mainly based on dietary advice. Data available suggest that breastfeeding must be encouraged. Prospective studies are very much needed to assess the importance of time and dose of gluten at its introduction in infants' diet.

Pro- and prebiotics in infancy

In other conditions characterized by a deranged immune response of the mucosal immune system, attention has been given to the possible role of intestinal bacteria. Probiotics have been suggested to influence immune development and type of immune response.[51] Therefore, it could be envisaged that probiotics may influence the type of immune reactivity to gluten in CD subjects; however, at present, there are no studies that have addressed this issue. In any case, the possibility of introducing other molecules to infants during weaning, which could drive the immune response to gluten proteins towards tolerance, is worth exploring.

Infections

Infectious episodes could potentially contribute to the aetiology of CD as they might increase gut permeability with increased antigen penetration and/or may drive the immune system towards a T_H1-type response

typical for CD. Moreover, rod-shaped bacteria adhering to the intestinal mucosa and differences in the glycosylation structure of the mucosa were recently demonstrated for untreated and treated CD patients,[52] suggesting a possible defect in innate immunity. The Swedish case-referent study found that children who experienced three or more infectious episodes before six months of age had an increased risk for CD before 2 years of age (adjusted OR = 1.4, 95% CI: 1.0–1.9), also after adjusting for differences in infant feeding including breastfeeding.[45]

Two recent papers have attracted the attention on the possible relationships between rotavirus infection and CD.[53, 54] A peptide sequence, specifically recognized by sera from untreated coeliac subjects, sharing a high degree of homology with the rotavirus serotype 1 major neutralizing protein VP7, has been identified. Furthermore, epidemiological observations on the seasonal pattern of incidence of CD have sustained the hypothesis of a viral infection triggering the disease.[55] Rotavirus, as appears from these two recent papers, is a good candidate. The observations pointing to a possible role played by rotavirus in the pathogenesis of CD open a new perspective for prevention strategies in this era of rotavirus vaccination. Further studies are needed to exclude any risk of inducing autoantibodies by mechanisms of molecular mimicry.

A life-course approach

It is likely that CD development, after the infant period, is also influenced by environmental factors, including life-style factors.[45] CD has several features in common with autoimmune diseases, although dependent on gluten exposure, and during the life course an increasing proportion of the population can be expected to be affected. Thus, the search for such causal factors, which exhibit their effect during different periods of the life span, should be intensified. This approach would most likely lead to the identification of a large range of entry points for primary prevention[45]

General or targeted preventive advice?

Preventive advice is the most effective if disseminated widely to the general population instead of approaching only certain risk groups. However, this strategy is only ethically acceptable, although the advice of no harm to anyone benefits the risk groups most.

Recommending breastfeeding of infants benefits all and is likely to be even more important for infants with an increased risk for CD as reflected by a first degree relative with the disease. Thus, such advice can be given generally, without targeting the CD families.

However, other preventive strategies may need to target high-risk subjects. First degree relatives of CD patients, as they are clearly recognized as a genetically susceptible group, represent an important target. Although they carry an approximate risk of 5–10%, it has become clear recently that in their context, there are individuals with a very high risk (up to 30%) on the basis of their HLA-DQ genotype.[56] With the increasing knowledge of other genetic factors of susceptibility, also of non-HLA genes, it will be possible to give to each individual a profile of risk and then to identify those most suitable to an active intervention aiming at prevention of CD.

As far as primary prevention of CD is concerned, major issues in need of investigation are reported in Table 3.

PUBLIC HEALTH

Public health implications

Over the last decades, CD has emerged as a public health problem,[57–60] being fairly common and mostly undiagnosed, and thereby also untreated. Many of the undiagnosed individuals simply accept a chronic state of vague ill-health as normal with reduced well-being, health and also reduced working capacity, while others spend time and resources chasing better health. A broad spectrum of symptoms vary considerably between individuals and within a single individual over time and are therefore often not thought of as being caused by CD, which results in unnecessary health examinations in addition to delayed or even missed diagnoses. Once diagnosed, the recommended GFD improves well-being and health for almost all coeliacs;[61, 62] however, dietary compliance in everyday life is a challenge that requires commitment and support. Higher household costs for foods are incurred by the use of specially produced gluten-free food items and also the cooking is more time-consuming as readymade foods often are gluten-containing and therefore not suitable. Thus, CD has considerable negative impact on the well-being and health of the public and also has negative economical consequences for both affected individuals and society as a whole.

Table 3. Primary prevention of coeliac disease – major issues in need of investigation	
Determining the role of breastfeeding	Long-term effects of breastfeeding
	The molecular basis for the suggested protective effect of breast milk
Determining the role of timing and dose of gluten during introduction	Optimal age for introducing gluten
	Timing in relation to breastfeeding and infectious episodes
	Optimal dose of gluten and pattern for introduction
	Mucosal immune response at the time of gluten introduction
Exploring the role of life style factors in children and adults	A life-course approach to CD development, thus, a search for potentially contributing causes, also after infancy
	The role of daily gluten intake
	The wide range of potential causal environmental factors such as infections, vaccinations, etc
Exploring the option of general and targeted prevention	Advice to the general population vs. genetically identified high-risk subjects
	Public health impact of different preventive strategies

CD, coeliac disease.

Health-related quality of life

HRQOL is a multidimensional concept encompassing physical, emotional, social and cognitive domains, variable over time and is getting increasing attention in medical and health care settings. What matters in HRQOL is the way patients feel about their functioning, not their functioning itself.[63] A majority of CD subjects, symptomatic as well as screening-detected, report improved HRQOL after initiation of treatment with a GFD.[61, 62] Interestingly, the HRQOL in treated CD subjects seems to vary between countries, e.g. in the Netherlands and Canada, it is reported to be comparable with the general population,[63, 64] while decreased as reported from an Italian study.[65] In a Swedish 10-year follow-up study of CD treated adults, the females scored lower and the males higher compared with gender-matched controls.[66] However, methods to measure HRQOL vary between the studies, which restrict comparability.

HRQOL needs to be measured by standardized HRQOL-CD questionnaires,[67] which will allow better comparisons between countries, while also enabling researchers and clinicians to determine better the consequences of CD and its treatment on the daily life of affected persons. By using also the EQ 5D instrument covering five dimensions of health, i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and containing the EQ 5D Visual Analogue Scale,[68] the results can be converted into a weighted health state index to be used to generate quality-adjusted life years (QALY). Also, to facilitate meaningful comparisons, it must be clearly described what group of CD subjects are included, i.e. children or adults, cases detected as a result of symptoms or screening, untreated or treated, and for the latter group also an estimate of compliance with the GFD. Importantly, collaborative studies involving representatives of the food industry, food policy makers and health care providers are needed to investigate, among many initiatives, whether the HRQOL in CD subjects can be improved by increased availability of gluten-free foods, improved food labelling and better education of physicians and dieticians about CD and the GFD.[69]

Is mass-screening a wise use of resources?

It is crucial, from a public health perspective, to increase the detection rate of CD. Since the 1980s, serological markers are available, which lately also can be supported by HLA-typing and in future by non-HLA risk factors. In primary care, CD detection rate can be considerably improved by increased awareness among health professionals.[70–72] Thus, active case-finding among patients who seek medical advice should be intensified. However, mass screening for CD, i.e. screening of the general population, would be the only way to identify a majority of people with CD. Importantly, most of the World Health Organization's criteria required for implementation of a mass screening program, are fulfilled for CD, i.e. it is a fairly common disease with an effective treatment, it is often unrecognized with extensive negative health consequences and serological markers with a high predictive value are available,[73] but still mass screening is a controversial issue.[74]

To be implemented, mass-screening for CD should be defendable from a health economy point of veiw,[75] and such evaluations are called for.[76–79] Both costs and savings related to CD diagnosis and treatment should be estimated. The screening procedure for CD and also the following case ascertainment, as well as the subsequent GFD in verified cases, are related to certain costs. However, adequate treatment of CD cases should reduce complications and the need for future health care, and most likely also result in increased productivity, these being factors which should also be considered. Long-term health consequences also should be evaluated in relation to degree of compliance with the GFD, as it has been suggested that screening detected CD persons tend to be less compliant with the GFD, compared with those diagnosed after actively seeking health care.[80] However, non-economical aspects such as changes in HQOL should also be taken into account, preferably with the EQ-5D instrument, as the result can be assessed in QALYs. This will allow for an estimate of costs per QALY gained by the increased CD case detection and subsequent treatment with a GFD, which then allows comparisons with the cost-effectiveness of other competing health interventions.

Willingness to pay (WTP) is a complementary health economy method that could be used to evaluate CD mass-screening. Before the screening for CD, the participants are given a detailed scenario, including the screening and diagnostic procedure, the risk for CD, and possible future complications, and also gains of being diagnosed. A hypothetical question is posed about their maximum WTP for the CD screening procedure. The WTP then represents the so called intangible costs and benefits, i.e. the value of improved health both in the shorter and in the longer perspectives, the inconvenience and discomfort of following a restricted diet, and the worry and anxiety that the screening may cause.

Global occurrence

The global occurrence of CD and changes over time need to be determined and this requires country cross-sectional screening studies involving age- and gender-representative samples of the populations and repeated screening over time. Finding variations in prevalence, and exploring reasons behind these, will increase our understanding of the CD aetiology. Such mapping also facilitates adequate health care planning including decisions whether or not to give priority to increase detection rate of CD and what strategy to use, i.e. active case-finding initiatives or screening of certain high-risk groups, or even the general population. Also, the overall economic consequences of CD in a specific country or region can be estimated.

Incidence registers, to which all newly diagnosed CD cases in a well-defined population are continuously reported, would enable analyses of temporal relationships between changes in environmental factors and incidence rates and thereby depict potential aetiological factors. Such longitudinal efforts would also provide the basis for long-term follow-up of coeliac subjects and facilitate in-depth studies and increase our understanding of the aetiology and natural history.

As far as public health aspects of CD are concerned, major issues in need of investigation are reported in Table 4.

Table 4. Public health aspects of coeliac disease – major issues in need of investigation	
Estimating consequences with respect to health related quality of life	Standardized instruments for measuring health related quality of life in untreated and treated subjects
	Consequences of CD and its treatment on the daily life of affected persons. Public health impact of CD
Evaluating consequences of mass-screening	Active-case finding and mass-screening strategies
	Costs and savings related to diagnosis and treatment
	Gains in health related quality of life estimated as QALYs
	Costs per QALY gained and comparison with other health interventions
Determining the global occurrence	Cross-sectional screening of age- and gender-representative population samples globally to facilitate health care planning
	Incidence registers for epidemiological surveillance and to be used as a basis for aetiological and long-term follow-up studies

CD, coeliac disease; QALY, quality-adjusted life year.

CONCLUSIONS

While addressing the public health problem of CD, the overall goal should be to improve HQOL of the European population by implementing primary prevention strategies, early diagnosis and improved treatments for CD.

It is urgent to increase the awareness of CD as a public health problem through educational efforts aiming at the public as well as health professionals. A likely consequence would be an increased CD case detection rate and improved support for those diagnosed. Also, other strategies for effective case-finding in high-risk families and even mass screening efforts in populations should be explored to decrease the large proportion of undiagnosed and untreated CD subjects. Such efforts should include evaluation of short- and long-term consequences both for participating individuals and for society, also considering health economy aspects.

Moreover, the magnitude of the CD problem worldwide and trends over time should be established taking into account distribution with respect to age, gender and different high-risk groups. The impact of CD on public health with respect to HQOL and burden of morbidity and mortality should be determined. While doing so, CD of different types should be considered as their health consequences might differ for symptomatic, silent, latent and potential cases.

New treatment strategies need to be developed. Notably this includes a standardized labelling of gluten-free foods and meeting the needs of the people affected by CD with safe, palatable and affordable foods. HQOL of CD subjects should be improved by developing novel therapeutic modalities. The designed strategy should include the development of an animal model of gluten sensitivity to analyse novel treatments for CD. Expected results are the identification of nutritional, immunomodulatory and biochemical strategies useful to treat CD subjects successfully.

The option of primary prevention should be fully explored, which requires combined epidemiological, clinical and basic scientific research efforts. Increased knowledge is needed on the potential impact of environmental factors including life-style factors and also genetic determinants and immunological pathways. Such studies should also consider the importance of gene–environment interactions in the development of CD. It is interesting to know that notwithstanding minor differences caused by the different perspective (North American and European) between the present manuscript and the NIH Consensus Statement on Coeliac Disease (http://consensus.nih.gov/cons/118/118cdc_intro.htm), there is almost a complete overlap as far as the recommendations for future research are concerned.

To achieve these goals and have a significant impact on the public health problem of CD, a collaboration of the stakeholders is fundamental, including research and patient associations as well as industries within both diagnostics and food production.

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CONFLICT OF INTEREST

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