Food Reactivity Autoimmunity and ♀ Health:

Implications for Personalised Diet Therapy

Nov 2020

Justine Bold

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

University of Worcester
www.worcester.ac.uk

1

This session

- Introduction (relevant research & publications)
- What is food reactivity ?
- Links to autoimmunity(AI), AI diseases & women's health
- Explore gender differences in allergy and AI
- Links to the gut microbiome
- Recap on gluten facts
- Gluten's impact on female in health in both coeliac disease (CD) and the controversial condition non coeliac gluten
- sensitivity (NCGS)
- Lectins and α-amylase trypsin inhibitors (ATI)
- Herbicides and role of exorphins
- Cooking / food production that can reduce food reactivity will be considered in the wider context of personalised diet therapy

2

Approach

To present the journal article so reference is provided and can be looked up

- Not there to read every word in presentation
- Discuss main points of paper

Insights from NT practice through to research and publication to help understand topics more and help create wider evidence base

3

Introduction

Worked at University of Worcester on MSc in NT since Jan 2008, also work as Programme Director of CPD at Cardiff University in the Medical School, Centre For Medical Education

Started to practice as NT 2003 (MBANT/CNHC) - Graduated in NT from BCNH

Assessor for NTEC

Working towards PhD by portfolio

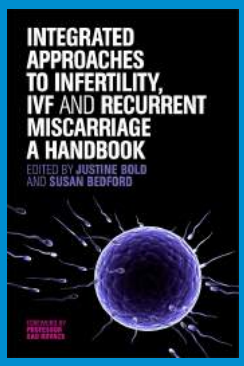
@justineboldfood

justine_bold

Nutrition Health Worcester

4

Published on female health & food reactivity



Mix of journals, text book chapters & academic books.

Research for this session is from research for a new chapter (not published yet) on grains and health for a book called Gluten Related Disorders

5

Open access publications on gluten

nutrients

MDPI

Editorial

Gluten-Free Diet Indications, Safety, Quality, Labels, and Challenges

Kamran Rostami [1], Justine Bold [2,*], Alison Parr [3] and Matt W. Johnson [4]

[1] Department of Gastroenterology, Milton Keynes University Hospital, Milton Keynes MK6 5LD, UK; kamran.rostami@nhs.net
[2] Allied Health and Social Sciences, Institute of Health and Society University of Worcester, Worcester WR2 6AJ, UK
[3] Freelance Nutrition Therapist, Manchester M33 5PD, UK; alison_parr@hotmail.com
[4] Department of Gastroenterology, Luton and Dunstable University Hospital, Luton LU4 0DZ, UK; matthew.johnson@ldh.nhs.uk
* Correspondence: j.bold@worc.ac.uk; Tel.: +44-1905-855-391

Received: 23 July 2017; Accepted: 31 July 2017; Published: 8 August 2017

Abstract: A gluten-free diet (GFD) is the safest treatment modality in patient with coeliac disease (CD) and other gluten-related disorders. Contamination and diet compliance are important factors behind persistent symptoms in patients with gluten related-disorders, in particular CD. How much gluten can be tolerated, how safe are the current gluten-free (GF) products, what are the benefits and side effects of GFD? Recent studies published in *Nutrients* on gluten-free products' quality, availability, safety, as well as challenges related to a GFD are discussed.

Keywords: gluten-free diet; coeliac disease; non-coeliac gluten sensitivity

1. Editorial

Gluten-free diets hit centre stage in the early 1950s, and universally changed our food culture. Not only was there interest in coeliac disease (CD) [ ], but there was also a resurgence of interest in the other gluten-related disorders [,]. Current evidence suggests that gluten and other wheat proteins play an important role in triggering symptoms in some people without CD [ ]. There has been a rapid increase in dietary interest to use it as a treatment modality in the management of both irritable bowels syndrome (IBS) and functional bowel disorders. This strategy has evolved as a result of improvements in our understanding of how these grains induced pathogenicity [,]. The grains that contain gluten seem to have the potential of antigenicity, relating not only to the gluten itself [ ] but also to their other proteins and additives. Junker et al. suggest that α-amylase/trypsin inhibitors (ATIs) in wheat represent strong activators of innate immune responses in monocytes, macrophages, and dendritic cells [ ]. Therefore, a large proportion of the world's population is currently avoiding gluten-containing grains for a variety of different reasons; including sensitivities, intolerances, and allergic reactions (Figure).

Gluten intake, in particular prolamin, is a well-known triggering antigen that initiates adaptive T cells (Th1-mediated) immune response in individuals carrying HLA-DQ2 or HLA-DQ8 against small bowel cells. This in turn leads to an architectural distortion in CD. Epithelial cell damage is the first event to occur within the small bowel, leading to antigen increased intestinal permeability and malabsorption (even in the absence of severe inflammation). Some studies suggest gluten may affect diabetes development by influencing proportional changes in immune cell populations or by modifying the cytokine/chemokine pattern towards an inflammatory profile. Gluten-induced intestinal inflammation might in fact play a primary role in the pathogenesis of type 1 diabetes,

Gastroenterology and Hepatology From Bed to Bench.
©2018 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

REVIEW ARTICLE

Non celiac gluten sensitivity and diagnostic challenges

Giovanni Casella[1], Vincenzo Villanacci[2], Camillo Di Bella[3], Gabrio Bassotti[4], Justine Bold[5], Kamran Rostami[6]
[1]*General Practioner National Health Italy*
[2]*Institute of Pathology Spedali Civili Brescia Italy*
[3]*Pathology Department, Carate Brianza Hospital, ASST-Vimercate (Monza Brianza), Italy*
[4]*Gastroenterology and Hepatology Section, Department of Medicine, University of Perugia School of Medicine, Perugia, Italy*
[5]*Department of Gastroenterology Milton Keynes University Hospital, Milton Keynes, UK*
[6]*Allied Health and Social Sciences, University of Worcester, UK*

ABSTRACT

Non-celiac gluten sensitivity (NCGS), also referred to as non-celiac wheat sensitivity (NCWS), is a clinical syndrome characterized by both intestinal and extra-intestinal symptoms responsive to the withdrawal of gluten-containing food from the diet. The aim of this review is to summarize recent advances in research and provide a brief overview of the history of the condition for the benefit of professionals working in gastroenterology. Academic databases such as PubMed and Google Scholar were searched using key words such as "non-celiac gluten sensitivity", "gluten related disorders", and the studies outlined in reference page were selected and analysed.

Most of the analysed studies agree that NCGS would need to be diagnosed only after exclusion of celiac disease and wheat allergy, and that a reliable serological marker is not available presently. The mechanisms causing symptoms in NCGS after gluten ingestion are largely unknown, but recent advances have begun to offer novel insights. The estimated prevalence of NCGS, at present, varies between 0.6 and 6%. There is an overlap between irritable bowel syndrome and NCGS with regard to the similarity of gastrointestinal symptoms. The histologic characteristics of NCGS are still under investigation, ranging from normal histology to slight increase in the number of T lymphocytes in the superficial epithelium of villi. Positive response to gluten free diet for a limited period (e.g., 6 weeks), followed by the reappearance of symptoms after gluten challenge appears, at this moment, to be the best approach for confirming diagnosis. The Salerno expert criteria may help to diagnose NCGS accurately in particular for research purposes but it has limited applicability in clinical practice.

Keywords: Celiac disease, Non celiac gluten sensitivity, Wheat allergy.
(Please cite as: Casella G, Villanacci V, Di Bella C, Bassotti G, Bold J, Rostami K. Non celiac gluten sensitivity and diagnostic challenges. Gastroenterol Hepatol Bed Bench 2018;11(3):197-202).

Non Celiac Gluten Sensitivity

Non-celiac gluten sensitivity (NCGS) is a clinical syndrome characterized by both intestinal and extra-intestinal symptoms responsive to the withdrawal of wheat and related cereals from the diet (1). These symptoms have been found to relapse following a gluten challenge. NCGS may be diagnosed only after exclusion of celiac disease (CD) and wheat allergy as an established serological marker is not yet available. NCGS is often suspected by the patients themselves leading to self-diagnosis and self-treatment (2). It is important to consider that wheat, in addition to gliadin, contains a number of other potentially bioactive components that may cause gastrointestinal symptoms such as amylase trypsin inhibitors (ATIs) (3) and fermentable oligo-disaccharides-monosaccharides and polyols (FODMAPs) (4). A large number of IBS patients appear to respond to GFD, suggesting that gluten-containing food may be a trigger for IBS symptoms in at least a significant subset of patients (5).

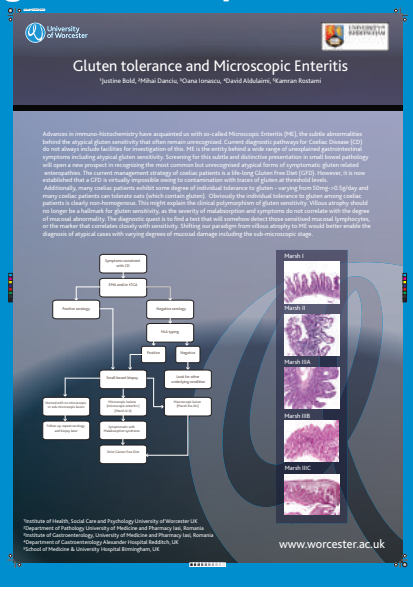
Received: 7 April 2018 *Accepted:* 18 May 2018
Reprint or Correspondence: **Kamran Rostami,** MD, PhD. *Allied Health and Social Sciences, University of Worcester, UK.*
E-mail: krostami@hotmail.com

History of NCGS

The concept of NCGS was described for the first time in 1978 by Ellis *et al*. (6). These authors reported some patients with abdominal pain and diarrhea without histological duodenal lesions who improved after GFD.

6

Other publications - food reactivity: gluten & sulphite sensitivity



Gastroenterology and Hepatology From Bed to Bench
©2012 RIGLD, Research Institute for Gastroenterology and Liver Diseases

EDITORIAL

Considerations for the diagnosis and management of sulphite sensitivity

Justine Bold
Senior Lecturer, Institute of Health & Society, University of Worcester, UK

[1] The review article by Vally and Misso (1) published in the current edition of this journal outlines the broad range of signs and symptoms associated with sulphite sensitivity. These include bronchoconstriction, wheezing, dyspnea, nausea, stomach cramps, diarrhoea, urticaria/angioderma, diaphoresis, hives, laryngeal oedema, generalised itching and swelling, tingling sensations, flushing, hypotension, cyanosis, shock and loss of consciousness (2). Many of the symptoms mirror those of anaphylaxis. Indeed reactions to sulphites can be life threatening, as a number of fatal cases have been reported (3, 4). In many areas of the world, sulphites are now one of the potential allergens (along with the likes of peanuts, fish, crustaceans, gluten and milk) that have to be labelled on food and drink products. In the European Union (EU), levels in foods and drinks above 10 mg/kg or 10 mg per litre have to be labelled. Warning labels are now commonplace, yet in practice there is still a huge amount of ignorance and misinformation about the use of sulphites in food, drinks and pharmaceutical products. Hence, Clinicians need to be aware of sulphite sensitivity in order to enable appropriate diagnosis and provide recommendations for treatment.

Precautions are recommended in a hospital setting where common pharmaceutical drugs, foods and beverages may cause reactions in sulphite sensitive individuals, particularly as sulphites are used in many commonly used drugs including some formulations of paracetamol, zithromax, epinephrine (5). It would also be important to consider the combined potential exposure a sensitive individual may encounter within a hospital or surgical environment from food, drink and pharmaceutical sources.

A low sulphite diet would be recommended if a sulphite sensitive patient is hospitalised in addition to avoidance of pharmaceutical products containing sulphites wherever possible. Management of a sulphite sensitive individual undergoing anaesthesia also presents particular challenges given sulphites may be in both local anaesthetic agents and epinephrine. It is important to remember risks may also be present for individuals that do not know they have a sulphite sensitivity, for example as in the case report of anaphylactic shock during epidural anaesthesia for caesarean section as a result of exposure to metabisulphite (6).

A report from the World Health Organisation International Programme on Chemical Safety states the ADI is 0 - 0.07 mg/kg body weight (7). In a low sulphite diet levels would need to be minimised as much as possible. This probably represents a major challenge for both clinicians and hospital catering staff given the many widespread and varied uses of sulphites. For example, sulphites can be used to modify the texture of dough, as the breaking of disulphide bonds weakens dough making it suitable

Reprint or Correspondence: Justine Bold. (*Nutrition Section Editor*) Senior Lecturer, Institute of Health & Society, University of Worcester, UK.
E-mail: j.bold@worc.ac.uk

Gastroenterol Hepatol Bed Bench 2012;5(1):3-6

7

Invite submissions of academic articles on gluten tolerance for journal special issue – Dec 21 deadline

Co-editing with gastroenterologist Andrew Day

- Accidental gluten exposure in CD
- Compliance to gluten free diet in CD & tolerance thresholds
- Tolerance thresholds in NCGS?
- Influence of some of the other factors that we will explore later?
  - Microbiome
  - ATI
  - Exorphins
  - Fermentation – sourdough

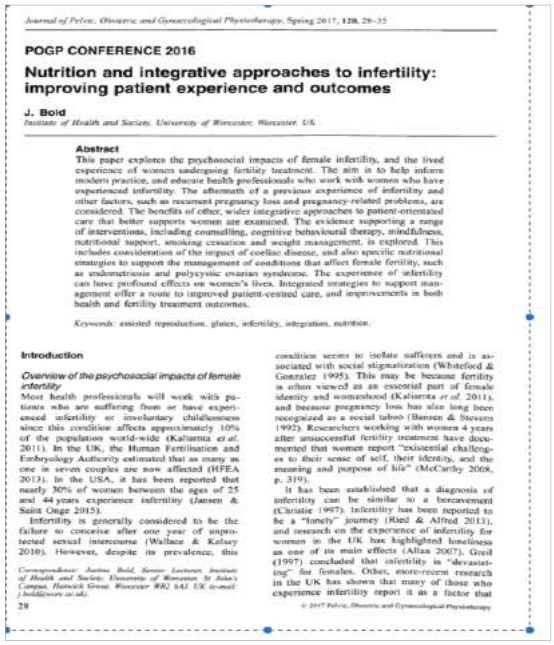
https://journals.sbmu.ac.ir/ghfbb/index.php/ghfbb/announcement

8

♀

Female health:
Infertility
2017 journal article:

Bold J (2017) Nutrition and integrative approaches to infertility: improving patient experience and outcomes. Journal of Pelvic Obstetric and Gynecological Physiotherapy Spring 120 28-35



Journal of Pelvic, Obstetric and Gynaecological Physiotherapy, Spring 2017, **120**, 28–35

POGP CONFERENCE 2016

Nutrition and integrative approaches to infertility: improving patient experience and outcomes

J. Bold
Institute of Health and Society, University of Worcester, Worcester, UK

Abstract

This paper explores the psychosocial impacts of female infertility, and the lived experience of women undergoing fertility treatment. The aim is to help inform modern practice, and educate health professionals who work with women who have experienced infertility. The aftermath of a previous experience of infertility and other factors, such as recurrent pregnancy loss and pregnancy-related problems, are considered. The benefits of other, wider integrative approaches to patient-orientated care that better supports women are examined. The evidence supporting a range of interventions, including counselling, cognitive behavioural therapy, mindfulness, nutritional support, smoking cessation and weight management, is explored. This includes consideration of the impact of coeliac disease, and also specific nutritional strategies to support the management of conditions that affect female fertility, such as endometriosis and polycystic ovarian syndrome. The experience of infertility can have profound effects on women's lives. Integrated strategies to support management offer a route to improved patient-centred care, and improvements in both health and fertility treatment outcomes.

Keywords: assisted reproduction, gluten, infertility, integration, nutrition.

Introduction

Overview of the psychosocial impacts of female infertility

Most health professionals will work with patients who are suffering from or have experienced infertility or involuntary childlessness since this condition affects approximately 10% of the population world-wide (Kaliarnta *et al.* 2011). In the UK, the Human Fertilisation and Embryology Authority estimated that as many as one in seven couples are now affected (HFEA 2013). In the USA, it has been reported that nearly 30% of women between the ages of 25 and 44 years experience infertility (Jansen & Saint Onge 2015).

Infertility is generally considered to be the failure to conceive after one year of unprotected sexual intercourse (Wallace & Kelsey 2010). However, despite its prevalence, this condition seems to isolate sufferers and is associated with social stigmatization (Whitehead & Gonzalez 1995). This may be because fertility is often viewed as an essential part of female identity and womanhood (Kaliarnta *et al.* 2011), and because pregnancy loss has also long been recognized as a social taboo (Jansen & Stevens 1992). Researchers working with women 4 years after unsuccessful fertility treatment have documented that women report "existential challenges to their sense of self, their identity, and the meaning and purpose of life" (McCarthy 2008, p. 319).

It has been established that a diagnosis of infertility can be similar to a bereavement (Christie 1997). Infertility has been reported to be a "lonely" journey (Rüd & Alfred 2013), and research on the experience of infertility for women in the UK has highlighted loneliness as one of its main effects (Allan 2007). Greil (1997) concluded that infertility is "devastating" for females. Other, more-recent research in the UK has shown that many of those who experience infertility report it as a factor that

Correspondence: Justine Bold, Senior Lecturer, Institute of Health and Society, University of Worcester, St John's Campus, Henwick Grove, Worcester WR2 6AJ, UK (e-mail: j.bold@worc.ac.uk).

9

Gastroenterology and Hepatology From Bed to Bench.

CASE REPORT

Non-coeliac gluten sensitivity and reproductive disorders

Justine Bold[1], Kamran Rostami[2]
[1]*Institute of Health & Society University of Worcester, United Kingdom*
[2]*Gastroenterology Unit, Milton Keynes Hospital, United Kingdom*

ABSTRACT

An association between coeliac disease and fertility disorders is well recognised in the current literature, but the information related to non-coeliac gluten sensitivity (NCGS) and infertility is lacking. This case highlights a possible role of treating NCGS in the reversal of infertility.

Keywords: Irritable bowel syndrome, Non-celiac gluten sensitivity, Infertility, Reproductive disorders, Gluten.
(Please cite as: Bold J, Rostami K. Non-coeliac gluten sensitivity and reproductive disorders. Gastroenterol Hepatol Bed Bench 2015;8(4):294-297).

Introduction

Coeliac disease may impair the reproductive life of affected women, eliciting delayed puberty, infertility, amenorrhea and precocious menopause. Clinical and epidemiological studies show that female patients with coeliac disease are at higher risk of spontaneous abortion, low birth weight of the newborn, reduced duration of lactation (1), polycystic ovarian syndrome and endometriosis (2, 3). No adequate studies are available on the non-coeliac gluten sensitivity (NCGS) and fertility disorders. Although iron, folic acid, vitamin D and B12 deficiency have been reported in a proportion of NCGS patients (4, 5). It is unclear whether other gluten related disorders like NCGS could induce malabsorption and deficiency of factors essential for organogenesis, e.g. iron, folic acid and vitamin B12. The overall impression is that patients with NCGS may also be a group particularly susceptible to reproductive abnormalities; however, the pathogenesis of NCGS-related reproductive disorders still awaits clarification. This case highlights the possible association between fertility disorders and NCGS.

Received: 21 August 2015 *Accepted:* 19 September 2015
Reprint or Correspondence: **Justine Bold** Senior Lecturer, Institute of Health & Society University of Worcester, UK.
E-mail: j.bold@worc.ac.uk

Case Report

We present a patient who commenced Assisted Reproduction Treatment (ART) after trying to conceive unsuccessfully for four years. At the time of initial presentation to her general practitioner, she was in her late thirties and had a history of irritable bowel syndrome (IBS) after a Campylobacter jejuni infection and many drug allergies, asthma and a history of miscarriage, but overall was in good health. She reported her IBS was well controlled if she avoided dairy products. The patient in this case study did not have a formal investigation or diagnosis of lactose intolerance, but it maybe that she had developed this after infection as ingestion of dairy foods caused her discomfort with bloating, abdominal distension and diarrhoea. Gastroenteritis may result in gluten or lactose intolerance and IBS is not an appropriate diagnosis in such cases (6).

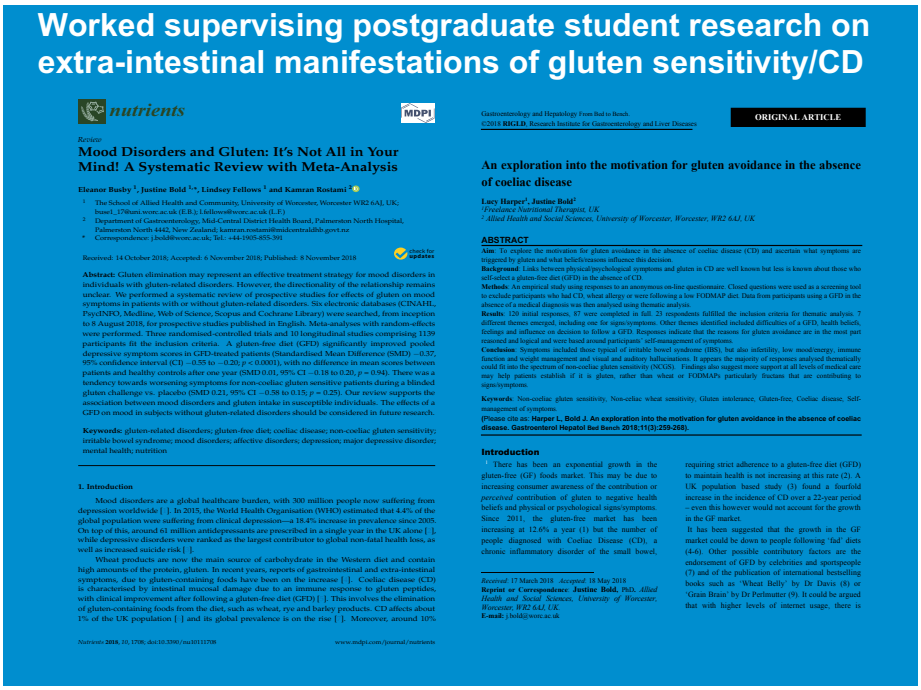
1st case report reporting NCGS & recurrent miscarriage

More case reports emerged since

Bennett S, Gupta A. (2018) Successful pregnancy on a gluten-free diet in a woman with seven miscarriages and non-celiac gluten sensitivity, *AACE clinical case reports*, Case report online ahead of print. https://doi.org/10.4158/accr-2018-0095

10

Worked supervising postgraduate student research on extra-intestinal manifestations of gluten sensitivity/CD



nutrients

MDPI

Review

Mood Disorders and Gluten: It's Not All in Your Mind! A Systematic Review with Meta-Analysis

Eleanor Busby [1], Justine Bold [1,*], Lindsey Fellows [1] and Kamran Rostami [2]

[1] The School of Allied Health and Community, University of Worcester, Worcester WR2 6AJ, UK; busel_1768uni.worc.ac.uk (E.B.); l.fellows@worc.ac.uk (L.F.)
[2] Department of Gastroenterology, Mid-Central District Health Board, Palmerston North Hospital, Palmerston North 4442, New Zealand; kamran.rostami@midcentraldhb.govt.nz
* Correspondence: j.bold@worc.ac.uk; Tel.: +44-1905-855-390

Received: 14 October 2018; Accepted: 6 November 2018; Published: 8 November 2018

Abstract: Gluten elimination may represent an effective treatment strategy for mood disorders in individuals with gluten-related disorders. However, the directionality of the relationship remains unclear. We performed a systematic review of prospective studies for effects of gluten on mood symptoms in patients with or without gluten-related disorders. Six electronic databases (CINAHL, PsycINFO, Medline, Web of Science, Scopus and Cochrane Library) were searched, from inception to 8 August 2018, for prospective studies published in English. Meta-analyses with random-effects were performed. Three randomised-controlled trials and 10 longitudinal studies comprising 1139 participants fit the inclusion criteria. A gluten-free diet (GFD) significantly improved pooled depressive symptom scores in GFD-treated patients (Standardised Mean Difference (SMD) −0.37, 95% confidence interval (CI) −0.55 to −0.20; $p < 0.0001$), with no difference in mean scores between patients and healthy controls after one year (SMD 0.01, 95% CI −0.18 to 0.20, $p = 0.94$). There was a tendency towards worsening symptoms for non-coeliac gluten sensitive patients during a blinded gluten challenge vs. placebo (SMD 0.21, 95% CI −0.58 to 0.15, $p = 0.25$). Our review supports the association between mood disorders and gluten intake in susceptible individuals. The effects of a GFD on mood in subjects without gluten-related disorders should be considered in future research.

Keywords: gluten-related disorders; gluten-free diet; coeliac disease; non-coeliac gluten sensitivity; irritable bowel syndrome; mood disorders; affective disorders; depression; major depressive disorder; mental health; nutrition

1. Introduction

Mood disorders are a global healthcare burden, with 300 million people now suffering from depression worldwide [ ]. In 2015, the World Health Organisation (WHO) estimated that 4.4% of the global population were suffering from clinical depression—a 18.4% increase in prevalence since 2005. On top of this, around 61 million antidepressants are prescribed in a single year in the UK alone [ ], while depressive disorders were ranked as the largest contributor to global non-fatal health loss, as well as increased suicide risk [ ].

Wheat products are now the main source of carbohydrate in the Western diet and contain high amounts of the protein, gluten. In recent years, reports of gastrointestinal and extra-intestinal symptoms, due to gluten-containing foods have been on the increase [ ]. Coeliac disease (CD) is characterised by intestinal mucosal damage due to an immune response to gluten peptides, with clinical improvement after following a gluten-free diet (GFD) [ ]. This involves the elimination of gluten-containing foods from the diet, such as wheat, rye and barley products. CD affects about 1% of the UK population [ ] and its global prevalence is on the rise [ ]. Moreover, around 10%

Gastroenterology and Hepatology From Bed to Bench.
©2018 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

ORIGINAL ARTICLE

An exploration into the motivation for gluten avoidance in the absence of coeliac disease

Lucy Harper[1], Justine Bold[2]
[1] Freelance Nutritional Therapist, UK
[2] Allied Health and Social Sciences, University of Worcester, Worcester, WR2 6AJ, UK

ABSTRACT

Aim: To explore the motivation for gluten avoidance in the absence of coeliac disease (CD) and ascertain what symptoms are triggered by gluten and what beliefs/reasons influence this decision.
Background: Links between physical/psychological symptoms and gluten in CD are well known but less is known about those who self-select a gluten-free diet (GFD) in the absence of CD.
Methods: An empirical study using responses to an anonymous on-line questionnaire. Closed questions were used as a screening tool to exclude participants who had CD, wheat allergy or were following a low FODMAP diet. Data from participants using a GFD in the absence of a medical diagnosis was then analysed using thematic analysis.
Results: 120 initial responses, 87 were completed in full. 23 respondents fulfilled the inclusion criteria for thematic analysis. 7 different themes emerged, including one for signs/symptoms. Other themes identified included difficulties of a GFD, health beliefs, feelings and influence on decision to follow a GFD. Responses indicate that the reasons for gluten avoidance are in the most part reasoned and logical and were based around participants' self-management of symptoms.
Conclusion: Symptoms included those typical of irritable bowel syndrome (IBS), but also infertility, low mood/energy, immune function and weight management and visual and auditory hallucinations. It appears the majority of responses analysed thematically could fit into the spectrum of non-coeliac gluten sensitivity (NCGS). Findings also suggest more support at all levels of medical care may help patients establish if it is gluten, rather than wheat or FODMAPs particularly fructans that are contributing to signs/symptoms.

Keywords: Non-coeliac gluten sensitivity, Non-celiac wheat sensitivity, Gluten intolerance, Gluten-free, Coeliac disease, Self-management of symptoms.
(Please cite as: Harper L, Bold J. An exploration into the motivation for gluten avoidance in the absence of coeliac disease. Gastroenterol Hepatol Bed Bench 2018;11(3):259-268).

Introduction

There has been an exponential growth in the gluten-free (GF) foods market. This may be due to increasing consumer awareness of the contribution or *perceived* contribution of gluten to negative health beliefs and physical or psychological signs/symptoms. Since 2011, the gluten-free market has been increasing at 12.6% a year (1) but the number of people diagnosed with Coeliac Disease (CD), a chronic inflammatory disorder of the small bowel, requiring strict adherence to a gluten-free diet (GFD) to maintain health is not increasing at this rate (2). A UK population based study (3) found a fourfold increase in the incidence of CD over a 22-year period – even this however would not account for the growth in the GF market.

It has been suggested that the growth in the GF market could be down to people following 'fad' diets (4-6). Other possible contributory factors are the endorsement of GFD by celebrities and sportspeople (7) and of the publication of international bestselling books such as 'Wheat Belly' by Dr Davis (8) or 'Grain Brain' by Dr Perlmutter (9). It could be argued that with higher levels of internet usage, there is

Received: 17 March 2018 *Accepted:* 18 May 2018
Reprint or Correspondence: Justine Bold, PhD. *Allied Health and Social Sciences, University of Worcester, Worcester, WR2 6AJ, UK.*
E-mail: j.bold@worc.ac.uk

11

Recent publication from a student research project on Gluten Free Diet in management of epilepsy in those with CD

gastrointestinal disorders

MDPI

Review

A Gluten Free Diet in the Management of Epilepsy in People with Coeliac Disease or Gluten Sensitivity

Zoë Gilbey [1] and Justine Bold [1,2,*]

[1] School of Allied Health & Community, University of Worcester, Worcester WR2 6AJ, UK; gila1_168uni.worc.ac.uk
[2] Centre for Medical Education, Medical School, Cardiff University, Cardiff CF14 4YS, UK
* Correspondence: j.bold@worc.ac.uk

Received: 2 August 2020; Accepted: 3 September 2020; Published: 8 September 2020

Abstract: The aim of this review was to assess the effects of a gluten free diet (GFD) in the management of epilepsy in people with coeliac disease (CD) or gluten sensitivity (GS). A systematic approach was used to undertake a literature review. Five electronic databases (PubMed; Scopus; Google Scholar; Cochrane Epilepsy Group specialised register; Cochrane Register of Controlled Trails (CENTRAL) via the Cochrane Register of Online Trials) were searched using predetermined relevant search terms. In total, 668 articles were identified. Duplicates were removed and predefined inclusion and exclusion criteria were applied, and a PRISMA flow chart was produced. Data was extracted using Covidence software. Twelve studies on Epilepsy and CD involving a total of 70 participants were selected for analysis; narrative synthesis was used owing to the small sample sizes in the selected studies. None of the 12 studies meeting inclusion criteria investigated gluten sensitivity and epilepsy. All the included studies support a link between epilepsy and CD. GFD was effective in 44 out of 70 participants across the studies in terms of a reduction of seizures, reduction of antiepileptic drugs (AEDs) or normalisation of EEG pattern. A total of 44 participants showed a reduction in seizures (across eight studies) and complete cessation of seizures was reported in 22 participants. In general, the earlier the GFD is implemented after the onset of seizures, the better the likelihood of the GFD being successful in supporting control of seizures. Mechanisms linking gluten with epilepsy are not fully understood; possible hypotheses include gluten mediated toxicity, immune-induced cortical damage and malabsorption. Evidence suggests the effectiveness of a GFD in supporting the management of epilepsy in patients with CD, although the quality of evidence is low. There appears to be a growing number of neurologists who are prepared to advocate the use of a GFD. A multidisciplinary approaches and further research are recommended. It could be argued that when balancing potential treatments such as AEDs or surgery, a GFD has a low likelihood of harm.

Keywords: epilepsy; seizures; ketogenic diet; gluten free diet; coeliac disease; non-coeliac gluten sensitivity; gluten ataxia

1. Introduction

1.1. Epilepsy

Epilepsy is a neurological disorder that affects around 70 million people worldwide [ ]. It can have a significant effect on the quality of life of those affected and their families [ ]. Seizures are usually sudden, acute and unpredictable. People with epilepsy and their cohabiting relatives report higher levels of anxiety, depression and social anxiety disorders compared with the general population [ ]. Epilepsy is not one disorder, but a term used to describe several conditions that share seizures as a common element [ ]. There are over 40 different types of seizure [ ] and the seizure type and

12

Publications for practice @ fertility/gluten too

Bold J (2016) Gluten and Female Infertility Forum Gluten Free Journal for Healthcare Professionals Edition 2 2016 5-7 Dr Schar Institute

13

What is Food reactivity?

Food allergies & sensitivities

14 FOOD ALLERGENS

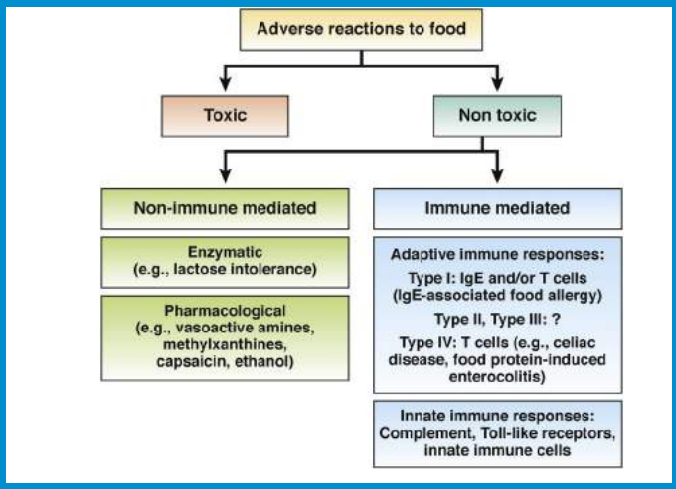
Main allergens identified on labelling

Images from istock

14

What is Food reactivity?

Classification of reactions to food from 2015 paper



More detail on reaction types

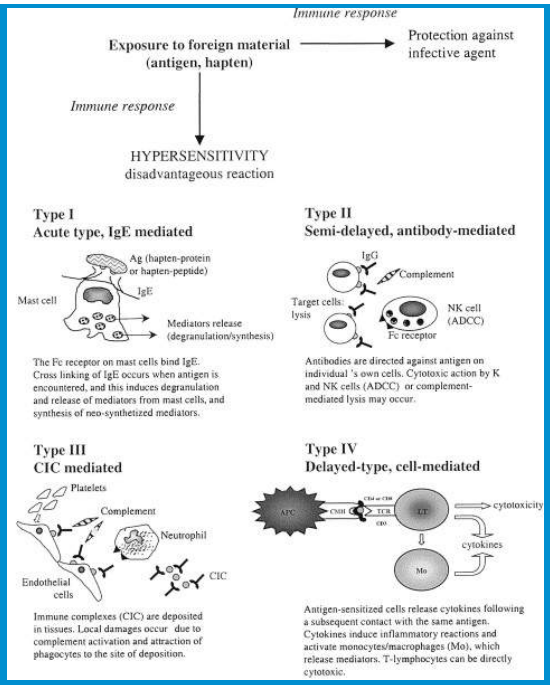
Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics.
Gastroenterology. 2015;148(6):1120-31.e4. doi:10.1053/j.gastro.2015.02.006

15

Type I, II, III, IV Reactions

Gell & Coombs 1963

Still widely used in medical practice but questioned as drug reactions don't fit !



16

How does food reactivity link to ♀ health?

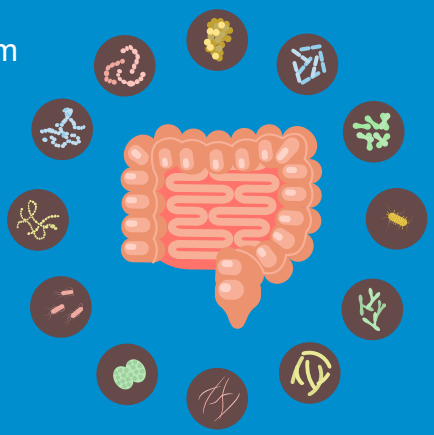
Image: female lifecycle istock

17

How does food reactivity link to health?

Affects gastrointestinal system & microbiome influencing

- Immunity
- Inflammation
- Nutritional status
- Hormones
- Metabolism
- Detoxification



Feeds into a functional medicine approach

Image: digestive tract and probiotics istock

18

How?

Review…

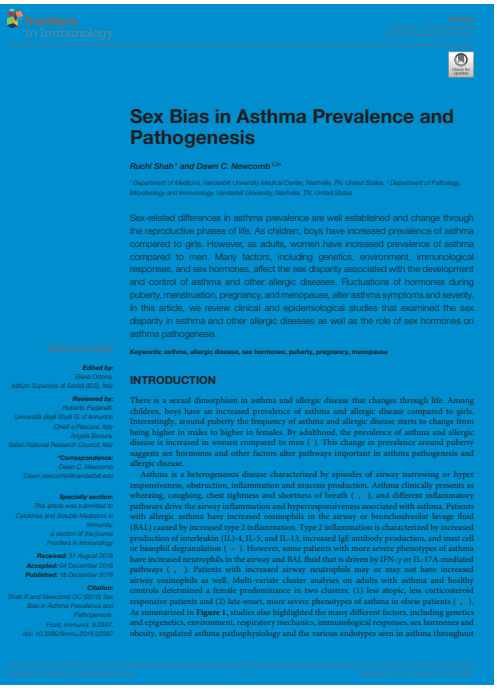
Gender differences & disparities in key conditions & circumstances

19

Gender differences in asthma & allergy

Rates of atopic disease higher in boys <18 years

- Around puberty this starts to change and in 18+ years rate is higher in females
- Evens out after menopause
  - Sex hormones ARE key



frontiers in Immunology

Sex Bias in Asthma Prevalence and Pathogenesis

Ruchi Shah[1] and Dawn C. Newcomb[1,2]

[1] Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States, [2] Department of Pathology, Microbiology and Immunology, Vanderbilt University, Nashville, TN, United States

Sex-related differences in asthma prevalence are well established and change through the reproductive phases of life. As children, boys have increased prevalence of asthma compared to girls. However, as adults, women have increased prevalence of asthma compared to men. Many factors, including genetics, environment, immunological responses, and sex hormones, affect the sex disparity associated with the development and control of asthma and other allergic diseases. Fluctuations of hormones during puberty, menstruation, pregnancy, and menopause, alter asthma symptoms and severity. In this article, we review clinical and epidemiological studies that examined the sex disparity in asthma and other allergic diseases as well as the role of sex hormones on asthma pathogenesis.

Keywords: asthma, allergic disease, sex hormones, puberty, pregnancy, menopause

INTRODUCTION

There is a sexual dimorphism in asthma and allergic disease that changes through life. Among children, boys have an increased prevalence of asthma and allergic disease compared to girls. Interestingly, around puberty the frequency of asthma and allergic disease starts to change from being higher in males to higher in females. By adulthood, the prevalence of asthma and allergic disease is increased in women compared to men ( ). This change in prevalence around puberty suggests sex hormones and other factors alter pathways important in asthma pathogenesis and allergic disease.

Asthma is a heterogeneous disease characterized by episodes of airway narrowing or hyper responsiveness, obstruction, inflammation and mucous production. Asthma clinically presents as wheezing, coughing, chest tightness and shortness of breath (,), and different inflammatory pathways drive the airway inflammation and hyperresponsiveness associated with asthma. Patients with allergic asthma have increased eosinophils in the airway or bronchoalveolar lavage fluid (BAL) caused by increased type 2 inflammation. Type 2 inflammation is characterized by increased production of interleukin (IL)-4, IL-5, and IL-13, increased IgE antibody production, and mast cell or basophil degranulation (,). However, some patients with more severe phenotypes of asthma have increased neutrophils in the airway and BAL fluid that is driven by IFN-γ or IL-17A-mediated pathways (,). Patients with increased airway neutrophils may or may not have increased airway eosinophils as well. Multi-variate cluster analyses on adults with asthma and healthy controls determined a female predominance in two clusters; (1) less atopic, less corticosteroid responsive patients and (2) late-onset, more severe phenotypes of asthma in obese patients (,). As summarized in **Figure 1**, studies also highlighted the many different factors, including genetics and epigenetics, environment, respiratory mechanics, immunological responses, sex hormones and obesity, regulated asthma pathophysiology and the various endotypes seen in asthma throughout

20

2019 article reports:

Studies across the world show more adult females than males have allergies

C section births enhance risk of food allergy overruling sex disparity

Isabella Pali-Schöll;Erika Jensen-Jarolim **Gender aspects in food allergy**
Current opinion in allergy and clinical immunology. , 2019, Vol.19(3), p.249-255

Purpose of review
The difference of food allergy prevalence between male and female individuals is well documented and should have more impact for personalized diagnosis and management. Although in younger age male sex dominates, in adults more women are affected by food allergies. This sex disparity diminishes again around menopause, underlining the influence of sex hormones, but in addition, also metabolic gender-specific factors and differences in microbiome composition might contribute to the different expression of food allergy in the two genders. The sex-dependent and gender-dependent influence on development of food allergy, disease severity, as well as on social, dietary and neuropsychological factors in studies mainly published within past 18 months are discussed in this review.

Recent findings
Sex and gender differences likely play a role in food allergy development, for instance via influence on immune cells and mediators, or on the composition of the microbiome, but only few controlled studies on this specific topic are available.

Summary
Future prospective studies need to clearly take into account the sex and gender difference in order to provide personalized diagnosis, management and treatment of food allergy.

21

Same article reports:

Variation in asthma severity through menstrual cycle (progesterone hypersensitivity). This can cause dermatitis, urticaria, asthma, and anaphylaxis.

Catamenial sensitivity - mild dermatitis, urticaria, asthma attack to angioedema and anaphylactic shock in the luteal phase of the menstrual cycle usually on the 20−21 day of the 28-day cycle

Sex hormone receptors on lymphocytes, monocytes, eosinophils, basophils, mast cells, lymph node cells & mast cell reactivity enhanced by oestrogen

22

Same article reports:

T cell responses vary with hormonal fluctuations (T helper cells important in mucosal immunity).

IgE antibodies lower before ovulation, whilst IgA /IgG are higher.

Skin prick testing reactivity differs through the menstrual cycle.

Asthma symptoms exacerbated before / during ovulation.

Sex differences in microbiome composition recently reported in murine studies - "female microbiota may be less efficient in preventing allergies"

23

Autoimmunity (AI) in female health

AI diseases affect @ 8% population

BUT more females than males

This article says 78% of those with AI disease are female and reasons why are NOT clear

The American Journal of Pathology, Vol. 173, No. 3, September 2008
Copyright © American Society for Investigative Pathology
DOI: 10.2353/ajpath.2008.071096

Review

Sex Differences in Autoimmune Disease from a Pathological Perspective

DeLisa Fairweather,*† Sylvia Frisancho-Kiss,* and Noel R. Rose†‡

From the Departments of Environmental Health Sciences* and Pathology,† and the W. Harry Feinstone Department of Molecular Microbiology and Immunology,‡ the Johns Hopkins Medical Institutions, Baltimore, Maryland

Autoimmune diseases affect ~8% of the population, 78% of whom are women. The reason for the high prevalence in women is unclear. Women are known to respond to infection, vaccination, and trauma with increased antibody production and a more T helper (Th)2-predominant immune response, whereas a Th1 response and inflammation are usually more severe in men. This review discusses the distribution of autoimmune diseases based on sex and age, showing that autoimmune diseases progress from an acute pathology associated with an inflammatory immune response to a chronic pathology associated with fibrosis in both sexes. Autoimmune diseases that are more prevalent in males usually manifest clinically before age 50 and are characterized by acute inflammation, the appearance of autoantibodies, and a proinflammatory Th1 immune response. In contrast, female-predominant autoimmune diseases that manifest during the acute phase, such as Graves' disease and systemic lupus erythematosus, are diseases with a known antibody-mediated pathology. Autoimmune diseases with an increased incidence in females that appear clinically past age 50 are associated with a chronic, fibrotic Th2-mediated pathology. Th17 responses increase neutrophil inflammation and chronic fibrosis. This distinction between acute and chronic pathology has primarily been overlooked, but greatly impacts our understanding of sex differences in autoimmune disease. (Am J Pathol 2008, 173:600–609; DOI: 10.2353/ajpath.2008.071096)

Autoimmune diseases are the third most common category of disease in the United States after cancer and cardiovascular disease, affecting ~5 to 8% of the population or 14.7 to 23.5 million people.[1] Conservative estimates indicate that ~78% of the people affected with autoimmune diseases are women.[2–4] For some time it has been known that the basic immune response differs between men and women. Women respond to infection, vaccination, and trauma with increased antibody production, whereas inflammation is usually more severe in men resulting in an increased mortality in men and protection against infection in women.[5–10]

Antibodies provide critical protection against infection, and are the key protective response induced by vaccination.[11] Naturally occurring autoantibodies are frequently found in the serum of normal humans and are important in clearing cellular debris induced by inflammation or physical damage.[11,12] However, autoantibodies may induce damage by binding self-antigens and activating the complement cascade, resulting in direct cytotoxicity or an immune complex (IC)-associated pathology. The number of different autoantibodies present in an individual is a good predictor of the risk of developing an autoimmune disease. For example, estimates based on first degree relatives show that the likelihood of a child developing type 1 diabetes within 5 years is 10% in the presence of one autoantibody, 30% for two autoantibodies, and 60 to 80% if three autoantibodies are present.[13] Thus, the risk for developing an autoimmune disease increases as the number of autoantibodies increases, and the number of autoantibodies increases as we age, regardless of sex (Figure 1).[14,15] So even though an increased antibody response protects women from infections, it also increases the risk of developing an autoimmune disease.

In a similar manner, immune cells may damage tissues directly by killing cells or indirectly by releasing cytotoxic cytokines, enzymes, or reactive nitrogen/oxygen intermediates. Cytokines and other mediators released by resident mast cells (MCs) and macrophages recruit inflammatory cells, such as neutrophils, macrophages, and T cells, to the site of damage. $CD4^+$ T cells have been

Supported by the National Institutes of Health (grants R01 HL067033 to D.F., and P30 ES03819 and R01 HL67290 to N.R.R.).
Accepted for publication March 6, 2008.
Address reprint requests to DeLisa Fairweather, Ph.D., Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe St., Room E7628, Baltimore, MD 21205. E-mail: dfairwea@jhsph.edu.

24

AI in women – from previous article

"Autoimmune diseases that are more prevalent in males usually manifest clinically before age 50 and are characterized by acute inflammation, the appearance of autoantibodies, and a proinflammatory Th1 immune response. In contrast, female predominant autoimmune diseases that manifest during the acute phase, such as Graves' disease and systemic lupus erythematosus, are diseases with a known antibody-mediated pathology

Women respond to infection, vaccination, and trauma with increased antibody production, whereas inflammation is usually more severe in men resulting in an increased mortality in men and protection against infection in women.

Antibodies provide critical protection against infection, and are the key protective response induced by vaccination."

DeLisa Fairweather,*† Sylvia Frisancho-Kiss,* and Noel R. Rose Sex Differences and Autoimmune Disease 601 AJP September 2008, Vol. 173, No. 3

25

AI in women

"Oestrogens favor the antibody production-enhancing Th2 response and, by doing so, possibly, increase the risk towards abnormal autoimmune function. Others have suggested that women are genetically predisposed towards abnormal autoimmune function, possibly because the X chromosome may confer susceptibility towards tolerance breakdown"

ELSEVIER

Journal of Autoimmunity 28 (2007) 1–6

auto journal of immunity

www.elsevier.com/locate/jautimm

Gender as risk factor for autoimmune diseases

Norbert Gleicher [a,b,c,*], David H. Barad [a,b,d,e]

[a] The Center for Human Reproduction, 21 East 69th Street, New York, NY 10021, USA
[b] The Foundation for Reproductive Medicine, New York, NY, USA
[c] Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA
[d] Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY, USA
[e] Department of Obstetrics, Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, NY, USA

Received 28 November 2006; revised 11 December 2006; accepted 11 December 2006

Abstract

Most autoimmune diseases occur significantly more frequently in women than men. This female preponderance for abnormal autoimmune function has largely gone unexplained. Many investigations have concentrated on the effects of female and male sex hormones on immune function, by suggesting that estrogens favor the antibody production-enhancing Th2 response and, by doing so, possibly, increase the risk towards abnormal autoimmune function. Others have suggested that women are genetically predisposed towards abnormal autoimmune function, possibly because the X chromosome may confer susceptibility towards tolerance breakdown. Recent developments have, however, opened new research avenues. The possible association between persistent *fetal–maternal* microchimerism and the development of autoimmune diseases has attracted special interest. Since, in analogy to allogeneic organ transplantation, *fetal–maternal* (and *maternal–fetal*) microchimerism may play an important role in the immunologic tolerance of the fetal semi-allograft, female preponderance for autoimmune diseases may be understood as a consequence of increased allogeneic cell traffic in females (in comparison to males), increased risk for long-term microchimerism and, therefore, as a consequence of the former two, the development of abnormal autoimmunity. Under an evolutionary view point the occurrence of autoimmune diseases, in general, can be seen as the price to be paid for successful reproduction. In view of increased exposure to cell traffic, women, of course, would be expected to pay a higher price, reflected in more autoimmunity.

Keywords: Autoimmunity; Autoimmune diseases; Gender; Gender differences; Microchimerism; Cell traffic; Pregnancy; Vaginal delivery; Cesarean section; Sex hormones; Evolution

To be a woman is something so strange, so confusing and so complicated that only a woman could put up with it.
–Kierkegaard

Why is it that approximately 78% of roughly 80 medical conditions, currently believed to be autoimmune in nature, affecting 5–8% of the general population, are bound to occur in women? [1]. Much has been written in attempts to explain this overwhelming female preponderance, and theories abound. A definite answer is, however, still lacking. This review is an attempt at summarizing long held beliefs, but also at integrating more recent concepts, which so far may not have received adequate attention.

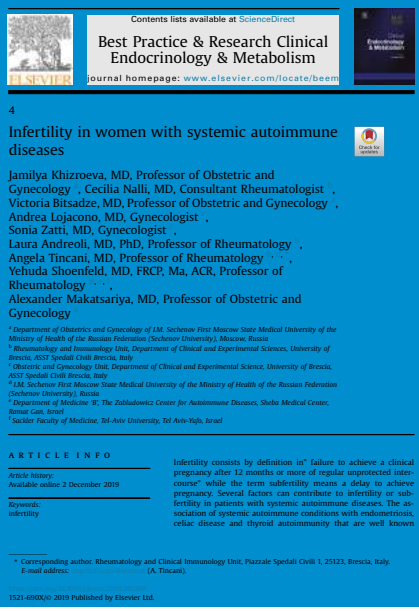
Our ultimate purpose is, however, to call attention to the fact that there must be considerable evolutionary purpose and value to the pathophysiology, responsible for women's dramatically increased predisposition towards abnormal autoimmunity. If such purpose and value did not exist, it is difficult to believe that evolutionary pressures would have maintained such an obvious risk to health and well-being. We have previously noted that, when challenged, evolution favors the creation of new life over its maintenance [2]. It, therefore, is tempting to speculate that, in some ways, exposing women

* Corresponding author. The Center for Human Reproduction, 21 East 69th Street, New York, NY 10021, USA. Tel.: +1 212 994 4400; fax: +1 212 994 4499.
E-mail address: ngleicher@thecrh.com (N. Gleicher).

26

Impacts of systemic AI disease on women

P3 of this article details some impacts – details on next slide



Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

4

Infertility in women with systemic autoimmune diseases

Jamilya Khizroeva, MD, Professor of Obstetric and Gynecology [a], Cecilia Nalli, MD, Consultant Rheumatologist [b], Victoria Bitsadze, MD, Professor of Obstetric and Gynecology [a], Andrea Lojacono, MD, Gynecologist [c], Sonia Zatti, MD, Gynecologist [c], Laura Andreoli, MD, PhD, Professor of Rheumatology [b], Angela Tincani, MD, Professor of Rheumatology [b, *], Yehuda Shoenfeld, MD, FRCP, Ma, ACR, Professor of Rheumatology [d, e, f], Alexander Makatsariya, MD, Professor of Obstetric and Gynecology [a]

[a] Department of Obstetrics and Gynecology of I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia
[b] Rheumatology and Immunology Unit, Department of Clinical and Experimental Sciences, University of Brescia, ASST Spedali Civili Brescia, Italy
[c] Obstetric and Gynecology Unit, Department of Clinical and Experimental Science, University of Brescia, ASST Spedali Civili Brescia, Italy
[d] I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Russia
[e] Department of Medicine 'B', The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Ramat Gan, Israel
[f] Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv-Yafo, Israel

ARTICLE INFO

Article history:
Available online 2 December 2019

Keywords:
infertility

Infertility consists by definition in" failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse" while the term subfertility means a delay to achieve pregnancy. Several factors can contribute to infertility or subfertility in patients with systemic autoimmune diseases. The association of systemic autoimmune conditions with endometriosis, celiac disease and thyroid autoimmunity that are well known

* Corresponding author. Rheumatology and Clinical Immunology Unit, Piazzale Spedali Civili 1, 25123, Brescia, Italy.
E-mail address: [redacted] (A. Tincani).

1521-690X/© 2019 Published by Elsevier Ltd.

27

Impacts of systemic AI disease

"Patients with systemic autoimmune diseases have less children than expected in the general population. Some of these women do not have children at all, some others report a prolonged time to pregnancy resulting in smaller family size than they expected [3]. Certainly, in this population, the number of children can be also related to the frequently associated organ specific autoimmune disease (i.e.: thyroiditis or celiac disease), to endometriosis that is known to have an increased rate of occurrence in women with systemic autoimmune diseases or to the wellknown increased rate of adverse pregnancy outcome such as miscarriages and fetal losses. However, many other factors should be taken into consideration. The disease itself and the musculoskeletal limitations linked to it can impair sexual function and psychologically impact on woman desire [4]. In addition, in several systemic autoimmune diseases, also the poor body image, the related poor self-esteem and depression can influence the personal and sexual relationships of these women [5,6]"

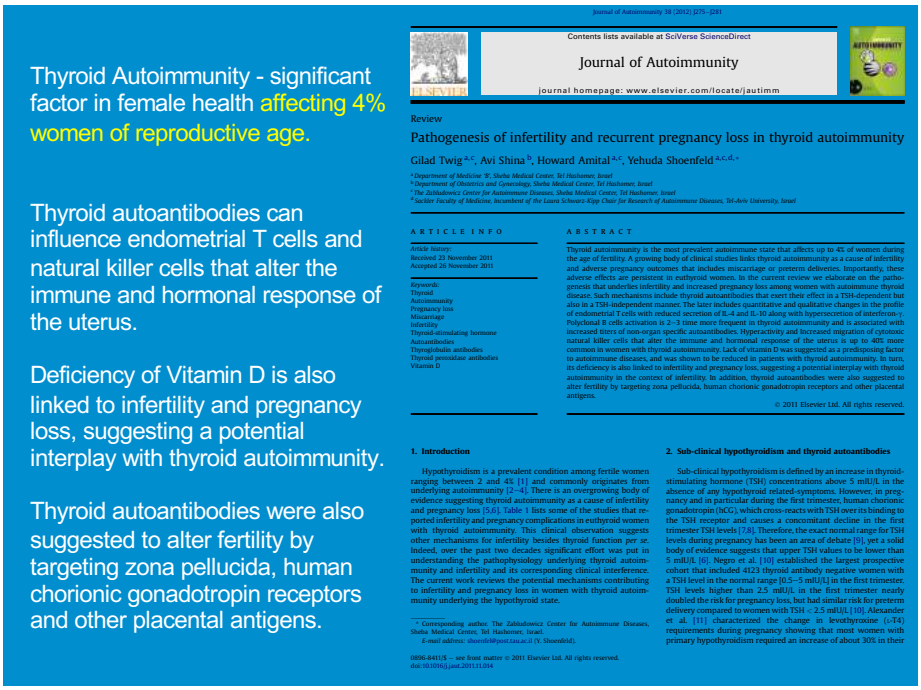
28

Thyroid Autoimmunity - significant factor in female health affecting 4% women of reproductive age.

Thyroid autoantibodies can influence endometrial T cells and natural killer cells that alter the immune and hormonal response of the uterus.

Deficiency of Vitamin D is also linked to infertility and pregnancy loss, suggesting a potential interplay with thyroid autoimmunity.

Thyroid autoantibodies were also suggested to alter fertility by targeting zona pellucida, human chorionic gonadotropin receptors and other placental antigens.



Journal of Autoimmunity 38 (2012) J275–J281

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/autimm

Review

Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity

Gilad Twig [a,c], Avi Shina [b], Howard Amital [a,c], Yehuda Shoenfeld [a,c,d,*]

[a] Department of Medicine 'B', Sheba Medical Center, Tel Hashomer, Israel
[b] Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel
[c] The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
[d] Sackler Faculty of Medicine, Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Tel-Aviv University, Israel

ARTICLE INFO

Article history:
Received 23 November 2011
Accepted 26 November 2011

Keywords:
Thyroid
Autoimmunity
Pregnancy loss
Miscarriage
Infertility
Thyroid-stimulating hormone
Autoantibodies
Thyroglobulin antibodies
Thyroid peroxidase antibodies
Vitamin D

ABSTRACT

Thyroid autoimmunity is the most prevalent autoimmune state that affects up to 4% of women during the age of fertility. A growing body of clinical studies links thyroid autoimmunity as a cause of infertility and adverse pregnancy outcomes that includes miscarriage or preterm deliveries. Importantly, these adverse effects are persistent in euthyroid women. In the current review we elaborate on the pathogenesis that underlies infertility and increased pregnancy loss among women with autoimmune thyroid disease. Such mechanisms include thyroid autoantibodies that exert their effect in a TSH-dependent but also in a TSH-independent manner. The later includes quantitative and qualitative changes in the profile of endometrial T cells with reduced secretion of IL-4 and IL-10 along with hypersecretion of interferon-γ. Polyclonal B cells activation is 2–3 time more frequent in thyroid autoimmunity and is associated with increased titers of non-organ specific autoantibodies. Hyperactivity and increased migration of cytotoxic natural killer cells that alter the immune and hormonal response of the uterus is up to 40% more common in women with thyroid autoimmunity. Lack of vitamin D was suggested as a predisposing factor to autoimmune diseases, and was shown to be reduced in patients with thyroid autoimmunity. In turn, its deficiency is also linked to infertility and pregnancy loss, suggesting a potential interplay with thyroid autoimmunity in the context of infertility. In addition, thyroid autoantibodies were also suggested to alter fertility by targeting zona pellucida, human chorionic gonadotropin receptors and other placental antigens.

1. Introduction

Hypothyroidism is a prevalent condition among fertile women ranging between 2 and 4% [1] and commonly originates from underlying autoimmunity [2–4]. There is an overgrowing body of evidence suggesting thyroid autoimmunity as a cause of infertility and pregnancy loss [5,6]. Table 1 lists some of the studies that reported infertility and pregnancy complications in euthyroid women with thyroid autoimmunity. This clinical observation suggests other mechanisms for infertility besides thyroid function *per se*. Indeed, over the past two decades significant effort was put in understanding the pathophysiology underlying thyroid autoimmunity and infertility and its corresponding clinical interference. The current work reviews the potential mechanisms contributing to infertility and pregnancy loss in women with thyroid autoimmunity underlying the hypothyroid state.

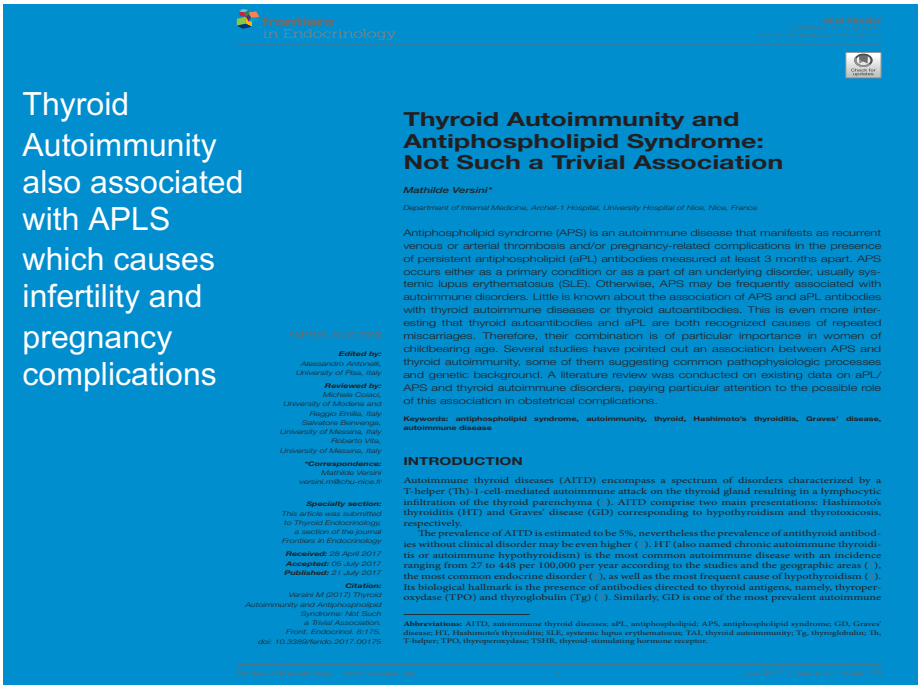
* Corresponding author. The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel.
E-mail address: shoenfeld@post.tau.ac.il (Y. Shoenfeld).

0896-8411/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jaut.2011.11.014

2. Sub-clinical hypothyroidism and thyroid autoantibodies

Sub-clinical hypothyroidism is defined by an increase in thyroid-stimulating hormone (TSH) concentrations above 5 mIU/L in the absence of any hypothyroid related-symptoms. However, in pregnancy and in particular during the first trimester, human chorionic gonadotropin (hCG), which cross-reacts with TSH over its binding to the TSH receptor and causes a concomitant decline in the first trimester TSH levels [7,8]. Therefore, the exact normal range for TSH levels during pregnancy has been an area of debate [9], yet a solid body of evidence suggests that upper TSH values to be lower than 5 mIU/L [6]. Negro et al. [10] established the largest prospective cohort that included 4123 thyroid antibody negative women with a TSH level in the normal range [0.5–5 mIU/L] in the first trimester. TSH levels higher than 2.5 mIU/L in the first trimester nearly doubled the risk for pregnancy loss, but had similar risk for preterm delivery compared to women with TSH < 2.5 mIU/L [10]. Alexander et al. [11] characterized the change in levothyroxine (L-T4) requirements during pregnancy showing that most women with primary hypothyroidism required an increase of about 30% in their

Thyroid Autoimmunity also associated with APLS which causes infertility and pregnancy complications



Frontiers in Endocrinology

Thyroid Autoimmunity and Antiphospholipid Syndrome: Not Such a Trivial Association

*Mathilde Versini**

Department of Internal Medicine, Archet-1 Hospital, University Hospital of Nice, Nice, France

Antiphospholipid syndrome (APS) is an autoimmune disease that manifests as recurrent venous or arterial thrombosis and/or pregnancy-related complications in the presence of persistent antiphospholipid (aPL) antibodies measured at least 3 months apart. APS occurs either as a primary condition or as a part of an underlying disorder, usually systemic lupus erythematosus (SLE). Otherwise, APS may be frequently associated with autoimmune disorders. Little is known about the association of APS and aPL antibodies with thyroid autoimmune diseases or thyroid autoantibodies. This is even more interesting that thyroid autoantibodies and aPL are both recognized causes of repeated miscarriages. Therefore, their combination is of particular importance in women of childbearing age. Several studies have pointed out an association between APS and thyroid autoimmunity, some of them suggesting common pathophysiologic processes and genetic background. A literature review was conducted on existing data on aPL/APS and thyroid autoimmune disorders, paying particular attention to the possible role of this association in obstetrical complications.

Keywords: antiphospholipid syndrome, autoimmunity, thyroid, Hashimoto's thyroiditis, Graves' disease, autoimmune disease

INTRODUCTION

Autoimmune thyroid diseases (AITD) encompass a spectrum of disorders characterized by a T-helper (Th)-1–cell-mediated autoimmune attack on the thyroid gland resulting in a lymphocytic infiltration of the thyroid parenchyma ( ). AITD comprise two main presentations: Hashimoto's thyroiditis (HT) and Graves' disease (GD) corresponding to hypothyroidism and thyrotoxicosis, respectively.

The prevalence of AITD is estimated to be 5%, nevertheless the prevalence of antithyroid antibodies without clinical disorder may be even higher ( ). HT (also named chronic autoimmune thyroiditis or autoimmune hypothyroidism) is the most common autoimmune disease with an incidence ranging from 27 to 448 per 100,000 per year according to the studies and the geographic areas ( ), the most common endocrine disorder ( ), as well as the most frequent cause of hypothyroidism ( ). Its biological hallmark is the presence of antibodies directed to thyroid antigens, namely, thyroperoxydase (TPO) and thyroglobulin (Tg) ( ). Similarly, GD is one of the most prevalent autoimmune

Abbreviations: AITD, autoimmune thyroid diseases; aPL, antiphospholipid; APS, antiphospholipid syndrome; GD, Graves' disease; HT, Hashimoto's thyroiditis; SLE, systemic lupus erythematosus; TAI, thyroid autoimmunity; Tg, thyroglobulin; Th, T-helper; TPO, thyroperoxydase; TSHR, thyroid-stimulating hormone receptor.

OPEN ACCESS

Edited by:
Alessandro Antonelli,
University of Pisa, Italy

Reviewed by:
Michele Colaci,
University of Modena and Reggio Emilia, Italy
Salvatore Benvenga,
University of Messina, Italy
Roberto Vita,
University of Messina, Italy

**Correspondence:*
Mathilde Versini
versini.m@chu-nice.fr

Specialty section:
This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology

Received: 28 April 2017
Accepted: 05 July 2017
Published: 21 July 2017

Citation:
Versini M (2017) Thyroid Autoimmunity and Antiphospholipid Syndrome: Not Such a Trivial Association. Front. Endocrinol. 8:175. doi: 10.3389/fendo.2017.00175

APLS also linked with coeliac disease

Rev Esp Enferm Dig. 2008 Feb;100(2):102-3.[Celiac disease associated with antiphospholipid syndrome].[Article in Spanish] Jorge O1, Jorge A, Camus G.

INTRODUCTION:

celiac disease may be associated with pathologies of immune etiology. We present its association with antiphospholipid syndrome. CASE 1: a 26-year-old female was diagnosed with celiac disease. Six months later she became pregnant, and experienced fetal death. The following year she became pregnant again. IgG anticardiolipin antibodies: 20 GPL U/ml (normal value < 11), and IgM anticardiolipin antibodies: 9 MPL U/ml (n. v. < 10). Hematological tests were otherwise uneventful. Medicated with acetylsalicylic acid she had a normal pregnancy. CASE 2: a 48-year-old female diagnosed with celiac disease presented with thrombosis in her left lower limb and renal infarction. Hematological tests showed no prothrombotic alterations (antiphospholipid antibodies were not measured). A year and a half later she had thrombosis in a finger of her hand. IgG anticardiolipin antibodies: 10 GPL (n. v. < 13), and IgM anticardiolipin antibodies: 35 MPL (n. v. < 12). CASE 3: a 38-year-old female was diagnosed with celiac disease. Some time later she experienced two spontaneous abortions and a transient ischemic cerebral attack. Nowadays, she is in her sixth month of pregnancy. IgM anticardiolipin antibodies: 75 MPL/ml (n. v. up to 20), and IgG anticardiolipin antibodies within normal values. Hematological tests revealed no other prothrombotic alterations.

DISCUSSION:

antiphospholipid syndrome is characterized by arterial and venous thrombosis, and spontaneous fetal death. Its association with celiac disease has been described in few cases. Celiac disease is associated with spontaneous fetal death; consequently, we hypothesize that antiphospholipid syndrome may be one of the causes for this event.

31

Gluten is a key food reactivity issue in autoimmunity

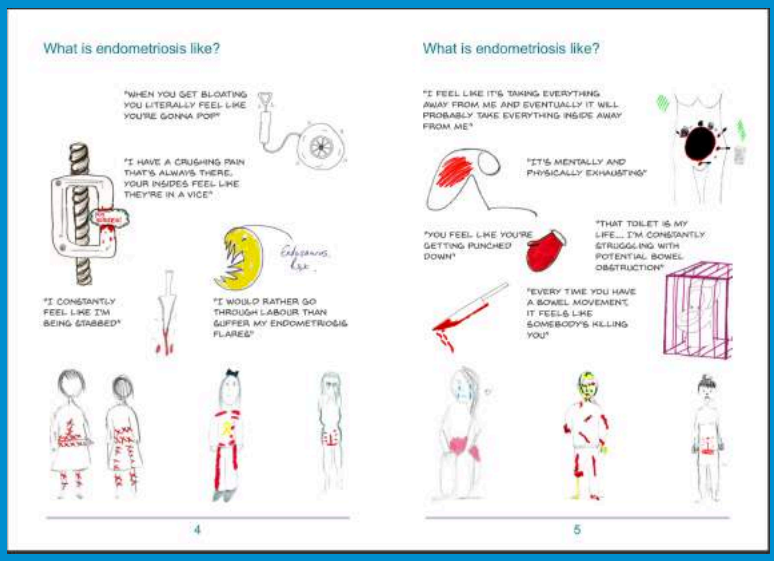
I am going to focus on food reactivity in the context of GRAINS

Autoimmune disorders are associated with CD

- Hashimoto's thyroiditis (Hadithi,et al., 2007),
- Psoriasis (Ungprasert et al., 2017)
- Systemic lupus erythematosus (SLE) (Lauret & Rodrigo 2013).

32

Endometriosis - AI?



Experiences of Endometriosis in Wales

https://www.cardiff.ac.uk/__data/assets/pdf_file/0007/1381336/Experiences-of-endometriosis-in-Wales-Oct-2018.pdf

33

Still not officially considered an AI disease

But is considered in many academic papers to be a chronic disease

Human Reproduction Update, Vol.25, No.4, pp. 486–503, 2019
Advance Access Publication on June 13, 2019 doi:10.1093/humupd/dmz014

human reproduction update

The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis

Nina Shigesi[1,2,*], Marina Kvaskoff[3,4], Shona Kirtley[5], Qian Feng[1], Hai Fang[2], Julian C. Knight[2], Stacey A. Missmer[6,7,8,9], Nilufer Rahmioglu[2,†], Krina T. Zondervan[1,2,*,†], and Christian M. Becker[1,†,‡]

TABLE OF CONTENTS

- Introduction
- Methods
  - Search strategy
  - Inclusion criteria and study selection
  - Data extraction
  - Quality assessment
  - Data synthesis and meta-analysis
- Results
  - Study selection
  - Study characteristics
  - Ascertainment of cases and controls
  - Quality of evidence
  - Data synthesis and meta-analysis
  - Sensitivity analysis
- Discussion
  - Possible explanations for the observed association between endometriosis and autoimmune diseases
- Conclusion

34

Patients with CD have increased risk of Endometriosis

Hum. Reprod. (2011) 26 (10): 2896-2901. doi: 10.1093/humrep/der263
First published online: August 12, 2011

Risk of endometriosis in 11 000 women with celiac disease

Olof Stephansson[1,2], Henrik Falconer[2] and Jonas F. Ludvigsson[1,3,*]
+ Author Affiliations
*Correspondence address. Tel: +46-19-6021000; Fax: +46-19-187915; E-mail: jonasludvigsson@yahoo.com

Received November 29, 2010.
Revision received July 8, 2011.
Accepted July 11, 2011.

Abstract

BACKGROUND Endometriosis is a common cause of infertility. Whereas celiac disease (CD) is present in ~1% of individuals in Western Europe, the prevalence in women undergoing investigation for infertility is often >2%. Still, the relationship between CD and endometriosis is unclear.

METHODS We identified 11 097 women with CD (Marsh 3: villous atrophy) through biopsy data from all 28 pathology departments in Sweden. Biopsies had been performed between 1973 and 2008. Data on inpatient and outpatient diagnoses of endometriosis were retrieved from the National Patient Register. We then used the Cox regression to estimate the hazard ratios (HRs) for endometriosis in women with CD to compare with those in 54 992 age-matched control women.

RESULTS During the follow-up, 118 individuals with CD and 399 matched controls developed endometriosis. Hence, patients with CD were at increased risk of subsequent endometriosis [HR = 1.39; 95% confidence interval (CI) = 1.14–1.70]. The absolute risk of endometriosis in patients with CD was 112/100 000 person-years with an excess risk of 31/100 000. Risk estimates were highest in the first year after diagnosis (HR = 1.49; 95% CI = 0.83–2.67) and gradually decreased (>5 years after CD diagnosis, HR = 1.33; 95% CI = 1.00–1.79).

CONCLUSION Endometriosis seems to be associated with prior CD. Potential explanations include shared etiological factors and CD-mediated inflammation.

35

Grains & health issues?

Quite a lot of debate & controversy over this in literature and media

- Is it Gluten?
- Or FODMAPs (particularly fructans)?
- Anti trypsin inhibitors?
- Lectins (wheat germ allglutin)?
- Exorphins?
- Herbicides?

Can they overlap?
Or are they mutually exclusive?

36

What is Gluten?

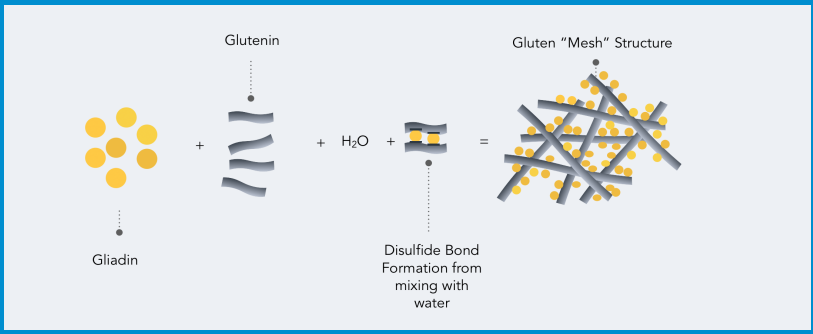


Image: Gliadin and Glutenin + H2O + disulphiide bonds = gluten mesh structure Paleo Foundation

Wheat flour comprises:-

- 35% glutenins,
- 45% gliadins
- & around 20% other protein

Wheat contains about 16% protein overall (Lakhneko et al., 2020).

37

Gluten related disorders

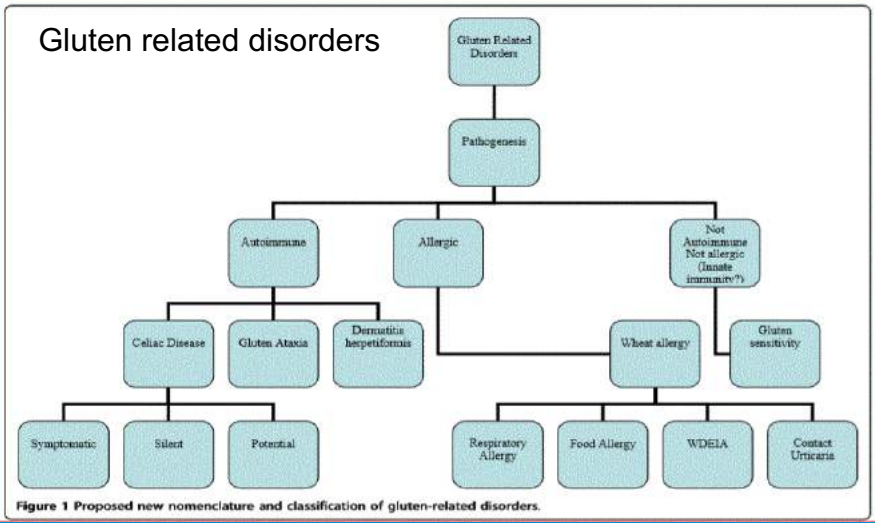


Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

Anna Sapone,Julio C Bai, Carolina Ciacci, Jernej Dolinsek, Peter HR Green, Marios Hadjivassiliou, Katri Kaukinen,Kamran Rostami, David S Sanders, Michael Schumann, Reiner Ullrich, Danilo Villalta, Umberto Volta, Carlo Catassi and Alessio Fasano *BMC Medicine* 201210:13

38

Gluten & food reactivity

Gluten proteins are resistant to digestion owing to their structure and proline/glutamine content & may not be fully broken down by digestive enzymes (Balakireva & Zamyatin, 2016).

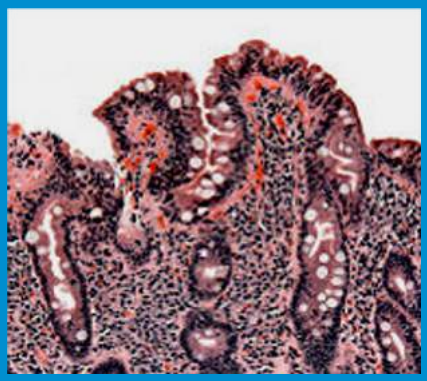
This can cause an inflammatory response as it can increase intestinal permeability (Chander, et al., 2018).

This may underpin the pathophysiology in both CD and NCGS (Balakireva & Zamyatin, 2016).

39

Coeliac Disease (CD)

Damaged villi



Healthy villi

IMAGES :
http://www.coeliacsociety.com.au/images/D1---Healthy-Villi.jpg

An autoimmune enteropathy (Balakireva and Zamyatnin 2016) affecting genetically susceptible individuals carrying HLA-DQ2 or HLA-DQ8 alleles

40

CD

Transglutaminase 2 (tTG, TG2) modifies gliadin peptides; it deaminates glutamine residues to glutamic acid, this activates CD4+ lymphocytes from the mucosa on the lamina propria.

Activation of CD4+ lymphocytes stimulates the excretion of proinflammatory cytokines/ chemokines that cause inflammation of the mucosa and villous atrophy which then further increases gut permeability (Leon, et al., 2007).

Serological testing for CD involves the measurement of the presence of serum antibodies against tissue transglutaminase (tTG).

41

Overview Coeliac Disease Tests

- Antibody testing
- Need to check total gA – rule out IgA deficiency
  - Tissue transglutaminase (tTG)
    - Serology often does not correlate to degree of mucosal damage
    - Can have damage to villi and negative antibody test
    - Serology can be positive (with no damage to villi at biopsy)
      - Latent coeliac disease
  - Consider endomysial antibodies (EMA) if IgA deficiency or weakly positive tTG
- Also IgG DGP (deamidated gliadin peptide)
  - Sapone et al 2012 say more reliable in IgA deficient patients under 3 years of age

42

CD

tTG can also crosslink with gliadin, producing a tTG-gliadin complex, this is considered a neo-antigen with possible immune toxicity (Pruimboom and de Punder 2005).

Crypt hyperplasia may be present with villous atrophy.

This is why in CD, gluten consumption is associated with the malabsorption of nutrients and symptoms such as bloating, pain and diarrhoea but it should be noted that CD can also be asymptomatic (Pruimboom and de Punder 2005)

43

Development of CD

Not everyone who is HLA-DQ2 or HLA-DQ8 positive develops CD (Verdu et al., 2015), other factors may be involved in the pathogenesis of active CD.

Studies have demonstrated that gastrointestinal infections and microbiome alterations are associated with the onset or activity of CD (Verdu et al, 2015).

Alterations in the composition of the microbiome between patients with CD (Valitutti et al., 2019) and those without it have been established, but there is no typical CD microbial profile.

44

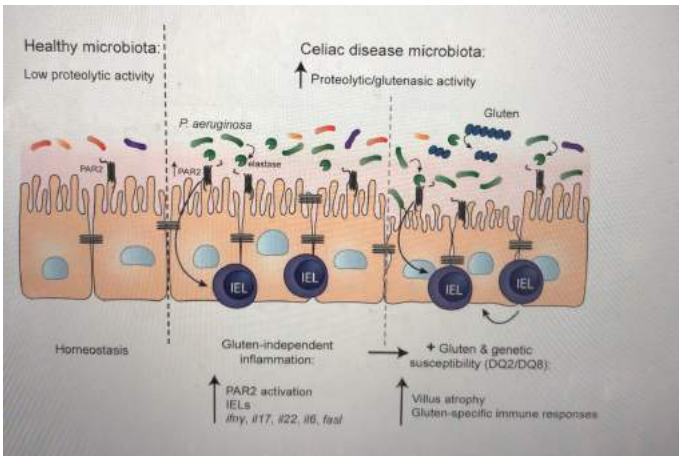
Microbiome & CD

Duodenal biopsies from patients with CD have increased Proteobacteria including *Pseudomonas*, have increased proteolytic activity against gluten and that the bacterial enzyme elastase triggers an inflammation mediated by the cell surface receptor proteinase activated receptor 2 (PAR-2) Caminero et al., (2019a)

Gluten that is not completely digested can be metabolized by bacteria such as *Pseudomonas aeruginosa*, and this causes the production of shorter immunogenic peptides that can more easily permeate the gut mucosa (Caminero et al., 2016)

45

Immune activation by bacterial enzyme elastase in genetically predisposed individuals



"clinical association studies have demonstrated shifts in microbial composition between individuals with celiac disease and those without celiac disease. This is similar to what we have learned in other chronic inflammatory diseases, such as IBD"

Proteinase-activated receptor 2 (PAR2) is a cell surface receptor. It's emerging as a pharmaceutical target for various diseases incl. metabolic dysfunction / obesity

"*Pseudomonas aeruginosa* and commensal bacteria, like *Lactobacillus*, can participate in gluten metabolism but they generate different patterns of gluten peptides harbouring different immunogenic properties".

https://naturemicrobiologycommunity.nature.com/channels/346-behind-the-paper/posts/45610-duodenal-bacterial-proteolytic-activity-determines-sensitivity-to-dietary-antigen-through-par-2-receptor

46

Zonulin

A protein synthesised in the liver & intestine - regulates the tight junctions between the epithelial cells.

If levels are elevated it reduces the effectiveness the mucosal barrier increasing intestinal permeability (Fasano, 2011).

Gluten triggers zonulin to be released (Fasano, 2012b). In healthy people most peptides from digestion remain within the GI tract & pass through before an immune response is initiated (Fasano 2009).

47

Zonulin in AI

Zonulin expression is increased in autoimmune conditions including CD (Fasano 2012a) & there is an accompanying increase in intestinal permeability. In CD & Type 1 Diabetes there is tight junction dysfunction (Fasano 2012a)

Zonulin is high in the acute phase of CD (Fasano 2000).

48

Gender in Coeliac Disease

Clinical Gastroenterology and Hepatology Volume 17, Issue 10, September 2019, Pages 1954-1968.e13 Sex Difference in Celiac Disease in Undiagnosed Populations: A Systematic Review and Meta-analysis
Jansson-Knodell Isabel A. Huibel Colin P. West Veena Taneja Larry J. Prokop Alberto Rubio-Tapia Joseph A. Murray

Background & Aims
A higher proportion of female vs male patients receive a diagnosis of celiac disease. Little is known about sex-based differences in the prevalence of celiac disease in undiagnosed populations. We aimed to address this knowledge gap with a systematic review and meta-analysis.

Methods
We searched MEDLINE, Embase, Cochrane, and Scopus databases through 2017 for studies of screen-detected or undiagnosed celiac disease. Our final analysis included studies that included screening and confirmatory tests (either second serologic analysis or a small intestine biopsy) and provided information on the sex of participants. Studies were excluded if they were performed with specific, high-risk, or referral populations. The primary outcome was the percentage of undetected celiac disease among female and male patients.

Results
We identified 4070 articles and analyzed data from 87. Our meta-analysis comprised data from 291,969 study participants. The pooled prevalence of undetected celiac disease in female participants was 0.589% (95% CI, 0.549%–0.629%) and in male participants was 0.415% (95% CI, 0.343%–0.487%). The risk of undetected celiac disease was higher among female than male participants (relative risk [RR], 1.42; 95% CI, 1.27–1.57; $P < .00001$). The I^2 was 5% (low heterogeneity among studies). In subgroup analyses, the RR of celiac disease for girls vs boys was 1.79 (95% CI, 1.44–2.22; $P < .00001$; $I^2 = 18\%$), the RR for female vs male blood donors was 1.13 (95% CI, 0.76–1.69; $P = .54$; $I^2 = 0$), and the RR for women vs men with villous atrophy was 1.38 (95% CI, 1.07–1.79; $P = .01$; $I^2 = 0$).

Conclusions
In a systematic review and meta-analysis, we found a higher risk for celiac disease in women than men in an undiagnosed populations (identified through general population screening). The increased risk for celiac disease among girls and women should be considered for screening, diagnosis, and management strategies

49

CD is associated with later menarche, earlier menopause, low bone mineral density and also infertility and obstetric complications, breastfeeding problems

REVIEW

Women's HEALTH

Celiac disease: an underappreciated issue in women's health

Sveta Shah[1] & Daniel Leffler*[1]

Celiac disease (CD) is an immune-mediated enteropathy that is secondary to gluten ingestion and classically associated with gastrointestinal symptoms. Diagnosis is based on serology and confirmatory duodenal biopsy, and the only treatment is lifelong avoidance of gluten. CD has been increasingly recognized to encompass a wide variety of manifestations that are relevant to women's health, including infertility, adverse pregnancy outcomes and reduced BMD. Currently, CD is underdiagnosed, largely owing to lack of recognition of the diverse manifestations by general practitioners. Increased awareness of the clinical spectrum of this disease, as well as targeted testing in at-risk individuals (including women with unexplained infertility and previous adverse pregnancy outcomes, and in specific populations with reduced BMD) is greatly needed in order to improve rates of diagnosis.

Celiac disease (CD) is an immune-mediated enteropathy triggered by ingestion of foods containing gluten, for which the only treatment is a life-long adherence to a gluten-free diet (GFD) [1]. The prevalence is thought to be 1% or higher in the general population, although fewer than 5% are diagnosed in many regions [2–4]. Classically thought to be a disease with primarily gastrointestinal manifestations and affecting children under 2 years, the epidemiology of CD has shifted such that the majority of patients are now presenting as adults with diverse symptomatology in the fourth to fifth decade of life, which accounts for the high rate of missed diagnoses [5,6]. CD is diagnosed predominantly in women. The female predominance of CD is partially due to true increased prevalence in women relative to men, but is also related to the fact that women use healthcare services more than men [7,8]. Currently, in most populations women constitute 60–70% of individuals with diagnosed CD [9,10].

The spectrum of systemic manifestations associated with CD is broad and encompasses iron deficiency anemia, hyposplenism, reduction in BMD, liver function abnormalities, neuropathy, psychological disturbances, fatigue, myalgias, arthralgias, asthma, weight loss, bloating, abdominal pain, bowel changes, alopecia, headaches, menstrual irregularities, infertility and adverse pregnancy outcomes [1,11]. Aside from the classic symptoms of abdominal pain, bloating and bowel changes, many of the nonspecific symptoms associated with CD do not routinely prompt primary care physicians to test for this disease [12]. While there are a multitude of potential complications of CD including osteoporosis, autoimmune disorders and malignancy, undiagnosed CD may be particularly devastating in women who experience unexplained infertility, recurrent abortions and perinatal complications. Excellent general reviews of CD have been published in recent years, however, little attention has been paid to the significant potential impact of CD on women's health [1,13,14]. In this article, we review the major areas where CD and health concerns specific to women intersect.

Pathophysiology of celiac disease

The protein responsible for the immune response in CD is gluten, which is derived from wheat and similar proteins that are found in rye and barley [15]. Gliadin peptides, which are derived from gluten, contain the majority of toxic substances and are resistant to degradation by proteases, thereby allowing them to remain intact within the intestinal lumen after ingestion [16]. In individuals with CD, these peptides then enter the lamina propria, triggering chronic inflammatory changes.

It is notable that gluten peptides in their native form are not toxic. In order for gluten peptides to cause inflammation, they must first be altered by the enzyme tissue transglutaminase (tTG), which is normally involved in tissue remodeling and protein cross-linking. tTG is normally present in nearly all organs and is increased in areas of inflammation. In the submucosa of the intestine, tTG deamidates gluten peptides, changing peptide shape and charge. These altered gluten peptides are then able to bind tightly to HLA-DQ2 and HLA-DQ8 molecules on antigen-presenting cells. This binding triggers

[1]The Celiac Center, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA
*Author for correspondence:
Tel.: +1 617 667 1272
Fax: +1 617 667 8144
dleffler@bidmc.harvard.edu

Keywords
• bone-density celiac disease • fertility • gluten • osteopenia • osteoporosis • pregnancy • screening • tissue transglutaminase

10.2217/WHE.10.57 © 2010 Future Medicine Ltd
Women's Health (2010) 6(5), 753–766
ISSN 1745-5057

50

Non Coeliac Gluten Sensitivity (NCGS)

Research has linked it to systemic inflammation (Uhde et al 2016) and an innate immune response; the innate immune system is composed of physical and chemical barriers, phagocytic leukocytes, dendritic cells, natural killer cells and plasma proteins.

CD in contrast also involves the adaptive immune system.

However in NCGS there may also be adaptive immune involvement as increased expression of IFN-γ (Brottveit et al., 2013) has been shown and elevated immunoglobulin IgG antigliadin (AGA) antibodies are also present in some people with NCGS (Aziz et al., 2015).

Is now widely medically recognised as clinical entity.

51

NCGS

No reliable biomarkers have been identified for diagnosis.

Gluten exclusion and reintroduction are currently used to confirm diagnosis of NCGS following the Salerno protocol using a challenge of 8g/gluten/day (Catassi et al. 2015).

This involves the avoidance of gluten followed by a double blind placebo controlled (DBPC) challenge with cross over, gluten free diet using a modified self-administered questionnaire for clinical evaluation (Catassi et al., 2015).

Medical diagnosis is made by challenge and excluding CD, WA.

52

Fermentable Oligo, Di and Monosaccharides and Polyols (FODMAPs)

FODMAPs are a group of short chain carbohydrates and sugar alcohols that are rapidly fermentable in the human gut and have over the last decade been studied in relationship to functional gastrointestinal disorders such as irritable bowel syndrome (IBS).

FODMAPs include fructose which is a monosaccharide, lactose a disaccharide and the oligosaccharides fructans and galactans and also polyols.

FODMAPs are found in many foods including fruits, vegetables, dairy produce and wheat.

53

FODMAPs

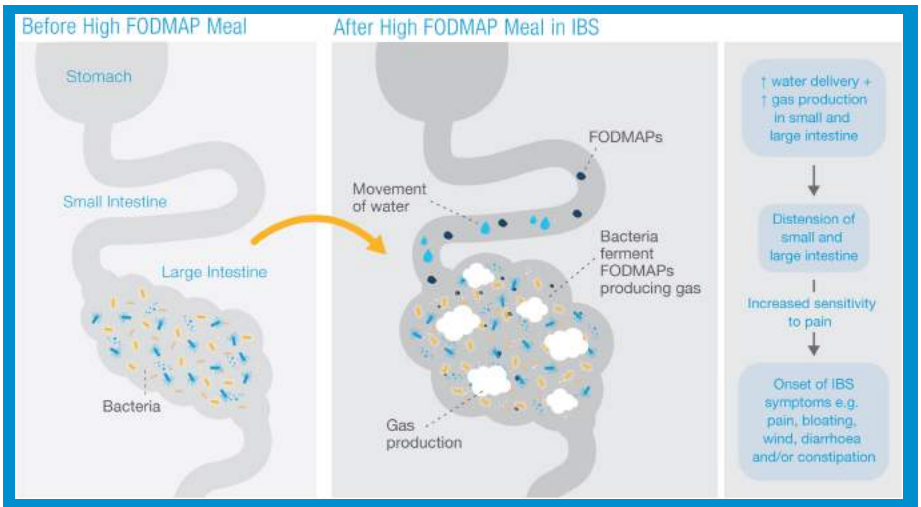
A low FODMAP's diet is now accepted as one of the most effective dietary therapies for IBS and provides relief for about 75% of patients (Gibson and Shepherd 2009).

Yet the long-term impact of following a low FODMAP diet is not fully understood; it may for example potentially impact the gut microbiome (Staudacher 2017).

Is a low gluten diet actually a modified version of a low fodmap diet as it's low in fructans?

Is it easier to implement?

54



Role of FODMAPs in triggering symptoms of IBS

J.G. Muir, J.E. Varney, M. Ajamian, P.R. Gibson, Gluten-free and low-FODMAP sourdoughs for patients with coeliac disease and irritable bowel syndrome: A clinical perspective, International Journal

55

Wheat germ agglutinin (WGA)

Lectin in wheat. Lectins are proteins that selectively bind carbohydrates and agglutinate red blood cells and used in blood typing (van Buul Brounds 2014).

Generally resistant to heat/digestive enzymes - stable in acidic environments and they resist being broken down in the digestive tract.

The indigestibility protects plants from pathogens (Peumans 1995) and functions as a natural insecticide (Mikaye et al 2007).

56

Lectins

Symptoms after consumption can include vomiting, diarrhoea and nausea (Miyake et al 2007).

Raw red kidney beans contains the lectin phytohemagllutinin lectin (PHA) and are widely recognised as having adverse health effects.

Lectins are soluble in water and so can be reduced by soaking or cooking in water and also by processing foods, for example boiling or stewing in water for a few hours can inactivate most lectins. (Harvard School of Public Health ND).

57

WGA

The highest concentration found in wheat germ.
Unprocessed products contain higher amounts than processed cereals (de Punder and Pruimboom 2013).

Lectins in high concentrations of the active forms can damage the gut in animals causing areas of epithelial cell necrosis - results not consistently replicated in vitro (Miyake 2007),

Known to cause increased intestinal permeability (El Asmar et al, 2002).

Animal studies demonstrate WGA induces inflammatory responses (de Punder and Pruimboom 2013).

58

Lectins - controversy

Lectins can inhibit the repair of the plasma membrane of damaged cells (Miyake et al 2007).

Implicated in the development of human inflammatory diseases (de Punder and Pruimboom 2013).

Other researchers claim there is no evidence that dietary lectins in cooked and baked foods are not associated with negative health effects in humans (van Buul and Brouns 2014).

Further research needed.

59

α-amylase/trypsin inhibitors (ATI)

Found in all gluten containing cereals (Ziegler et al., 2019).

Compact, protease resistant non-gluten proteins found in the endosperm.

ATI protect the seed from insects and parasites (Zevallos et al 2017).

It has been suggested that ATI activate innate immune responses in monocytes, macrophages and dendritic cells (Junker, 2012).

60

ATI

In animal studies (on mice) ingestion is associated with intestinal myeloid cell infiltration in the colon, ileum and duodenum and dendritic cells were activated in mesenteric lymph nodes (Zevallos et al 2017).

Activate the toll like receptors and the TLR4– MD2-CD14 complex activating NF- κB signalling and interferon responsive factor 3 pathway (Zevallos et al 2017).

NF- κB is a protein transcription factor that regulates innate immune responses (Benedict 2019) involved in inflammation.

61

Exorphins

Exogenous peptides with opioid activity produced by the action of the proteolytic enzymes - they are considered to be neurotransmitters and neuro-hormones (Stefanucci et al., 2018).

Share a common terminal amino acid sequence (known as an opoid motif) with enkaphalins, endorphins and dynorphins (Stefanucci et al., 2018).

The bacterial enzyme elastase (which can be elevated in microbiome dysbiosis) can also produce exorphins (Stefanucci et al., 2018).

62

Exorphins

Hypothesised they mask GI symptoms of CD (owing to the opoid effects), and this is responsible for asymptomatic presentation in silent or atypical CD (de Punder and Pruimboom 2013).

It has also been demonstrated that they can increase transit time (de Punder and Pruimboom 2013).

May also be involved in the comorbidity of mental health and neurological problems in patients with CD (Stefanucci et al., 2018).

63

Herbicides and wheat

Glyphosate is the most used herbicide in agriculture (Rueda-Ruzafa et al., 2019) and used extensively in wheat agriculture.

- It is a broad spectrum herbicide used on wheat and in a product known as Roundup patented by Monsanto Technology LLC (Samsel and Seneff 2013).

64

Herbicides

Data on global pesticide use is scarce but globally the use of glyphosate has increased 15 fold and in the USA from 1974 onwards more than 1.6 billion kilograms of glyphosate active ingredient have been used (Benbrook 2016).

In the USA more herbicides are applied to Spring Wheat and Durum Wheat than Winter Wheat (USDA 2014).

65

Glyphosate

Was considered to not be toxic to humans (Williams et al. 2000).

Glyphosate inhibits the enzyme 5-enolpyruvylshikimate-3-phospate synthase (EPSP synthase) in both plants and bacteria (Rueda-Ruzafa et al.,2019).

This is involved in the synthesis of amino acids containing an aromatic ring including phenylalanine, tryptophan and tyrosine in both bacteria and plants (Schönbrunn et al., 2001).

66

Glyphosate

Pathway is not present in humans (Samsel and Seneff 2013). So amino acids must be obtained from food and are important for making serotonin, melatonin, dopamine and thyroid hormone.

A controlled study on 77 patients with CD, was undertaken by van Hees et al., (2015); this demonstrated lower serum concentrations of tyrosine, phenylalanine and tryptophan (all $p < 0.005$) in CD patients.

A 2013 paper suggest glyphosate maybe contributing to the high rates of obesity in humans as well as other health conditions such as cancer, infertility and Alzheimer's disease (Samsel and Seneff 2013).

67

Glyphosate

In intestinal microbiota - affects mainly beneficial bacteria rather than pathogens such as *Clostridium* spp. and *Salmonella* (Rueda-Ruzafa et al.,2019).

A report on exposure in fish demonstrated adverse effects throughout the digestive system (Senapati et al., 2009).

Enzyme activity was reduced in the oesophagus, stomach and intestine; protease, amylase and lipase activity was diminished and there was damage similar to the damage seen in CD in humans including damage to the microvilli and mucosal folds (Senapati et al., 2009).

68

Glyphosate

Suggested that an imbalance in the microbiome caused by glyphosate may play a role in the development of CD in humans, as protein breakdown may be affected leaving larger fragments of wheat that then trigger an immune response
(Samsel and Seneff 2013).

In animal studies, glyphosate is associated with an overgrowth of pathogens (which can in turn activate zonulin which induces increased intestinal permeability) and glyphosate is also associated with inflammatory bowel disease
(Samsel and Seneff 2013).

Glyphosate can also interfere with the P450 cytochrome enzymes that are important in detoxification. Also can chelate iron and cobalt.

69

Therapy

Personalised

FM Testing

Client preferences & goals

Address underpinning imbalances, triggers/mediators

?

e.g. genetics.

70

Nutritional therapy

Personalised?

Food first in general – but sometimes use supplements first if think it will help may person feel better and better able to make changes

Gluten free grains, also soaking, sprouting grains

Low grain diets –
consideration of ALL GRAIN FACTORS
fodmaps ATI, WGA, exorphins etc

Testing – Refer on re any
infections / diagnosis / needs for medication

71

Nutritional therapy

Explore grain tolerance – quality of life

- Sourdoughs
- Organic grains/wheat

Support for gut mucosa/microbiome:

- Live fermented foods
- Bone broths
- Supportive supplements
- Antimicrobials, gut repair/probios/amino acids, enzymes)
- 5 Rs
- Rainbow diet – nutrient dense / phytonutrition

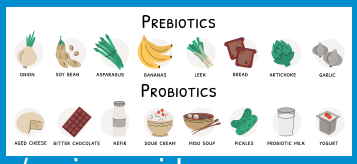


Image: istock

72

Sourdough

Produced using a traditional method of slow fermentation.

The starter cultures used in the bread's production contain yeasts and lactic acid bacteria (LAB) that have proteolytic activity.

Sourdough bread has been shown to contain less FODMAPs (Menezes et al., 2018) and the yeast proteases seem to degrade the gluten as well (Poutanen et al, 2009).

Lactobacilli for example are a source of gluten degrading enzymes known as glutenases (Chander et al., 2018) and it is reported they can degrade ATIs too (Caminero et al., 2019b).

73

Sourdough

50 species of LAB and more than 25 species of yeasts, mostly from the genera *Saccharomyces* and *Candida*, can be found in mature sourdoughs (Nionelli and Rizzello 2016).

Other research suggests a lower post prandial glucose response after consumption of sourdough bread (Stamataki et al., 2017).

Sourdough fermentation is also known to have other nutritional benefits as it decreases phytic acid and can increase the bioavailability of minerals as well as increasing shelf life of the bread (Chander et al., 2018).

74

Sourdough

50 species of LAB and more than 25 species of yeasts, mostly from the genera *Saccharomyces* and *Candida*, can be found in mature sourdoughs (Nionelli and Rizzello 2016).

Other research suggests a lower post prandial glucose response after consumption of sourdough bread (Stamataki et al., 2017).

Sourdough fermentation is also known to have other nutritional benefits as it decreases phytic acid and can increase the bioavailability of minerals as well as increasing shelf life of the bread (Chander et al., 2018).

75

Sourdough

Sourdough fermentation acidifies bread which can increase shelf life as it inhibits endospore germination and *Bacillus* sp. growth (Kirschner and Von Holy 1989).

This is because LAB synthesize antimicrobial substances such as bacteriocins, organic acids and hydrogen peroxide (Chander et al., 2018).

Sourdough LAB are now being researched for their potential to decrease the risk of contamination in gluten-free products, as in vitro studies using celiac tissue from the GI tract and in vivo studies on CD patients demonstrate the proteolytic activity is promising for both removing traces of gluten and potentially also for the manufacture of baked goods that can be tolerated by those with CD (Gobbetti et al., 2007).

76

Developments in wheat breeding

Wheat has now been produced with a low gliadin content through the use of gene editing technology.

A line (E82) has demonstrated positive nutritional properties and low immunogenic gluten which appeared to have a low stimulatory effect on the T-cells in celiac patients.

In non-celiac wheat sensitivity (NCWS) a trial demonstrated the consumption of bread made with E82 low gliadin wheat induced positive changes in the microbiome (Molina et al.,2019).

77

Thank you for listening

- Worcester virtual stand
- j.bold@worc.ac.uk

@justineboldfood

justine_bold

Nutrition Health Worcester

78

Questions

79

Bibliography & References

In addition to the ones provided in the presentation

80

Aziz et al. (2014) Change in awareness of gluten-related disorders among chefs and the general public in the UK: a 10-year follow-up study. *Eur J Gastroenterol Hepatol.* 26 (11):1228-33.

Aziz, I., Dwivedi, K., & Sanders, D. S. (2016). From coeliac disease to noncoeliac gluten sensitivity; should everyone be gluten free?. *Current opinion in gastroenterology*, *32*(2), 120–127. https://doi.org/10.1097/MOG.0000000000000248

Aziz, Hadjivassilou & Sanders (2015) The spectrum of noncoeliac gluten sensitivity. *Nat. Rev. Gastroenterol. Hepatol.* 12:516–526.
Balakireva AV, Zamyatnin AA. (2016) Properties of Gluten Intolerance: Gluten Structure, Evolution, Pathogenicity and Detoxification Capabilities. Nutrients. 2016;8(10):644. Oct 18. doi:10.3390/nu8100644

Bender, William; Smith, Margaret. Population, food, and nutrition. Population Bulletin; Washington Vol. 51, Iss. 4, (Feb 1997): 2-48.

Benedict A. What Is Nuclear Factor Kappa B (NF-κB) Doing in and to the Mitochondrion? Frontiers in Cell and Developmental Biology 7, 2019 154
https://www.frontiersin.org/article/10.3389/fcell.2019.00154

Benbrook, C.M. Trends in glyphosate herbicide use in the United States and globally. Environ Sci Eur 28, 3 (2016). https://doi.org/10.1186/s12302-016-0070-0

Biesiekierski JR. What is gluten?. J Gastroenterol Hepatol. 2017;32 Suppl 1:78-81. doi:10.1111/jgh.13703

Biesiekierski J, and Iven J (2015) Non-coeliac gluten sensitivity: piecing the puzzle together United European Gastroenterol J. 2015 Apr; 3(2): 160–165.

Bold, J., & Rostami, K. (2011). Gluten tolerance; potential challenges in treatment strategies. Gastroenterology and hepatology from bed to bench, 4(2), 53–57.

Bold, J., Rostami, K. (2015) Non-coeliac gluten sensitivity and reproductive disorders, Gastroenterology and Hepatology from Bed to Bench. 8(4):294-297. http://dx.doi.org/10.22037/ghfbb.v8i4.819

81

Branchii et al (2015) Noncoeliac gluten sensitivity: a diagnostic dilemma. *Curr Opin Clin Nutr Metab Care*. 18:508 – 514

Brottveit et al. (2013) Mucosal cytokine response after short-term gluten challenge in celiac disease and non-celiac gluten sensitivity. *Am J Gastroenterol.* 108 (5) 842-50

Burnett, C., Bergfeld, W. F., Belsito, D. V., Hill, R. A., Klaassen, C. D., Liebler, D. C., … Heldreth, B. (2018). Safety Assessment of Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten as Used in Cosmetics. *International Journal of Toxicology*, *37*(1_suppl), 55S-66S. https://doi.org/10.1177/1091581818776013

Busby, E.; Bold, J.; Fellows, L.; Rostami, K. Mood Disorders and Gluten: It's Not All in Your Mind! A Systematic Review with Meta-Analysis. *Nutrients* 2018, *10*, 1708.

Caminero, A. et al. (2016)Duodenal bacteria from patients with celiac disease and healthy subjects distinctly affect gluten breakdown and immunogenicity. Gastroenterology 151, 670–683 (2016).

Caminero, A., McCarville, J.L., Galipeau, H.J. et al.(2019a) Duodenal bacterial proteolytic activity determines sensitivity to dietary antigen through protease-activated receptor-2. Nat Commun 10, 1198 (2019). https://doi.org/10.1038/s41467-019-09037-9

Caminero A, McCarville JL, Zevallos VF, et al. (2019b) Lactobacilli Degrade Wheat Amylase Trypsin Inhibitors to Reduce Intestinal Dysfunction Induced by Immunogenic Wheat Proteins. Gastroenterology.;156(8):2266-2280. doi:10.1053/j.gastro.2019.02.028

Carroccio A, Rini G, Mansueto P. (2014) Non-celiac wheat sensitivity is a more appropriate label than non-celiac gluten sensitivity. *Gastroenterology*.;146(1):320-321. doi:10.1053/j.gastro.2013.08.061

Catassi et al. (2015) Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria. *Nutrients* 7:4966-4977.

Chander AM, Yadav H, Jain S, Bhadada SK, Dhawan DK. Cross-Talk Between Gluten, Intestinal Microbiota and Intestinal Mucosa in Celiac Disease: Recent Advances and Basis of Autoimmunity. Front Microbiol. 2018;9:2597. Published 2018 Nov 1. doi:10.3389/fmicb.2018.02597

Charmet, G. 2011. Wheat domestication: lessons for the future. C. R. Biol. 334:212–220. http://dx.doi.org/10.1016/j.crvi.2010.12.013

82

Coeliac Australia (No Date) Gluten Challenge Fact Sheet https://www.coeliac.org.au/uploads/65701/ufiles/Fact_sheets/GlutenChallenge.pdf [Date accessed 20th July 2020]

Delcour, J. A., & Hoseney, RC. (2010). Principles of cereal science and technology. AACC International, St. Paul, MN.

de Punder, K., & Pruimboom, L. (2013). The dietary intake of wheat and other cereal grains and their role in inflammation. *Nutrients*, *5*(3), 771–787. https://doi.org/10.3390/nu5030771

El Asmar et al, (2002) Host-dependent zonulin secretion causes the impairment of the small intestine barrier function after bacterial exposure. *Gastroenterology* vol 123, I5;1607-2625

Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, Goldblum SE. (2000). Zonulin, a newly discovered modulator of intestinal permeability, its expression in coeliac disease. Lancet 358: 1518–1519.

Fasano A. Surprises from Celiac Disease Scientific American Vol. 301, No. 2 (August 2009), pp. 54-61 (8 pages)

Fasano A. (2011) Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity and Cancer Physiological Reviews 91:1, 151-175

Fasano A (2012a) Zonulin, regulation of tight junctions (TJ), and autoimmune diseases Ann N Y Acad Sci. 2012 July ; 1258(1): 25–33. doi:10.1111/j.1749-6632.2012.06538.x.

Fasano, A. (2012b) Leaky Gut and Autoimmune Diseases. Clinic Rev Allerg Immunol 42, 71–78. https://doi.org/10.1007/s12016-011-8291-x

Freed, DLJ. Do dietary lectins cause disease? The evidence is suggestive—and raises interesting possibilities for treatment. BMJ. 1999 Apr 17; 318(7190): 1023–1024.

83

Garsed, K. and B.B. Scott, *Can oats be taken in a gluten-free diet? A systematic review.* Scandinavian Journal of Gastroenteroloy, 2007. **42**(2): p. 171-178.

Garthwaite D, Barker I, Ridley L, Mace A, Parrish G, MacArthur R, Lu Y.
Land Use & Sustainability Team PESTICIDE USAGE SURVEY REPORT 271 ARABLE CROPS IN THE UNITED KINGDOM 2016 https://secure.fera.defra.gov.uk/pusstats/surveys/documents/arable2016-v9.pdf

Gibson, P. R., & Shepherd, S. J. (2010). Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. *Journal of gastroenterology and hepatology*, *25*(2), 252–258. https://doi.org/10.1111/j.1440-1746.2009.06149.x

Gobbetti M, Giuseppe Rizzello C, Di Cagno R, De Angelis M. Sourdough lactobacilli and celiac disease. *Food Microbiol*. 2007;24(2):187-196. doi:10.1016/j.fm.2006.07.014

Hadithi, M., de Boer, H., Meijer, J. W., Willekens, F., Kerckhaert, J. A., Heijmans, R., Peña, A. S., Stehouwer, C. D., & Mulder, C. J. (2007). Coeliac disease in Dutch patients with Hashimoto's thyroiditis and vice versa. World journal of gastroenterology, 13(11), 1715–1722. https://doi.org/10.3748/wjg.v13.i11.1715

Halford NG, Belton PS, Tatham AS. The structure and properties of gluten: an elastic protein from wheat grain. *Philos Trans R Soc Lond B Biol Sci*. 2002;357(1418):133-142. doi:10.1098/rstb.2001.1024

Hall, S.W.; Shaoul, R.; Day, A.S. The Contribution of Non-Food-Based Exposure to Gluten on the Management of Coeliac Disease. Gastrointest. Disord. 2020, 2, 140-143.

Harper, L., Bold, J. (2018). An exploration into the motivation for gluten avoidance in the absence of coeliac disease. *Gastroenterology and Hepatology from Bed to Bench* 11 (3): 259-268.

Harvard School of Public Health No Date Nutrition Source Lectins https://www.hsph.harvard.edu/nutritionsource/anti-nutrients/lectins/#:~:text=When%20consumed%2C%20lectins%20in%20their,blood%20cells%20to%20clump%20together.

84

Hossard, L., Philibert, A., Bertrand, M. et al. Effects of halving pesticide use on wheat production. Sci Rep 4, 4405 (2015). https://doi.org/10.1038/srep04405

Junker Y, Zeissig S, Kim SJ, Barisani D, Wieser H, Leffler DA, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-likereceptor 4. J Exp Med 2012;209:2395-408.

Kirschner L., Von Holy A. Rope spoilage of bread. S. Afr. J. Sci. 1989;85:425–427.

Lakhneko O, Danchenko M, Morgun B, Kováč A, Majerová P, Škultéty Ľ. Comprehensive Comparison of Clinically Relevant Grain Proteins in Modern and Traditional Bread Wheat Cultivars. *Int J Mol Sci*. 2020;21(10):3445. Published 2020 May 13. doi:10.3390/ijms21103445

Lauret, E., & Rodrigo, L. (2013). Celiac disease and autoimmune-associated conditions. BioMed research international, 2013, 127589. https://doi.org/10.1155/2013/127589

Leon, A., et al., *The pattern of cytokine expression determines the degree of mucosal damage*. Gut, 2007. 56(3): p. 441-443.

Lester DR. Gluten measurement and its relationship to food toxicity for celiac disease patients. Plant Methods. 2008;4:26. Published 2008 Oct 28. doi:10.1186/1746-4811-4-26

Mahroug H, Ribeiro M, Rhazi L, et al. How microwave treatment of gluten affects its toxicity for celiac patients? A study on the effect of microwaves on the structure, conformation, functionality and immunogenicity of gluten. *Food Chem*. 2019;297:124986.

Martinez DA, Loening UE, Graham MC. Impacts of glyphosate-based herbicides on disease resistance and health of crops: a review. *Environ Sci Eur*. 2018;30(1):2. doi:10.1186/s12302-018-0131-7

Menezes LAA, Minervini F, Filannino P, Sardaro MLS, Gatti M, Lindner JD. Effects of Sourdough on FODMAPs in Bread and Potential Outcomes on Irritable Bowel Syndrome Patients and Healthy Subjects. Front Microbiol. 2018;9:1972. Published 2018 Aug 21

85

Miyake K, Tanaka T, McNeil PL. Lectin-based food poisoning: a new mechanism of protein toxicity. *PLoS One*. 2007;2(8):e687. Published 2007 Aug 1. doi:10.1371/journal.pone.0000687

Molina G, Giménez MJ, Sánchez-León S, Barro F. Gluten Free Wheat: Are We There?. Nutrients. 2019;11(3):487. Published 2019 Feb 26. doi:10.3390/nu11030487

Muir J , Varney J , Ajamian M, Gibson P. Gluten-free and low-FODMAP sourdoughs for patients with coeliac disease and irritable bowel syndrome: A clinical perspective,
International Journal of Food Microbiology, Volume 290,2019,Pages 237-246,

Nionelli L, Rizzello CG. Sourdough-Based Biotechnologies for the Production of Gluten-Free Foods. Foods. 2016;5(3):65. Published 2016 Sep 20. doi:10.3390/foods5030065

O'Keeffe, M, Jansen, C, Martin, L, et al. Long-term impact of the low-FODMAP diet on gastrointestinal symptoms, dietary intake, patient acceptability, and healthcare utilization in irritable bowel syndrome. Neurogastroenterol Motil. 2018; 30:e13154. https://doi.org/10.1111/nmo.13154

Poutanen K, Flander L, Katina K. Sourdough and cereal fermentation in a nutritional perspective. Food Microbiol. 2009;26(7):693-699. doi:10.1016/j.fm.2009.07.011

Peumans WJ, Van Damme EJ. Lectins as plant defense proteins. Plant physiology. 1995 Oct;109(2):347.

86

Pruimboom L, de Punder K. The opioid effects of gluten exorphins: asymptomatic celiac disease. *J Health Popul Nutr.* 2015;33:24. Published 2015 Nov 24. doi:10.1186/s41043-015-0032-y

Rostami, K., Bold, J., Parr, A., and Johnson, M.W. (2017) Gluten-Free Diet Indications, Safety, Quality, Labels, and Challenges Nutrients 9(8), 846; doi:10.3390/nu9080846
https://www.ncbi.nlm.nih.gov/books/NBK26846/

Rueda-Ruzafa L, Cruz F, Roman P, Cardona D. Gut microbiota and neurological effects of glyphosate, NeuroToxicology, Volume 75, 2019, Pages 1-8, https://doi.org/10.1016/j.neuro.2019.08.006.

Samsel A, Seneff S. Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. *Interdiscip Toxicol.* 2013;6(4):159-184. doi:10.2478/intox-2013-0026

Sapone et al. (2011) Divergence of gut permeability and mucosal immune gene expression in tow gluten associated conditions: coeliac disease and gluten sensitivity. *BMC Medicine* 9:23.

Sapone A , Bai J, Ciacci C, Dolinsek J, Green P, Hadjivassiliou M, Kaukinen K, Rostami K, Sanders D, Schumann M, Ullrich R, Villalta D, Volta U, Catassi C and Fasano A *BMC Medicine* 201210:13 https://doi.org/10.1186/1741-7015-10-13

Schalk K, Lexhaller B, Koehler P, Scherf KA (2017) Isolation and characterization of gluten protein types from wheat, rye, barley and oats for use as reference materials. PLOS ONE 12(2): e0172819. https://doi.org/10.1371/journal.pone.0172819

Schönbrunn E, Eschenburg S, Shuttleworth WA, et al. Interaction of the herbicide glyphosate with its target enzyme 5-enolpyruvylshikimate 3-phosphate synthase in atomic detail. Proc Natl Acad Sci U S A. 2001;98(4):1376-1380. doi:10.1073/pnas.98.4.1376

Senapati T, Mukerjee AK, Ghosh AR. Observations on the effect of glyphosate based herbicide on ultra structure (SEM) and enzymatic activity in different regions of alimentary canal and gill of Channa punctatus (Bloch) Journal of Crop and Weed. 2009;5(1):236–245.

87

Shahbazkhani et al (2015) Non-Celiac Gluten Sensitivity Has Narrowed the Spectrum of Irritable Bowel Syndrome: A Double-Blind Randomized Placebo-Controlled Trial. *Nutrients* (7) 4542-4554.

Shewry PR, Halford NG, Belton PS, Tatham AS. The structure and properties of gluten: an elastic protein from wheat grain. Philos Trans R Soc Lond B Biol Sci. 2002;357(1418):133-142. doi:10.1098/rstb.2001.1024

Shewry PR, Tatham AS. The prolamin storage proteins of cereal seeds: structure and evolution. Biochem J. 1990 Apr 1;267(1):1-12. doi: 10.1042/bj2670001. PMID: 2183790; PMCID: PMC1131235.

Skodje GI, Sarna VK, Minelle IH, et al. Fructan, Rather Than Gluten, Induces Symptoms in Patients With Self-Reported Non-Celiac Gluten Sensitivity. *Gastroenterology*. 2018;154(3):529-539.e2. doi:10.1053/j.gastro.2017.10.040

Shotwell M, Boyer S, Chesnut R, Larkins B Analysis of seed storage protein genes of oats.J. Biol. Chem. 1990 265: 9652-9658.

Stamataki NS, Yanni AE, Karathanos VT. Bread making technology influences postprandial glucose response: a review of the clinical evidence. Br J Nutr. 2017;117(7):1001-1012. doi:10.1017/S0007114517000770

Staudacher, H. M. (2017) Nutritional, microbiological and psychosocial implications of the low FODMAP diet. Journal of Gastroenterology and Hepatology, 32: 16– 19. doi: 10.1111/jgh.13688.

Stefanucci A, Mollica A, Macedonio G, Zengin G, Abdelkareem A. A Novellino (2018) Exogenous opioid peptides derived from food proteins and their possible uses as dietary supplements: A critical review, Food Reviews International, 34:1, 70-86, DOI: 10.1080/87559129.2016.1225220

Takahashi M, Fukunaga H, Kaneto H, Fukudome S, Yoshikawa M. Behavioral and pharmacological studies on gluten exorphin A5, a newly isolated bioactive food protein fragment, in mice. Jpn J Pharmacol. 2000;84(3):259–65.

88

Tammaro A, Narcisi A, De Marco G, Persechino S. Cutaneous hypersensitivity to gluten. Dermatitis. 2012;23(5):220-221. doi:10.1097/DER.0b013e318262ca9b

Tesfaigzi and Daheshia Encyclopedia of Respiratory Medicine, 2006 Elsevier

Thompson T, Grace T. Gluten in cosmetics: is there a reason for concern?. J Acad Nutr Diet. 2012;112(9):1316-1323. doi:10.1016/j.jand.2012.07.011

Tosi P, Gritsch CS, He J, Shewry PR. Distribution of gluten proteins in bread wheat (Triticum aestivum) grain. *Ann Bot*. 2011;108(1):23-35. doi:10.1093/aob/mcr098

Uhde, M., Ajamian, M., Caio, G., De Giorgio, R., Indart, A., Green, P. H., Verna, E. C., Volta, U., & Alaedini, A. (2016). Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease. *Gut*, *65*(12), 1930–1937. https://doi.org/10.1136/gutjnl-2016-311964

Ullah S, Zuberi A, Alagawany M, Farag MR, Dadar M, Karthik K, Tiwari R, Dhama KIqbal HM. 2018. Cypermethrin induced toxicities in fish and adverse health outcomes: Its prevention and control mesure adaptation. J. Environ. Mang. 206:863–871.

Ungprasert, P., Wijarnpreecha, K., & Kittanamongkolchai, W. (2017). Psoriasis and Risk of Celiac Disease: A Systematic Review and Meta-analysis. Indian journal of dermatology, 62(1), 41–46. https://doi.org/10.4103/0019-5154.198031

United States Department of Agriculture Pesticide Use in U.S. Agriculture: 21 Selected Crops, 1960-2008, EIB-124 Economic Research Service/USDA Bulletin
Number 124 May 2014 https://www.ers.usda.gov/webdocs/publications/43854/46734_eib124.pdf

Vahedi, K., Mascart, F., Mary, J. Y., Laberenne, J. E., Bouhnik, Y., Morin, M. C., Ocmant, A., Velly, C., Colombel, J. F., & Matuchansky, C. (2003). Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease. *The American journal of gastroenterology*, *98*(5), 1079–1087. https://doi.org/10.1111/j.1572-0241.2003.07284.x

89

Valerii et al. (2015) Responses of peripheral blood mononucleated cells from non-celiac gluten sensitive patients to various cereal sources. *Food chemistry* 176:167-174.

Valitutti F, Cucchiara S, Fasano A. (2019) Celiac Disease and the Microbiome. Nutrients. Oct 8;11(10):2403. doi: 10.3390/nu11102403. PMID: 31597349; PMCID: PMC6835875.

van Hees NJM, Giltay EJ, Tielemans SMAJ, Geleijnse JM, Puvill T, Janssen N, et al. (2015) Essential Amino Acids in the Gluten-Free Diet and Serum in Relation to Depression in Patients with Celiac Disease. PLoS ONE 10(4): e0122619. https://doi.org/10.1371/journal.pone.0122619

van Overbeek FM, Uil-Dieterman IG, Mol IW, Kohler-Brands L, Heymans HS, Mulder CJ. The daily
gluten intake in relatives of patients with coeliac disease compared with that of the general Dutch population. Eur J Gastroenterol Hepatol 1997; 9: 1097-99.

Verdu, E., Galipeau, H. & Jabri, B. Novel players in coeliac disease pathogenesis: role of the gut microbiota. Nat Rev Gastroenterol Hepatol 12, 497–506 (2015). https://doi.org/10.1038/nrgastro.2015.90

van Buul V, Brouns F, Health effects of wheat lectins: A review, Journal of Cereal Science, Volume 59, Issue 2, 2014, Pages 112-117, ISSN 0733-5210, https://doi.org/10.1016/j.jcs.2014.01.010.
(http://www.sciencedirect.com/science/article/pii/S0733521014000228)

Volta et al. (2012) Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol.* 46(8):680-5

Volta, U., Caio, G., Tovoli, F., & De Giorgio, R. (2013). Non-celiac gluten sensitivity: questions still to be answered despite increasing awareness. *Cellular & molecular immunology*, *10*(5), 383–392. https://doi.org/10.1038/cmi.2013.28

Wieser H. Chemistry of gluten proteins. *Food Microbiol*. 2007;24(2):115-119. doi:10.1016/j.fm.2006.

Williams, G. M., Kroes, R., & Munro, I. C. (2000). Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. *Regulatory toxicology and pharmacology : RTP*, *31*(2 Pt 1), 117–165. https://doi.org/10.1006/rtph.1999.1371

90

Zevallos VF, Raker V, Tenzer S, Jimenez-Calvente C, Ashfaq-Khan M, Russel N, et al. Nutritional wheat amylase-trypsin inhibitors promote intestinal inflammation via activation of myeloid cells. Gastroenterology 2017;152:1100-13.

Ziegler, K., Neumann, J., Liu, F., Fröhlich-Nowoisky, J., Cremer, C., Saloga, J., Reinmuth-Selzle, K., Pöschl, U., Schuppan, D., Bellinghausen, I., & Lucas, K. (2019). Nitration of Wheat Amylase Trypsin Inhibitors Increases Their Innate and Adaptive Immunostimulatory Potential in vitro. Frontiers in immunology, 9, 3174. https://doi.org/10.3389/fimmu.2018.03174

91