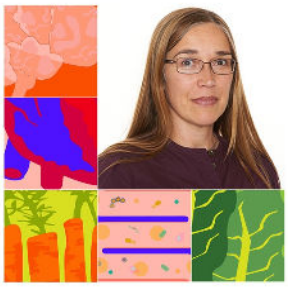
Microbiome, Gut and Systemic Health: New Frontiers in Personalised Nutrition



Justine Bold

Gluten Intolerance, Coeliac Disease and the Microbiome

2:00-2:45pm

An event by: Nutritional Medicine Institute

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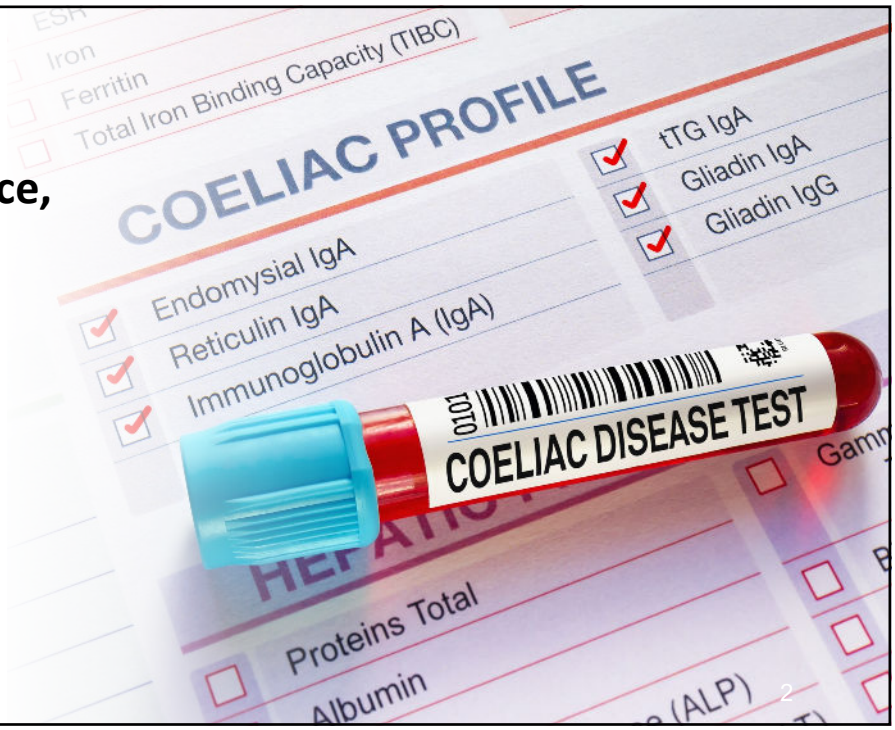
Gluten intolerance, Coeliac Disease and the Microbiome



Justine Bold

October 2023

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2

Today

- Introduction, affiliations
- Overview gluten and gluten related disorders
- Coeliac disease and microbiome
- Non coeliac gluten sensitivity and microbiome

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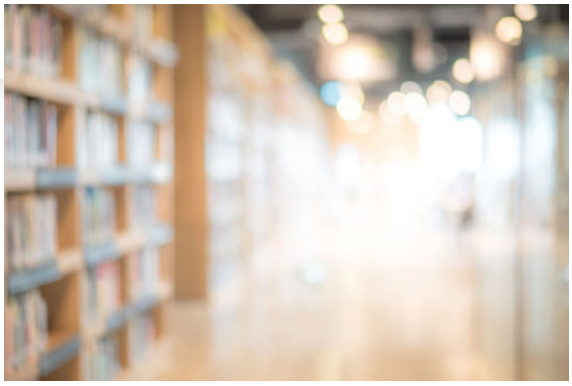
Introduction

Programme director for CPD in the Centre for Medical Education in the Medical School at Cardiff University.

- Research interest nutrition and lifestyle medicine, wellbeing, digestive disorders, gluten and malabsorption.

- I have been a senior lecturer at University of Worcester on MSc Nutrition & Lifestyle Medicine for over 15 years.



justineboldfood

justine_bold

Nutrition Health Worcester

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Other affiliations

- NMI editorial board member
- Delivered some educational CPD for Lamberts
- University of Northampton, Visiting Lecturer
- Fellow of BANT, PhD Student

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University of Worcester

Gluten is one of my main research and scholarship areas

Chapter 3

Gluten and its main food sources and other components of grains that may impact on health

Justine Bold[1,2]

[1]School of Allied Health & Community, University of Worcester, Worcester, United Kingdom, [2]Centre for Medical Education, Medical School, Cardiff University, Cardiff, United Kingdom

Chapter Outline

Introduction

Wheat is one of the main sources of gluten and among the most important agricultural crops in the world along with rice and maize [1]. It is the starch of choice in most industrialized countries [2]. In 2002 it was estimated that around 600 million tonnes of wheat were harvested across the world annually [1]. In 2015 production was reported to be >700 million tonnes [3]. *Triticum aestivum* L is the wheat milled for bread flour and it is one of the most valuable cereal crops produced for human consumption [4], though grains are also widely produced for animal feed as well. In contrast to wheat, the cereal crops of rice and maize are considered to be gluten-free (GF) grains. Areas of the world such as Asia that have traditionally eaten more rice are now seeing increasing wheat consumption [5]. The production of foods containing gluten has also increased through the course of human history [6] with the transition from a Paleolithic hunter-gather diet that was generally low in grains and the development of agriculture where more grain has been produced. Wheat was introduced to the human diet around 12,000 years ago in the Neolithic period [7], which is relatively recent in terms of human history. All common wheat varieties and derivatives such as malt contain gluten [8]. Wheat's widespread cultivation is largely attributed to the properties of wheat dough, which are very useful in baking, food production, and the fact that wheat can also give high yields in a range of growing conditions [1].

Gluten-Related Disorders. DOI: https://doi.org/10.1016/B978-0-12-821644-2.00007-3
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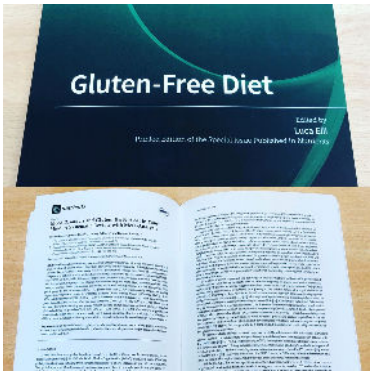
Busby, E.; Bold, J.; Fellows, L.; Rostami, K. (2019) Mood Disorders and Gluten: It's Not All in Your Mind! A Systematic Review with Meta-Analysis in Gluten-Free Diet Edited by Luca Elli mdpi.com/books/pdfview/book/1214



Bold J. Gluten and its main food sources and other components of grains that may impact on health. Published in Gluten Related Disorders Diagnostic Approaches, Treatment Pathways, and Future Perspectives Ed: Mohammad Rostami-Nejad 1st Sept 2021

Bold J, Diamantopoulou D. Views and experiences of infertile women regarding the role of gluten in their infertility. Obstetrics and Gynecology Research 5 (2022): 296-310

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Gluten

- Gluten is a protein found in wheat, rye, barley or their crossbred varieties and derivatives, to which some people are intolerant and that is insoluble in water. Humans started to eat gluten grains @9,000 years ago.
- In the main it's a combination of gliadin and glutenin.
- Wheat flour comprises approx. :-
  - 35% glutenins
  - 45% gliadins
  - & around 20% other protein

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Gluten

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

This can cause an inflammatory response as it can increase intestinal permeability.

This may underpin the pathophysiology in both CD and NCGS.

Balakireva AV, Zamyatnin AA. Properties of Gluten Intolerance:
Gluten Structure, Evolution, Pathogenicity and Detoxification Capabilities. *Nutrients*. 2016; 8(10):644.
https://doi.org/10.3390/nu8100644

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

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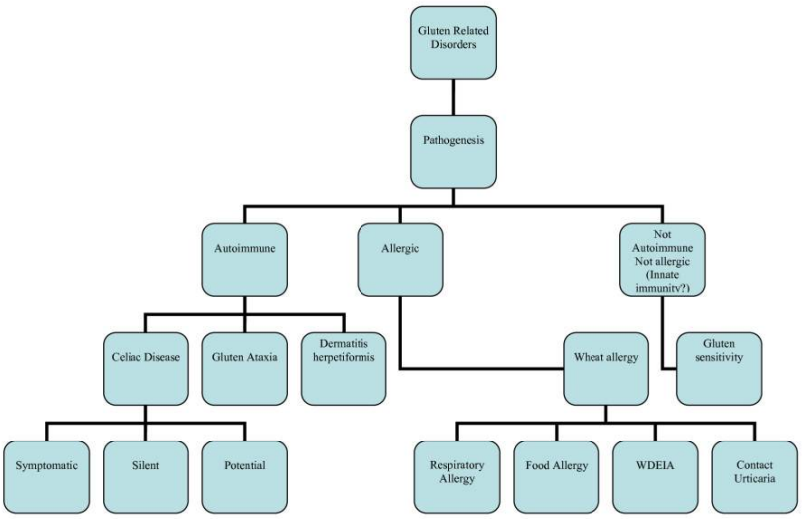
Wide Spectrum of Gluten Related Disorders

- Includes autoimmune conditions coeliac disease and gluten ataxia.
- As well as wheat allergy and gluten sensitivity.

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



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Why does Coeliac Disease develop?

- Approx. a third of the population have HLA DQ2/8 alleles.
  - These give a propensity for developing coeliac disease (CD)
- But CD affects approx. 1 in 100 of the population.

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Genetics

- Having a relative with the condition (e.g. 1st degree relative such as child, brother, sister or parent does not guarantee that person will have/get CD).
- The HLA type associated with CD are HLA DQ 2.5, HLA DQ8 or HLA DQ2.2 (it's very rare to have CD without these but it can happen)
- In addition to associations with HLA, other non-HLA regions of the genome, such as 5q31–33 seem to confer some risk for CD.

Babron M C, Nilsson S, Adamovic S. *et al* European genetics cluster on coeliac disease. Meta and pooled analysis of European coeliac disease data. Eur J Hum Genet 200311828–834.

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Microbiome & Coeliac disease (CD)

Conclusions of 2020 Review paper

Factors such as **infant feeding practices, diet, antibiotics, and infections, may be involved in the development of coeliac disease** due to their influence on gut microbial composition.

The efficacy of potential modulators of the gut microbiota such as probiotics, prebiotics, and fecal microbial transplant as adjunctive treatments to gluten-free diet in coeliac disease is unproven and requires further investigation.

Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. *Eur J Nutr*. 2020;59(8):3369-3390. doi:10.1007/s00394-020-02324-y

European Journal of Nutrition (2020) 59:3369–3390
https://doi.org/10.1007/s00394-020-02324-y

REVIEW

Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications

Anthony K. Akobeng[1,2] · Parul Singh[3] · Manoj Kumar[3] · Souhaila Al Khodor[3]

Received: 16 March 2020 / Accepted: 1 July 2020 / Published online: 10 July 2020
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Abstract
Purpose Although genetic predisposition and exposure to dietary gluten are considered necessary triggers for the development of coeliac disease, alterations in the gut microbial composition may also contribute towards the pathogenesis of coeliac disease. This review aims to provide an overview of the available data on the potential mechanisms through which the gut microbiota plays a role in the causation of coeliac disease and to discuss the potential therapeutic strategies that could diminish the consequences of microbial dysbiosis.
Method A search of the literature was performed using the PubMed, Embase, and JSTOR databases; relevant articles were included.
Results Recent studies in patients with coeliac disease have reported an increase in the relative amounts of gram negative bacterial genera such as *Bacteroides*, *Prevotella*, and *Escherichia*, and reduced amounts of protective anti-inflammatory bacteria such as *Bifidobacteria* and *Lactobacilli*. Dysbiotic microbiota may lead to a dysregulated immune response that may contribute to the pathogenesis of coeliac disease. In infancy, antibiotic use and certain infant feeding practices may lead to alterations in the developing gut microbiota to influence the immune maturation process and predispose to coeliac disease.
Conclusion The induction of the intestinal immune system and gluten intolerance may be influenced by the relative abundance of certain microbiota. Factors such as infant feeding practices, diet, antibiotics, and infections, may be involved in the development of coeliac disease due to their influence on gut microbial composition. The efficacy of potential modulators of the gut microbiota such as probiotics, prebiotics, and fecal microbial transplant as adjunctive treatments to gluten-free diet in coeliac disease is unproven and requires further investigation.

Keywords Coeliac disease · Microbiota · Metagenomics · Dysbiosis

Introduction

Coeliac disease is an autoimmune disorder triggered by the ingestion of gluten in genetically susceptible people [1]. The disorder is characterized by a mucosal disease of the proximal small bowel as a result of a T-cell mediated destruction of mucosal epithelial cells. It is generally acknowledged that coeliac disease affects about 1% of the population with an increasing prevalence [2] that varies between countries [3]. Patients with coeliac disease develop a permanent loss of immune tolerance to gluten [4, 5], a protein found in cereals such as wheat, rye, and barley. Upon ingestion, gluten can cause a pathological injury characterized by progressive degrees of inflammation and loss of villi in the proximal small bowel leading to the development of gastrointestinal malabsorption along with extra-gastrointestinal manifestations [3].

Coeliac disease is a multifactorial disease, characterized by a complex interplay of genetic and environmental factors. While genetic factors (such as the presence of Human Leukocytic Antigen—mainly HLA-DQ2 or HLA DQ-8) and exposure to dietary gluten are considered to be necessary triggers, they are not sufficient for disease development [6]. Additional factors such as infant feeding practices, the amount of gluten ingested, the age at which gluten is

Anthony K. Akobeng and Parul Singh equal first authors.

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[2] Weill Cornell Medicine, Cornell University, Doha, Qatar
[3] Research Department, Sidra Medicine, Doha, Qatar

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Weaning, barrier function and CD risk

Both early and late gluten exposure may be associated with an increased risk of CD in children already at an increased risk.

Study Conclusions

" In children at increased risk of developing celiac disease, timing of gluten exposure in the diet is associated with the appearance of CDA. Exposure to gluten in the first 3 months of life is thought to be associated with increased risk because of immature or incomplete intestinal barrier function. The authors speculate that late gluten exposure may have been associated with CDA because of greater amounts introduced in the older infants."

Goldsobel A B; Risk of Celiac Disease Autoimmunity and Timing of Gluten Introduction in the Diet of Infants at Increased Risk of Disease. *Pediatrics* August 2006; 118 (Supplement_1): S14–S15. 10.1542/peds.2006-0900X

Risk of Celiac Disease Autoimmunity and Timing of Gluten Introduction in the Diet of Infants at Increased Risk of Disease

Norris JM, Barriga K, Hoffenberg EJ, et al. *JAMA*. 2005;293:2343–2351

PURPOSE OF THE STUDY. Patients with HLA-DR3 or DR4 alleles are at increased risk for the development of celiac disease. However, not all genetically susceptible individuals develop celiac disease. The objective of this study was to investigate whether there was an association between the timing of exposure to gluten and subsequent development of celiac disease autoimmunity (CDA) in children with a genetic predisposition for celiac disease.

STUDY POPULATION. Children (n = 1560) were identified in the Denver, Colorado, metropolitan area with an increased risk for celiac disease (or type 1 diabetes), defined as having either a first-degree relative with type 1 diabetes or positive cord blood screening for HLA-DR3 or DR4 alleles. This study was conducted over 10 years with a mean follow-up of 4.8 years.

METHODS. This was a prospective, observational study. Infant diet data were collected during telephone or face-to-face interviews at 3, 6, 9, 12, and 15 months of age. No dietary advice was given to the families. Children had blood drawn at 9, 15, and 24 months and annually thereafter for the measurement of the celiac disease autoantigen, and tissue transglutaminase (tTG). After 1 or 2 positive tTG autoantibody results, small-bowel biopsy was offered to the families, although not all had this procedure performed. The primary outcome of the study was the time to development of CDA defined as the presence of tTG autoantibodies on 2 consecutive results or a positive small-bowel biopsy after a single tTG-positive test.

RESULTS. Fifty-one children developed CDA. Children exposed to foods containing wheat, barley, or rye in the first 3 months of life had a 5 times increased odds ratio (P = .02) of CDA as compared with children first exposed to gluten at 4 to 6 months of age. Twenty-five of the CDA-positive children had biopsy-proven celiac disease. In these children, exposure to gluten in the first 3 months of life had a 23 times increased risk (P = .001) of CDA. In the biopsy-proven cohort, children not exposed to gluten until >7 months of age also had a significantly increased risk of CDA (odds ratio: 4; P = .04). There was

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Breast feeding & CD risk

Breast feeding at time of gluten introduction is protective.

- Beneficial in terms of establishment of microflora in infant

- Meta-analysis of data of four studies indicated that children being breast fed at the time of gluten introduction had a 52% reduction in risk of developing CD compared with their peers who were not breast feeding at the time of gluten introduction.

Akobeng AK, Ramanan AV, Buchan I, Heller RF. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. *Arch Dis Child*. 2006;91(1):39-43. doi:10.1136/adc.2005.082016

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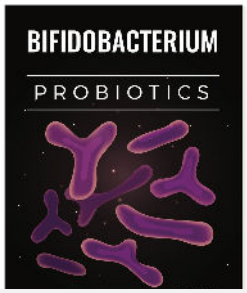
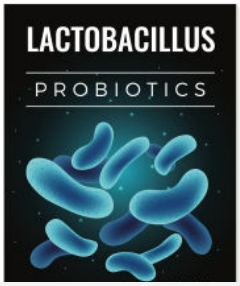
Microbiome in CD





"**Recent studies in patients with CD have reported an increase in the relative amounts of gram negative bacterial genera such as *Bacteroides*, *Prevotella*, and *Escherichia*, and reduced amounts of protective anti-inflammatory bacteria such as *Bifidobacteria* and *Lactobacilli***.

Dysbiotic microbiota may lead to a dysregulated immune response that may contribute to the pathogenesis of CD".

Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. *Eur J Nutr*. 2020;59(8):3369-3390. doi:10.1007/s00394-020-02324-y

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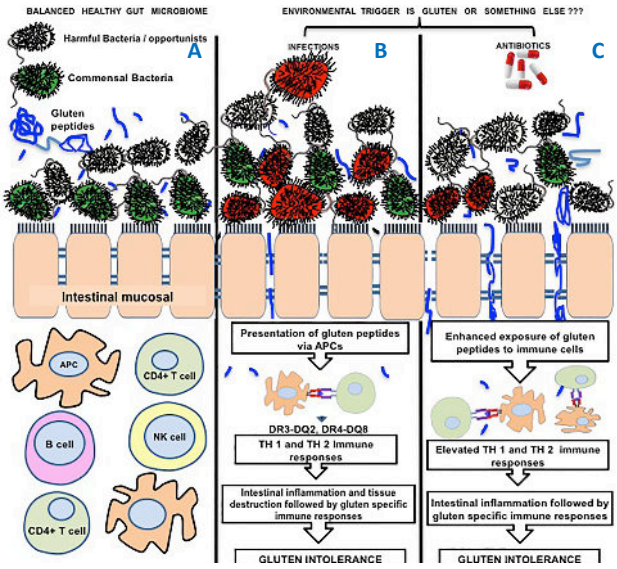
Microbiome in CD

2018 paper showing involvement of microbiota in barrier integrity and what happens when that is compromised.

Going to review A,B, C over next few slides.



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

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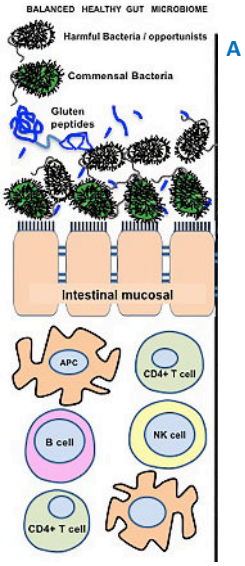
Microbiome in CD

A

Healthy balance between beneficial bacteria (green) and harmful bacteria (red yellow).

Beneficial microbes prevent adhesion of harmful ones to mucosa.



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Microbiome in CD

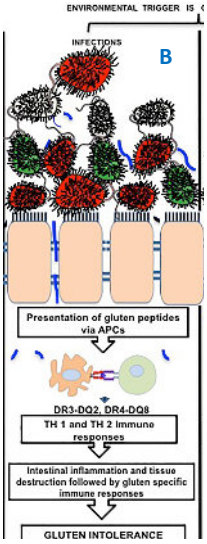
B

Exposure to infectious agents (red) compete with the beneficial microbes & adhere to mucosa then they disturb tight junctions by activating inflammatory pathways.

Disturbed intestinal barrier leads to exposure of intestinal immune cells to gluten.

Elastase activity to the peptides increases potency to translocate through intestinal barrier.

Gluten peptides (blue coloured) are presented by APCs to the T lymphocytes causing immune processes leading to gluten specific immune responses & tissue remodelling.



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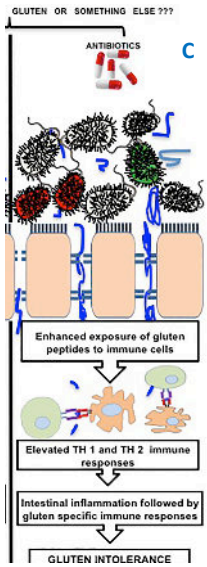
Microbiome in CD

C

Highlights that the catalyst role of antibiotics, which eradicate infections along with beneficial microbes leading to dysbiosis.

Then opportunistic harmful microbes may prove to be dangerous because beneficial microbes can no longer protect intestinal mucosa leading to adherence of the harmful microbes to the intestinal epithelial cells and creating disease susceptible microenvironment.



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Transglutaminase 2 & CD4 lymphocytes

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).

León AJ, Gómez E, Garrote JA, Arranz E. The pattern of cytokine expression determines the degree of mucosal damage. *Gut*. 2007;56(3):441-443. doi:10.1136/gut.2006.110361

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Primary event

"The primary event of a gluten-induced inflammatory immune response requires **that gluten peptides translocate via intracellular or paracellular mechanisms through the intestinal epithelial barrie**r and have access to the lamina propria".

Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. *Eur J Nutr*. 2020;59(8):3369-3390. doi:10.1007/s00394-020-02324-y

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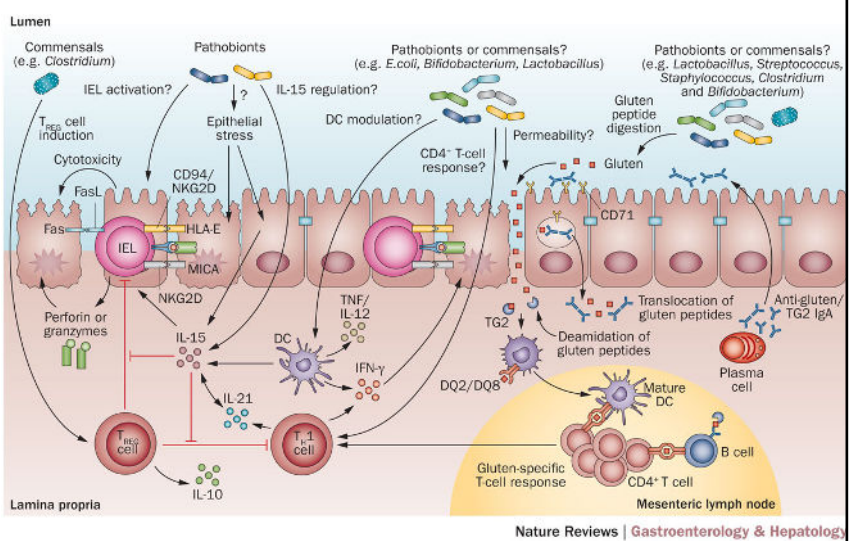
Microbiome disturbance

2015 paper also highlights translocation and microbial, infective and environmental triggers in the development of CD and the inflammatory cascade that is initiated.

Not fully understood.

Potential microbial modulation of coeliac disease pathogenesis



Verdu, E. F. *et al.* (2015) Novel players in coeliac disease pathogenesis: role of the gut microbiota *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2015.90

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Tight junctions and genetic factors 2020 paper

"Integrity of the tight junction …is compromised partly due to the upregulation of zonulin. Nonetheless, the relatively poor digestion of these proteins or the resulting increased gut permeability is not sufficient to cause coeliac disease.

The multifactorial pathogenesis of CD appears to stem from genetic susceptibility which, in addition to **other unknown contributing factors, triggers the innate and adaptive immune response"**.

Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. *Eur J Nutr*. 2020;59(8):3369-3390. doi:10.1007/s00394-020-02324-y

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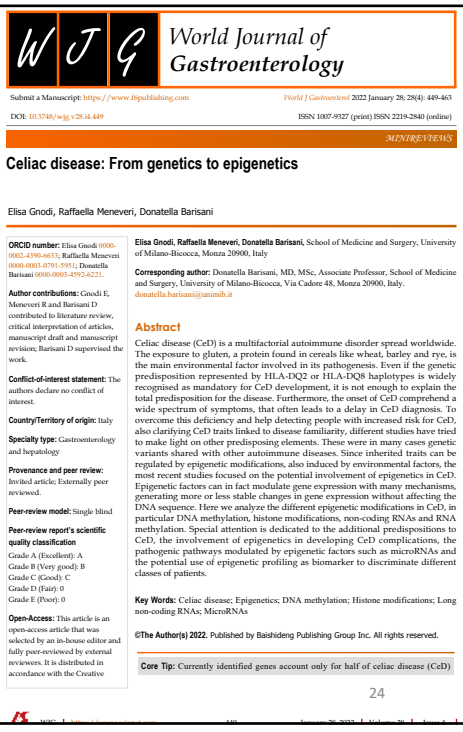
Genetics and Epigenetics

Genetic variants of CD shared with other autoimmune diseases

Currently identified genes account only for half of celiac disease (CeD) predisposition.

An important role could be played by epigenetics, inheritable traits without DNA sequence alterations, which could be influenced by gluten exposure.

Gnodi E, Meneveri R, Barisani D. Celiac disease: From genetics to epigenetics. *World J Gastroenterol*. 2022; 28(4):449-463. doi:10.3748/wjg.v28.i4.449



World Journal of Gastroenterology

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DOI: 10.3748/wjg.v28.i4.449 ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Celiac disease: From genetics to epigenetics

Elisa Gnodi, Raffaella Meneveri, Donatella Barisani

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Author contributions: Gnodi E, Meneveri R and Barisani D contributed to literature review, critical interpretation of articles, manuscript draft and manuscript revision; Barisani D supervised the work.

Conflict-of-interest statement: The authors declare no conflict of interest.

Country/Territory of origin: Italy

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Celiac disease (CeD) is a multifactorial autoimmune disorder spread worldwide. The exposure to gluten, a protein found in cereals like wheat, barley and rye, is the main environmental factor involved in its pathogenesis. Even if the genetic predisposition represented by HLA-DQ2 or HLA-DQ8 haplotypes is widely recognised as mandatory for CeD development, it is not enough to explain the total predisposition for the disease. Furthermore, the onset of CeD comprehend a wide spectrum of symptoms, that often leads to a delay in CeD diagnosis. To overcome this deficiency and help detecting people with increased risk for CeD, also clarifying CeD traits linked to disease familiarity, different studies have tried to make light on other predisposing elements. These were in many cases genetic variants shared with other autoimmune diseases. Since inherited traits can be regulated by epigenetic modifications, also induced by environmental factors, the most recent studies focused on the potential involvement of epigenetics in CeD. Epigenetic factors can in fact modulate gene expression with many mechanisms, generating more or less stable changes in gene expression without affecting the DNA sequence. Here we analyze the different epigenetic modifications in CeD, in particular DNA methylation, histone modifications, non-coding RNAs and RNA methylation. Special attention is dedicated to the additional predispositions to CeD, the involvement of epigenetics in developing CeD complications, the pathogenic pathways modulated by epigenetic factors such as microRNAs and the potential use of epigenetic profiling as biomarker to discriminate different classes of patients.

Key Words: Celiac disease; Epigenetics; DNA methylation; Histone modifications; Long non-coding RNAs; MicroRNAs

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Core Tip: Currently identified genes account only for half of celiac disease (CeD)

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Genetics and Epigenetics

"DNA methylation, histone modifications and non-coding RNAs act on different gene expression steps, from gene transcription to post-translational ones.

Epigenetic changes can be additional predisposition factors or specific of CD stages (active disease, gluten-free diet)".

Gnodi E, Meneveri R, Barisani D. Celiac disease: From genetics to epigenetics. *World J Gastroenterol*. 2022; 28(4):449-463. doi:10.3748/wjg.v28.i4.449

Abstract

Celiac disease (CeD) is a multifactorial autoimmune disorder spread worldwide. The exposure to gluten, a protein found in cereals like wheat, barley and rye, is the main environmental factor involved in its pathogenesis. Even if the genetic predisposition represented by HLA-DQ2 or HLA-DQ8 haplotypes is widely recognised as mandatory for CeD development, it is not enough to explain the total predisposition for the disease. Furthermore, the onset of CeD comprehend a wide spectrum of symptoms, that often leads to a delay in CeD diagnosis. To overcome this deficiency and help detecting people with increased risk for CeD, also clarifying CeD traits linked to disease familiarity, different studies have tried to make light on other predisposing elements. These were in many cases genetic variants shared with other autoimmune diseases. Since inherited traits can be regulated by epigenetic modifications, also induced by environmental factors, the most recent studies focused on the potential involvement of epigenetics in CeD. Epigenetic factors can in fact modulate gene expression with many mechanisms, generating more or less stable changes in gene expression without affecting the DNA sequence. Here we analyze the different epigenetic modifications in CeD, in particular DNA methylation, histone modifications, non-coding RNAs and RNA methylation. Special attention is dedicated to the additional predispositions to CeD, the involvement of epigenetics in developing CeD complications, the pathogenic pathways modulated by epigenetic factors such as microRNAs and the potential use of epigenetic profiling as biomarker to discriminate different classes of patients.

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Genetics and Epigenetics

DNA methylation features in CD showing links to other auto-immune conditions and inflammatory cascade.

DNA methylation features in celiac disease

Predisposition to CeD	What	Result	Highlight in CeD
Allele-specific methylation (ASM)[24]		ASM in rs2762051 in *DLEU1* gene	Linked to CeD phenotype
Rs906868 in *LBH* gene promoter[23]	Risk variant shared with RA	Disease-specific methylation	Different methylation in rs906868 can predispose to CeD or RA → influence on Wnt signalling
Methylation in HLA region in CeD[30]	Specific patterns in epithelial and immune cells	Genotype-independent methylation (except for HLA-DPB2)	Methylation patterns in HLA region → CeD predisposition
Methylation profiling in HLA-DQB1 and SLC17A3[32]	Bead-chip on saliva samples	Different methylation profiles, not confirmed in bigger cohort	Potential methylation-based screening Major validation needed
Opioid like-effect of gliadin[27]		Modulation of glutathione and DNA methylation	Predisposition to inflammation and oxidation
CeD pathogenesis			
Methylation in NFkB-related genes[26]	NFkB pathway↑↑	Disruption of regulatory equilibrium	Co-methylation patterns typical of active CeD in NFkB pathway genes
Cell-specific methylation[30]		Epithelium → 43 DMP Immune cells → 310 DMP	Cell-specific methylation signature & gene expression in CeD *vs* controls
Different methylation of SB2H3, IL-21, cREL and TNFAIP3[31]	Epithelium and lamina propria - specificity	Correlation with pro-inflammatory(↑) and cell adhesion(↓) pathways	Methylation of SB2H3 → epithelium Methylation of IL21 → lamina propria Typical of CeD samples.
Tumor development			

CeD: Celiac disease; ASM: Allele specific methylation; RA: Rheumatoid arthritis; DMP: Differentially methylated positions; CpGs: CpG islands.

Gnodi E, Meneveri R, Barisani D. Celiac disease: From genetics to epigenetics. *World J Gastroenterol*. 2022; 28(4):449-463. doi:10.3748/wjg.v28.i4.449

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Microbial signatures of children with active CD

^{S} decrease

$^{\#}$ increase

Table 1 Microbial signatures in children with active coeliac disease relative to healthy controls[a]

Study	Sample source	Subject details	Methodology	Conclusion (microbiota signatures in coeliac disease) compared to controls
[75]	Stool	26 coeliac patients and 23 controls	Culture	#Bacteroides #Staphylococcus #Clostridium
[76]	Stool and duodenal biopsies	30 Coeliac patients, 30 controls	PCR	Stool sample: ^{S}*Bifidobacterium count* ^{S}*Bifidobacterium Longum* Duodenal biopsies: ^{S}*Bifidobacterium count* ^{S}*Bifidobacterium Longum* ^{S}*Bifidobacterium cantenulatum* #*B. lactis*
[77]	Stool and duodenal biopsies	25–30 Coeliac patients, 8–30 controls	PCR	Stool sample: #*E. coli* prevalence and count ^{S}*Bifidobacterium* count ##*Clostridium leptum* counts #*Staphylococcus* prevalence and counts Duodenal biopsies: ^{S}Bifidobacterium count #Bacteroides counts #Clostridium leptum #E. coli count #Staphylococcus counts ^{S}*C. coccoides* prevalence
[79]	Duodenal biopsies	20 Coeliac patients, 10 controls	PCR	#*Bacteroides vulgatus* prevalence #*E. coli* prevalence

Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. *Eur J Nutr*. 2020;59(8):3369-3390. doi:10.1007/s00394-020-02324-y

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Microbial signatures of children with active CD

^{S} decrease

$^{\#}$ increase

[74]	Stool sample and duodenal biopsies	19 Coeliac patients, 15 controls	PCR/Culture	Stool sample and duodenal Biopsies: #Eubacteria diversity ^{S}*Lactobacillus* counts ^{S}*Enterococcus* counts ^{S}Bifidobacterium counts #Bacteroides #Porphyromonas #Prevotella #*Staphylococcus*
[193]	Stool sample	20 Coeliac patients, 20 controls	PCR/Culture	#*Staphylococcus epidermidis* #*Staphylococcus haemolyticus* ^{S}*Enterococcus faecium*
[89]	Duodenal biopsies	32 Coeliac patients, 8 controls	Culture/ 16S rRNA sequencing	^{S}*Streptococcus mutans* ^{S}*Streptococcus anginosus* ^{S}*Firmicutes* #*Staphylococcacea* #*Staphylococcus epidermidis* #*Staphylococcus pasteuri* ^{S}*Streptococcaceae* #*Proteobacteria* #*Enterobacteriaceae* #*Klebsiella oxytoca*
[64]	Duodenal biopsies	10 Coeliac patients, 9 controls	16S rRNA sequencing	#*Prevotella melaninogenica* #*Haemphilus* #*Serratia* ^{S}*Prevotella oralis* ^{S}*Proteus* ^{S}*Clostridium stercorarium* ^{S}*Ruminococcus bromii* ^{S}*Papllibacter cinnamivorans*
[78]	Duodenal biopsies	8 Coeliac Disease, 5 controls	16S rRNA gene sequencing	^{S}Streptococcus ^{S}Prevotella #Neisseria #Haemophilus

[a]This table only includes the comparison of the patients with active or untreated Coeliac disease and healthy controls

#Increase in relative abundance

^{S}Decrease in relative abundance

Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. *Eur J Nutr*. 2020;59(8):3369-3390. doi:10.1007/s00394-020-02324-y

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Microbial signatures of adults with CD

$ decrease

increase

Table 2 Microbial signatures in adults with active coeliac disease relative to healthy controls[a]

Study	Sample source	Subject details	Methodology	Conclusion (microbiota signatures in coeliac disease) compared to controls
[78]	Stool sample	10 Coeliac patients, 11 controls	PCR	$*Lactobacillus* diversity $*Lactobacillus sakei* $*Bifidobacterium*
[84]	Duodenal biopsy*	10 Treated Coeliac patients with persistent symptoms, 10 treated Coeliac patients' symptoms free	16 S rRNA sequencing	#Proteobacteria $Bacteroidetes $Firmicutes
[85]	Duodenal biopsy	6 Coeliac patients, 11 controls	16 S rRNA sequencing	$Bacteroidetes $Fusobacteria
[82]	Stool sample and Duodenal biopsy	23 Coeliac patients, 24 controls	16S rRNA gene sequencing	Stool sample: $Akkermanisia $Dorea Duodenal biopsy: #Helicobacter #Megasphaera
[78]	Duodenal biopsy	5 Coeliac Disease, 5 controls	16S rRNA gene sequencing	#*Mycobacterium spp* #*Methylobacterium spp*

This table only includes the comparison of the microbial profiles in patients with active or untreated Coeliac disease and healthy controls. However, since very few studies are available in adults, we included one study[a] that allowed us to compare the treated coeliac patients (with persistent symptoms) with symptoms free treated Coeliac patients

#Increase in relative abundance

$Decrease in relative abundance

Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. *Eur J Nutr*. 2020;59(8):3369-3390. doi:10.1007/s00394-020-02324-y

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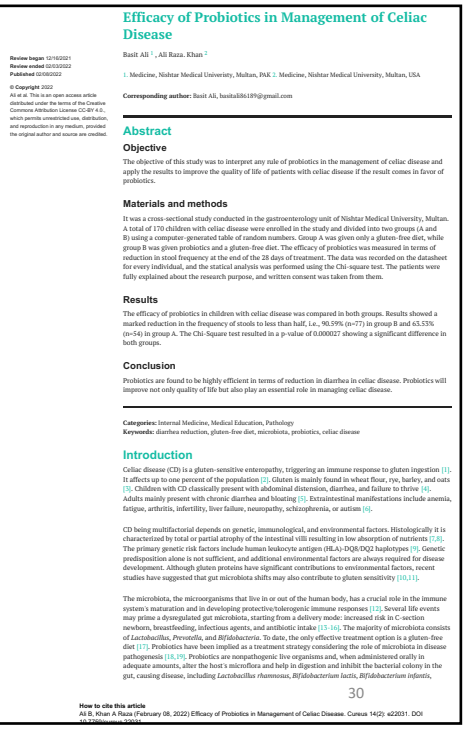
Interventions Supporting Microbiome

- Intervention to assess probiotics to help manage CD – and improve Quality of Life.
- 170 children aged 8-10 years old with CD recently confirmed by intestinal biopsy – were split into 2 groups with different interventions.
- Excluded other causes of diarrhoea such as giardia, cystic fibrosis etc.



Efficacy of Probiotics in Management of Celiac Disease

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Review began 12/16/2021
Review ended 02/03/2022
Published 02/08/2022

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Abstract

Objective

The objective of this study was to interpret any rule of probiotics in the management of celiac disease and apply the results to improve the quality of life of patients with celiac disease if the result comes in favor of probiotics.

Materials and methods

It was a cross-sectional study conducted in the gastroenterology unit of Nishtar Medical University, Multan. A total of 170 children with celiac disease were enrolled in the study and divided into two groups (A and B) using a computer-generated table of random numbers. Group A was given only a gluten-free diet, while group B was given probiotics and a gluten-free diet. The efficacy of probiotics was measured in terms of reduction in stool frequency at the end of the 28 days of treatment. The data was recorded on the datasheet for every individual, and the statical analysis was performed using the Chi-square test. The patients were fully explained about the research purpose, and written consent was taken from them.

Results

The efficacy of probiotics in children with celiac disease was compared in both groups. Results showed a marked reduction in the frequency of stools to less than half, i.e., 90.59% (n=77) in group B and 63.53% (n=54) in group A. The Chi-Square test resulted in a p-value of 0.000027 showing a significant difference in both groups.

Conclusion

Probiotics are found to be highly efficient in terms of reduction in diarrhea in celiac disease. Probiotics will improve not only quality of life but also play an essential role in managing celiac disease.

Categories: Internal Medicine, Medical Education, Pathology
Keywords: diarrhea reduction, gluten-free diet, microbiota, probiotics, celiac disease

Introduction

Celiac disease (CD) is a gluten-sensitive enteropathy, triggering an immune response to gluten ingestion [1]. It affects up to one percent of the population [2]. Gluten is mainly found in wheat flour, rye, barley, and oats [3]. Children with CD classically present with abdominal distension, diarrhea, and failure to thrive [4]. Adults mainly present with chronic diarrhea and bloating [5]. Extraintestinal manifestations include anemia, fatigue, arthritis, infertility, liver failure, neuropathy, schizophrenia, or autism [6].

CD being multifactorial depends on genetic, immunological, and environmental factors. Histologically it is characterized by total or partial atrophy of the intestinal villi resulting in low absorption of nutrients [7,8]. The primary genetic risk factors include human leukocyte antigen (HLA)-DQ8/DQ2 haplotypes [9]. Genetic predisposition alone is not sufficient, and additional environmental factors are always required for disease development. Although gluten proteins have significant contributions to environmental factors, recent studies have suggested that gut microbiota shifts may also contribute to gluten sensitivity [10,11].

The microbiota, the microorganisms that live in or out of the human body, has a crucial role in the immune system's maturation and in developing protective/tolerogenic immune responses [12]. Several life events may prime a dysregulated gut microbiota, starting from a delivery mode: increased risk in C-section newborn, breastfeeding, infectious agents, and antibiotic intake [13-16]. The majority of microbiota consists of *Lactobacillus*, *Prevotella*, and *Bifidobacteria*. To date, the only effective treatment option is a gluten-free diet [17]. Probiotics have been implied as a treatment strategy considering the role of microbiota in disease pathogenesis [18,19]. Probiotics are nonpathogenic live organisms and, when administered orally in adequate amounts, alter the host's microflora and help in digestion and inhibit the bacterial colony in the gut, causing disease, including *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, *Bifidobacterium infantis*,

How to cite this article
Ali B, Khan A Raza (February 08, 2022) Efficacy of Probiotics in Management of Celiac Disease. Cureus 14(2): e22031. DOI 10.7759/cureus.22031

Ali B, Khan AR. Efficacy of Probiotics in Management of Celiac Disease. *Cureus*. 2022;14(2):e22031. Published 2022 Feb 8. doi:10.7759/cureus.22031

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Interventions Supporting Microbiome

- 2 groups with different interventions.
  - Group A - gluten free diet.
  - Group B - gluten free diet and probiotics for 28 days Probiotic was Gutcare™sachet 500mg (*Clostridiumbutyricum* and *Bifidobacterium*) diluted in 75-100ml of boiled water twice a day.
  - Effects measured by reduction in stool frequency (diarrhoea).

Ali B, Khan AR. Efficacy of Probiotics in Management of Celiac Disease. *Cureus*. 2022;14(2):e22031. Published 2022 Feb 8. doi:10.7759/cureus.22031

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Interventions Supporting Microbiome

- Both groups showed significant difference in stool frequency.
- Bigger difference with in Group B with probiotics.

Results

The efficacy of probiotics in children with celiac disease was compared in both groups. Results showed a marked reduction in the frequency of stools to less than half, i.e., 90.59% (n=77) in group B and 63.53% (n=54) in group A. The Chi-Square test resulted in a p-value of 0.000027 showing a significant difference in both groups.

Conclusion

Probiotics are found to be highly efficient in terms of reduction in diarrhea in celiac disease. Probiotics will improve not only quality of life but also play an essential role in managing celiac disease.

Ali B, Khan AR. Efficacy of Probiotics in Management of Celiac Disease. *Cureus*. 2022;14(2):e22031. Published 2022 Feb 8. doi:10.7759/cureus.22031

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Gluten free diet and microbial composition GI tract

- Gut dysbiosis in CD improves on a GFD but on-going dysbiosis may contribute to some of persistent symptoms of CD.
- SIBO a factor in CD? Studies show benefits of antibiotics on persistent symptoms.

Caio G, Lungaro L, Segata N, et al. Effect of Gluten-Free Diet on Gut Microbiota Composition in Patients with Celiac Disease and Non-Celiac Gluten/Wheat Sensitivity. *Nutrients*. 2020;12(6):1832. Published 2020 Jun 19. doi:10.3390/nu12061832

6. Gut Microbiota Is Conditioned by Gluten in CD

Compared to asymptomatic controls, CD patients show a gut microbiota characterized by a higher number of total bacteria and a lower ratio of beneficial to harmful bacteria. These findings support the occurrence of gut dysbiosis in CD, which improves following gluten withdrawal [91,92]. A prototypic example of dysbiosis is given by small intestine bacterial overgrowth (SIBO), which may explain why some CD patients show poor responsiveness to GFD. Several studies have clearly indicated a beneficial effect on SIBO-related symptoms by using antibiotics, particularly the poorly absorbable class, such as rifaximin [93]. In CD, bacteria known for their protective effect, e.g., *Bifidobacteria*, *Firmicutes*, *Lactobacilli* and *Streptococceae*, are lower in number than in healthy controls, while the number of harmful Gram-negative bacteria (*Bacteroides*, *Bacterioidetes*, *Bacteroides fragilis*, *Prevotella*, *E. Coli*, *Proteobacteria*, *Haemophilus*, *Serratia*, *Klebsiella*) increase [94–97]. In duodenal biopsy of adult patients with active CD, *Proteobacteria* phylum and *Neisseria flavescens* were prominent, while *Firmicutes* and *Actinobacteria* were the least abundant [7,98]. These findings suggest that intestinal dysbiosis affects CD patients and contribute to persistent symptoms, even in those on a strict GFD regimen. An imbalance in the microbiota composition was also found by De Palma et al. in infants with genetic susceptibility to CD [99]. Indeed, feces of new-borns, bearing the HLA-DQ predisposing phenotype, were characterized by a higher number of *Bacterioides fragilis* and *Staphylococcus spp.* and a lower number of *Bifidobacteria* and *B. Longum* vs. healthy controls. The reason for this imbalance in the bacterial ratio could be ascribed to the glycocalyx mucous layer, a carbohydrate coating on the mucosal surface of the gastrointestinal tract. Each individual has a personal composition of the mucous glycocalyx (a genetically determined feature), which predisposes to CD by changing the specificity of bacterial adhesion and colonization. However, the hypothesis that the glycocalyx layer could play a role in CD onset has been recently questioned [100]. Breastfeeding is of crucial importance as it can help to restore the microbiota composition in babies carrying HLA-DQ2 haplotypes [99].

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Glycocalyx mucous layer

- Glycocalyx mucous layer (genetically determined) influences bacterial adhesion/colonisation.
- Could underpin bacterial imbalances seen in CD.

Caio G, Lungaro L, Segata N, et al. Effect of Gluten-Free Diet on Gut Microbiota Composition in Patients with Celiac Disease and Non-Celiac Gluten/Wheat Sensitivity. *Nutrients*. 2020;12(6):1832. Published 2020 Jun 19. doi:10.3390/nu12061832

The structure of the glycocalyx was found to be intact, but in some children with treated celiac disease the layer of glycocalyx was either thin or absent on the surface of individual cell microvilli.

Dyduch A, Karczewska K, Grzybek H, Kamiński M. Transmission electron microscopy of microvilli of intestinal epithelial cells in celiac disease in remission and transient gluten enteropathy in children after a gluten-free diet. *J Pediatr Gastroenterol Nutr*. 1993;16(3):269-272. doi:10.1097/00005176-199304000-00008

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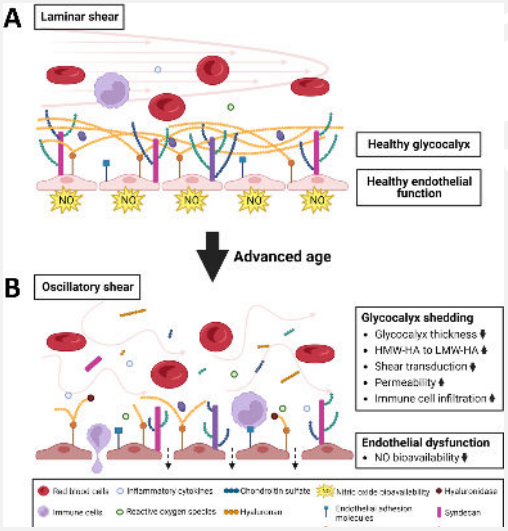
Glycocalyx mucous layer



"The endothelial glycocalyx (EG) is a gel-like structure that forms a layer in between the surface of the endothelium and lumen. EG was once thought to be merely a structural support for the endothelium. However, in recent years, the importance of EG as a first line of defence and a key regulator to endothelial integrity has been illuminated".

Jisok Lim, Daniel Robert Machin, Anthony John Donato,
Chapter Six - The role of hyaluronan in endothelial glycocalyx and potential preventative lifestyle strategy with advancing age, Editor(s): Ibra S. Fancher, Andreia Z. Chignalia,
Current Topics in Membranes, Academic Press, Volume 91, 2023, Pages 139-156, https://doi.org/10.1016/bs.ctm.2023.02.006.

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Non coeliac gluten sensitivity (NCGS)

" NCGS is a disorder of gut-brain interaction.

It remains unclear if gluten is the only wheat component involved in NCGS.

The mechanisms underlying symptom generation in NCGS remain to be fully clarified, although in the past few years, the research has significantly moved forward with new data linking NCGS to changes in gut motility, permeability and innate immunity".

Barbaro MR, Cremon C, Wrona D, et al. Non-Celiac Gluten Sensitivity in the Context of Functional Gastrointestinal Disorders. *Nutrients*. 2020;12(12):3735. Published 2020 Dec 4. doi:10.3390/nu12123735

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Review

Non-Celiac Gluten Sensitivity in the Context of Functional Gastrointestinal Disorders

Maria Raffaella Barbaro [1,2], Cesare Cremon [1,2], Diana Wrona [1,2], Daniele Fuschi [1,2], Giovanni Marasco [1,2], Vincenzo Stanghellini [1,2] and Giovanni Barbara [1,2,*]

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Received: 9 October 2020; Accepted: 1 December 2020; Published: 4 December 2020

Abstract: Gluten-free diets are increasingly chosen in the Western world, even in the absence of a diagnosis of celiac disease. Around 10% of people worldwide self-report gluten-related complaints, including intestinal and extra-intestinal symptoms. In most cases, these subjects would be labeled as patients suffering from irritable bowel syndrome (IBS) who place themselves on a gluten-free diet even in the absence of celiac disease. In some instances, patients report a clear benefit by avoiding gluten from their diet and/or symptom worsening upon gluten reintroduction. This clinical entity has been termed non-celiac gluten sensitivity (NCGS). The symptoms referred by these patients are both intestinal and extra-intestinal, suggesting that similarly to functional gastrointestinal disorders, NCGS is a disorder of gut–brain interaction. It remains unclear if gluten is the only wheat component involved in NCGS. The mechanisms underlying symptom generation in NCGS remain to be fully clarified, although in the past few years, the research has significantly moved forward with new data linking NCGS to changes in gut motility, permeability and innate immunity. The diagnosis is largely based on the self-reported reaction to gluten by the patient, as there are no available biomarkers, and confirmatory double-blind challenge protocols are unfeasible in daily clinical practice. Some studies suggest that a small proportion of patients with IBS have an intolerance to gluten. However, the benefits of gluten-free or low-gluten diets in non-celiac disease-related conditions are limited, and the long-term consequences of this practice may include nutritional and gut microbiota unbalance. Here, we summarize the role of gluten in the clinical features, pathophysiology, and management of NCGS and disorders of gut–brain interaction.

Keywords: functional gastrointestinal disorders; disorders of gut-brain interaction; diet; gluten; IBS; DGBI; NCGS

1. Introduction

Patients suffering from gastrointestinal complaints often report that symptom onset or worsening occurs with food ingestion and ask for dietary advice from their physicians. Accordingly, up to 84% of patients suffering the irritable bowel syndrome (IBS), which is one of the most common functional gastrointestinal disorders, now called disorders of gut–brain interaction (DGBI), report that symptoms were related to at least one food item [1]. Recently, there has been increasing attention to the role of diets in gastrointestinal disorders. New trends include the adoption of gluten-free, low-carbohydrate, low-fermentable oligosaccharide, disaccharide, monosaccharide, and polyols (FODMAPs), and anti-allergy diets. In this review, we will summarize current concepts related to the increasing attention to gluten-free diets in conditions such as gluten sensitivity and DGBI.

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NCGS – challenge of biomarkers

- Historically been controversial because it was a clinical diagnosis and there was a lack of biomarkers.
- But in 2022 a multi-centre study cross sectional was published that has found histological criteria.

Rostami K, Ensari A, Marsh MN, Srivastava A, Villanacci V, Carroccio A, Asadzadeh Aghdaei H, Bai JC, Bassotti G, Becheanu G, et al. Gluten Induces Subtle Histological Changes in Duodenal Mucosa of Patients with Non-Coeliac Gluten Sensitivity: A Multicentre Study. *Nutrients*. 2022; 14(12):2487. https://doi.org/10.3390/nu14122487

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Article

Gluten Induces Subtle Histological Changes in Duodenal Mucosa of Patients with Non-Coeliac Gluten Sensitivity: A Multicentre Study

Kamran Rostami [1,2,*], Arzu Ensari [3], Michael N. Marsh [4], Amitabh Srivastava [5], Vincenzo Villanacci [6], Antonio Carroccio [7], Hamid Asadzadeh Aghdaei [8], Julio C. Bai [9], Gabrio Bassotti [10], Gabriel Becheanu [11], Phoenix Bell [12], Camillo Di Bella [13], Anna Maria Bozzola [6], Moris Cadei [6], Giovanni Casella [14], Carlo Catassi [15], Carolina Ciacci [16], Delia Gabriela Apostol Ciobanu [17], Simon S. Cross [18], Mihai Dancia [17], Prasenjit Das [19], Rachele Del Sordo [20], Michael Drage [21], Luca Elli [22], Alessio Fasano [23], Ada Maria Florena [24], Nicola Fusco [25], James J. Going [26], Stefano Guandalini [27], Catherine E. Hagen [28], David T. S. Hayman [29], Sauid Ishaq [30], Hilary Jericho [31], Melanie Johncilla [32], Matt Johnson [33], Katri Kaukinen [34,35], Adam Levene [32], Sarah Ligtvoet [36], Laura Lu [37], Govind K. Makharia [38], Sherly Mathews [37], Giuseppe Mazzarella [39], Roxana Maxim [17], Khun La Win Myint [29], Hamid Mohaghegh-Shalmani [8], Afshin Moradi [40], Chris J. J. Mulder [41], Ronnie Ray [32], Chiara Rizzi [42], Mohammad Rostami-Nejad [8], Anna Sapone [32], David S. Sanders [18], Juha Taavela [43], Umberto Volta [44], Marjorie Walker [45] and Mohammad Derakhshan [36,46]

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Citation: Rostami, K., Ensari, A., Marsh, M.N., Srivastava, A., Villanacci, V., Carroccio, A., Asadzadeh Aghdaei, H., Bai, J.C., Bassotti, G., Becheanu, G., et al. Gluten Induces Subtle Histological Changes in Duodenal Mucosa of Patients with Non-Coeliac Gluten Sensitivity: A Multicentre Study. *Nutrients* **2022**, *14*, 2487. https://doi.org/10.3390/nu14122487

Academic Editor: Ben Wittenan

Received: 16 May 2022
Accepted: 10 June 2022
Published: 15 June 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Rostami K, Ensari A, Marsh MN, Srivastava A, Villanacci V, Carroccio A, Asadzadeh Aghdaei H, Bai JC, Bassotti G, Becheanu G, et al. Gluten Induces Subtle Histological Changes in Duodenal Mucosa of Patients with Non-Coeliac Gluten Sensitivity: A Multicentre Study. *Nutrients*. 2022; 14(12):2487.https://doi.org/10.3390/nu14122487

Study shows reduced villus height in NCGS

"Our findings indicate that NCGS mucosae are associated with
(i) reduced villus height,
(ii) increased crypt depth,
(iii) increased lymphocyte infiltration of
either villi or crypts and corresponding alterations in villus/crypt ratios even at Marsh 0 stage".

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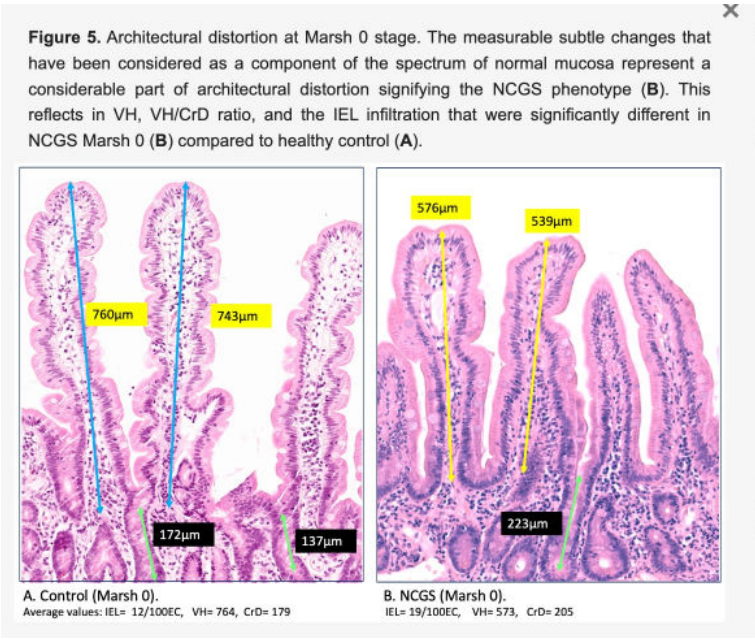
Villi in NCGS



Rostami K, Ensari A, Marsh MN, Srivastava A, Villanacci V, Carroccio A, Asadzadeh Aghdaei H, Bai JC, Bassotti G, Becheanu G, et al. Gluten Induces Subtle Histological Changes in Duodenal Mucosa of Patients with Non-Coeliac Gluten Sensitivity: A Multicentre Study. *Nutrients*. 2022;14(12):2487.https://doi.org/10.3390/nu14122487

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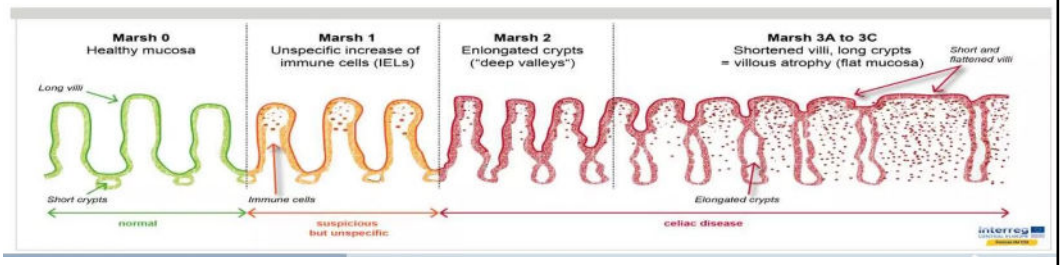
Marsh Criteria

The Classic pathology changes of celiac disease in the small bowel are categorized by 'MARSH CLASSIFICATION"

- Marsh Stage 0: Normal mucosa.
- Marsh stage 1: Intestinal lining has been infiltrates with IELS (Intraepithelial Lymphocytes) seen in patients on a gluten free diet along with Dermatitis Herpetiformis is seen
- Marsh Stage 2: proliferation of the crypts of Lieberkuhn.
- Marsh Stage 3: Patrial or complete villous atrophy.
- Marsh stage 4: Hypoplasia of the small bowel architecture



https://www.slideshare.net/SakshiKanwer/celiac-disease-copy

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Mucosal alterations in NCGS

- "We identified mucosal alterations associated with NCGS and provided evidence that architectural distortion starts at the Marsh 0 stage.
- This suggests that the spectrum of what is considered to be normal mucosa needs to be refined further so it can be reliably distinguished from the minimal and subtle alterations of NCGS and CeD".

Rostami K, Ensari A, Marsh MN, Srivastava A, Villanacci V, Carroccio A, Asadzadeh Aghdaei H, Bai JC, Bassotti G, Becheanu G, et al. Gluten Induces Subtle Histological Changes in Duodenal Mucosa of Patients with Non-Coeliac Gluten Sensitivity: A Multicentre Study. *Nutrients*. 2022; 14(12):2487. https://doi.org/10.3390/nu14122487

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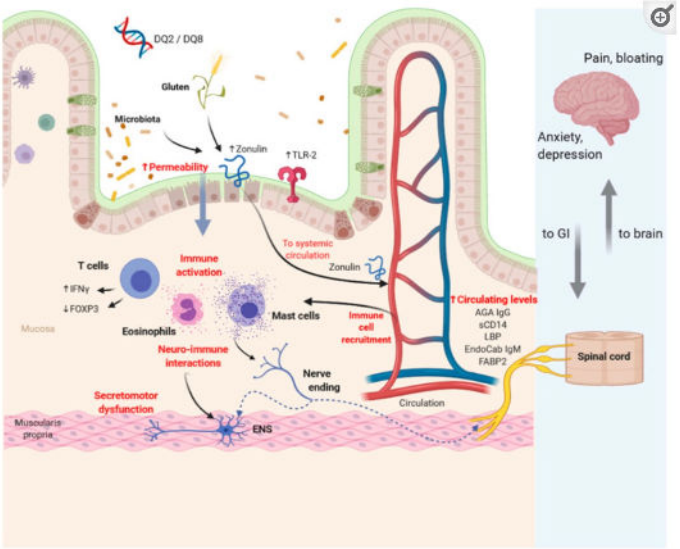
Microbiome in Non Coeliac Gluten Sensitivity

"The physiopathology involves immune activation, permeability alteration, neuro-immune interactions and genetic factors.

Gluten and microbiota can increase epithelial permeability favouring the passage of different antigens into the mucosa and the consequent immune system activation".



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Barbaro MR, Cremon C, Wrona D, et al. Non-Celiac Gluten Sensitivity in the Context of Functional Gastrointestinal Disorders. *Nutrients*. 2020;12(12):3735. Published 2020 Dec 4. doi:10.3390/nu12123735

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2023 review paper

- Use of pre and probiotics of benefit in CD
  - Lactobacillus and Bifidobacterium

Mendez Diaz NM, Pleitez Molina SA, Valient Vasquez KA, Probiotics and prebiotics for patients with celiac disease and non-celiac gluten sensitivity. Alerta 2023; 6(2):165-171

Narrative review article

Probiotics and prebiotics for patients with celiac disease and non-celiac gluten sensitivity

DOI: 10.5377/alerta.v6i2.16208

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Abstract
Celiac disease and non-celiac gluten sensitivity are entities that have shown an increase in incidence, making them a topic of interest to provide innovative therapeutic approaches and improve intestinal and extraintestinal symptoms. This review intends to determine the effects of the use of probiotics and prebiotics in celiac disease and non-celiac gluten sensitivity. A narrative review was undertaken by searching for original and review articles no older than five years since publication through databases consulted: HINARI, PubMed and Scopus in Spanish and English. The use of probiotics and prebiotics in celiac disease has shown benefits by restoring the composition of the intestinal microbiota, especially with the use of *Lactobacilli* and *Bifidobacterium* spp.; in non-celiac gluten sensitivity, its use is limited as its pathophysiology is not exactly known, therefore, a gluten-free diet is currently considered to be the best therapeutic guideline. The use of probiotics and prebiotics could alleviate gastrointestinal symptoms and improve dysbiosis in patients with celiac disease and non-celiac gluten sensitivity. However, more studies are needed to demonstrate the benefits of its use as a therapeutic alternative.

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Few NCGS interventions with Probiotics

- Area for future research

Mendez Diaz NM, Pleitez Molina SA, Valient Vasquez KA, Probiotics and prebiotics for patients with celiac disease and non-celiac gluten sensitivity. Alerta 2023; 6(2):165-171

recommended for patients following a diet low in oligo-dimonosaccharides. Few clinical studies have been performed in patients with NCGS investigating the effect of probiotics and prebiotics to reduce the toxic effects of the external precursors, or to improve symptomatology. Hence, there is a need to investigate the pathophysiology, aiming to find more effective interventions apart from the gluten-free diet[44-46].

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Mechanisms of action

Mechanism of probiotics in celiac disease

Mechanism	Possible probiotics
Enzymatic gluten degradation or pre-ingestion fermentation	VSL#3 long-lasting fermentation by Lactobacilli and fungal proteases
Maintenance of barrier of gastrointestinal tract	Bifidobacterium and Lactobacilli play a fundamental role

Ramedani N, Sharifan A, Gholam-Mostafaei FS, Rostami-Nejad M, Yadegar A, Ehsani-Ardakani MJ. The potentials of probiotics on gluten hydrolysis; a review study. *Gastroenterol Hepatol Bed Bench*. 2020;13(Suppl1):S1-S7.

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2020 paper – probiotics and Gluten Hydrolysis

Bio-tech may be able to use probiotics to remove gluten contamination from foods.

Biotechnological strategy based on probiotic treatment could degrade gluten. Research has shown that combination of the probiotic enzyme is more effective than single probiotic on gluten hydrolysis. The result of different studies showed that probiotic mixture has the capacity to hydrolyze a considerable concentration of the 33-mer of gliadin completely. The present study was aimed to investigate associations between the capacities of probiotics on gluten hydrolysis.

Ramedani N, Sharifan A, Gholam-Mostafaei FS, Rostami-Nejad M, Yadegar A, Ehsani-Ardakani MJ. The potentials of probiotics on gluten hydrolysis; a review study. *Gastroenterol Hepatol Bed Bench*. 2020;13(Suppl1):S1-S7.

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Health benefits of probiotic & fermented foods

- Many publications on fermented foods
- 2019 review outlines benefits

Şanlier N, Gökcen BB, Sezgin AC. Health benefits of fermented foods. *Crit Rev Food Sci Nutr*. 2019;59(3):506-527.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2019, VOL. 59, NO. 3, 506–527
https://doi.org/10.1080/10408398.2017.1383355

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Health benefits of fermented foods

Nevin Şanlier[a], Büşra Başar Gökcen[b], and Aybüke Ceyhun Sezgin[c]

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ABSTRACT

In the past, the beneficial effects of fermented foods on health were unknown, and so people primarily used fermentation to preserve foods, enhance shelf life, and improve flavour. Fermented foods became an important part of the diet in many cultures, and over time fermentation has been associated with many health benefits. Because of this, the fermentation process and the resulting fermented products have recently attracted scientific interest. In addition, microorganisms contributing to the fermentation process have recently been associated with many health benefits, and so these microorganisms have become another focus of attention. Lactic acid bacteria (LAB) have been some of the most studied microorganisms. During fermentation, these bacteria synthesize vitamins and minerals, produce biologically active peptides with enzymes such as proteinase and peptidase, and remove some non-nutrients. Compounds known as biologically active peptides, which are produced by the bacteria responsible for fermentation, are also well known for their health benefits. Among these peptides, conjugated linoleic acids (CLA) have a blood pressure lowering effect, exopolysaccharides exhibit prebiotic properties, bacteriocins show anti-microbial effects, sphingolipids have anti-carcinogenic and anti-microbial properties, and bioactive peptides exhibit anti-oxidant, anti-microbial, opioid antagonist, anti-allergenic, and blood pressure lowering effects. As a result, fermented foods provide many health benefits such as anti-oxidant, anti-microbial, anti-fungal, anti-inflammatory, anti-diabetic and anti-atherosclerotic activity. However, some studies have shown no relationship between fermented foods and health benefits. Therefore, this paper aims to investigate the health effects of fermented foods.

KEYWORDS

Fermented food; bioactive peptides; cardiovascular disease; anti-carcinogenic; lactic acid bacteria

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Sourdough

- The cultures contain yeasts and lactic acid bacteria (LAB) that have proteolytic activity. *Lactobacilli* for example are a source of gluten degrading enzymes known as glutenases, so it can be more suitable for non coeliac gluten sensitivity – but it is not OK for coeliac patients unless it is a gluten free sourdough.
- 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.
- Contain less of the hard to digest carbohydrates (FODMAPs), so maybe beneficial re digestive disorders such as irritable bowel syndrome (IBS).
- There's evidence for a lower post prandial glucose response after consumption.

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- Animal studies show pesticides exert negative effects on gut microbiota.
- Growing body of literature linking these to behavioural issues via gut brain axis.
- This topic needs further research.

ISME

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REVIEW ARTICLE OPEN

Check for updates

Pesticide exposure and the microbiota-gut-brain axis

Rie Matsuzaki[1,2], Eoin Gunnigle[1], Violette Geissen[3], Gerard Clarke[1,4], Jatin Nagpal[1,5] and John F. Cryan[1,2]✉

The gut microbiota exist within a dynamic ecosystem shaped by various factors that includes exposure to xenobiotics such as pesticides. It is widely regarded that the gut microbiota plays an essential role in maintaining host health, including a major influence on the brain and behaviour. Given the widespread use of pesticides in modern agriculture practices, it is important to assess the long-term collateral effects these xenobiotic exposures have on gut microbiota composition and function. Indeed, exposure studies using animal models have shown that pesticides can induce negative impacts on the host gut microbiota, physiology and health. In tandem, there is a growing body of literature showing that the effects of pesticide exposure can be extended to the manifestation of behavioural impairments in the host. With the increasing appreciation of the microbiota-gut-brain axis, in this review we assess whether pesticide-induced changes in gut microbiota composition profiles and functions could be driving these behavioural alterations. Currently, the diversity of pesticide type, exposure dose and variation in experimental designs hinders direct comparisons of studies presented. Although many insights presented, the mechanistic connection between the gut microbiota and behavioural changes remains insufficiently explored. Future experiments should therefore focus on causal mechanisms to examine the gut microbiota as the mediator of the behavioural impairments observed in the host following pesticide exposure.

The ISME Journal; https://doi.org/10.1038/s41396-023-01450-9

Matsuzaki, R., Gunnigle, E., Geissen, V. *et al.* Pesticide exposure and the microbiota-gut-brain axis. *ISME J* (2023).

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To conclude strategies for supporting for gut mucosa/microbiome in CD/NCGS:

- GFD – needs ongoing support, education around contamination etc
- Live fermented foods
- Yoghurt
- Keffir
- Stocks and bone broths made into soups (rich in amino acids, minerals, collagen)*

*considered anti-inflammatory

Mar-Solís LM, Soto-Domínguez A, Rodríguez-Tovar LE, et al. Analysis of the Anti-Inflammatory Capacity of Bone Broth in a Murine Model of Ulcerative Colitis. *Medicina (Kaunas)*. 2021;57(11):1138

- 5+ a day fruits and veg
- Gluten free fiber (soluble, insoluble)
- Rainbow diet

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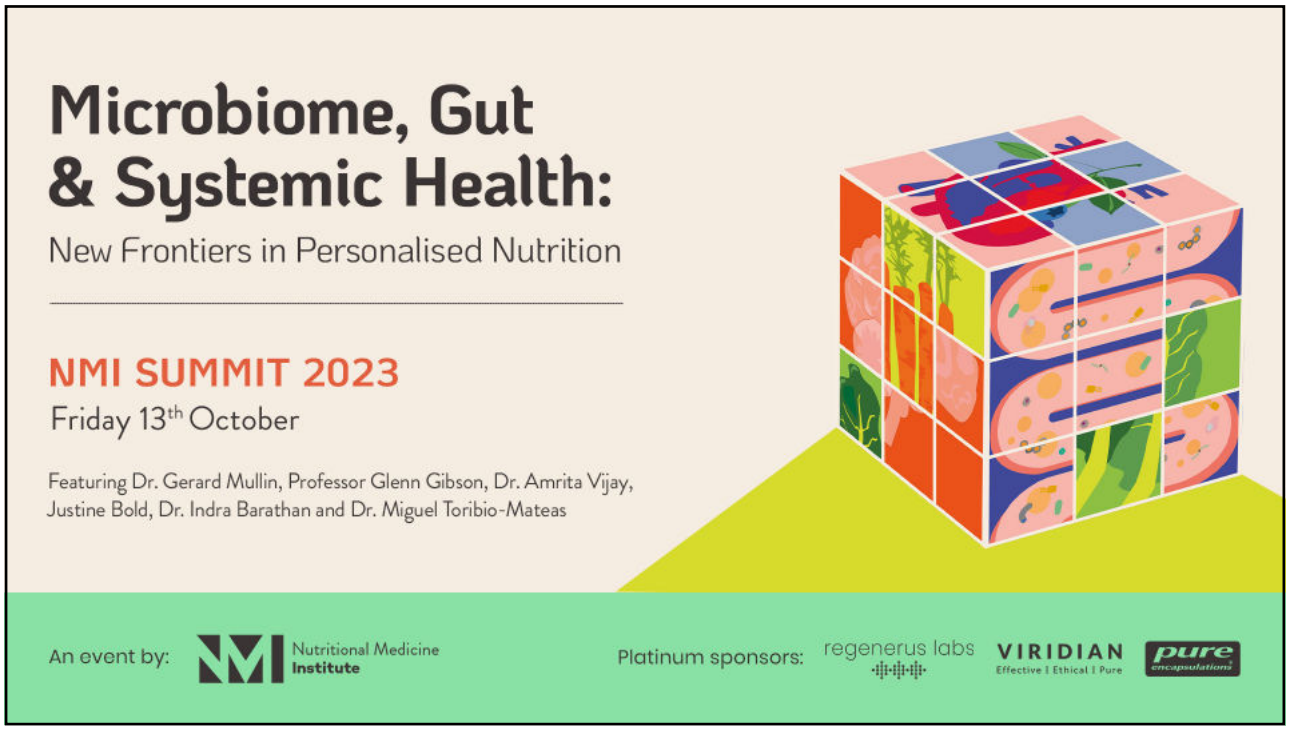
Microbiome, Gut
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