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Leaky Gut: Fact or Fantasy?

Presented by:

Sheila Dean, DSc, RDN, LDN, CCN, CDE, IFMCP

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INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

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INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Learning Objectives

- Describe the relationship between food exposure (i.e. gluten) and intestinal permeability
- Explain the relationship between intestinal permeability and inflammation
- Discuss the relationship between inflammation and the spectrum of chronic disease
- Identify a medical nutrition therapy (MNT) based treatment plan

HEALTH fresh

Has Your Gut Sprung a Leak?

Forget the plumber. Here's what you really need to know about this hot health topic.
By Jessica Migala

Is "leaky gut" real? In a word—yes.

The medical name for leaky gut is "intestinal permeability" and it's neither disease nor symptom—it's a natural biological function. Lining your intestines is a barrier of cells; between each cell is a tight junction that keeps bad things (like toxins and bad bacteria) out of your body and allows good things (nutrients) in.

The issue is that this natural permeability can go awry if the barrier becomes faulty. In genetically susceptible people, leaky gut can be triggered by gut bacteria disruptions from poor diet, some medications or gluten. Importantly, experts don't agree on what is and isn't a trigger.

But once permeability is disrupted, the bad guys "leak" into your bloodstream and trigger inflammation, causing other health issues. So then: when intestinal permeability goes wrong, what problems does it start?

There's strong evidence that leaky gut can cause food allergies, inflammatory bowel disease (IBD) and celiac disease, says Alessio Fasano, M.D., chief of the division of pediatric gastroenterology and nutrition at Massachusetts General Hospital and director of the Center for Celiac Research. There's good evidence leaky gut may lead to type 1 diabetes or multiple sclerosis, and more limited research links it to nonalcoholic fatty liver disease and type 2 diabetes. Other experts like Amy Myers, M.D., author of *The Autoimmune Solution*, believe leaky gut contributes to a wider host of ills, such as seasonal allergies, depression and eczema.

"Leaky gut has become one of those things that people blame all their health issues on," says Purna Kashyap, M.B.B.S., assistant professor of medicine in the department of gastroenterology and hepatology at Mayo Clinic. While research *does* support that certain conditions may be caused by leaky gut, unless you've been diagnosed with one of these, it's hard to say for sure if your gut has sprung a leak.

GUT FEELINGS Find out how your gut influences your well-being at eatingwell.com/webextra

CAN YOU EAT TO BEAT THE LEAK?

Google "leaky gut" and you'll find a host of diets that are said to be a sure-fire cure. But how you fix leaky gut depends on your condition. "Unless you know what you are treating, it's hard to tell someone to go on a dietary regime to improve leaky gut," says Kashyap. These four diets draw a lot of attention for helping leaky gut. Here's how they really stack up.

1 LOW FODMAP
If you have IBD or irritable bowel syndrome (conditions linked to leaky gut), you may have a hard time digesting "FODMAPs": fermentable oligo-, di- and monosaccharides and polyols. Some high-FODMAP foods include beans, apples and mushrooms. Low-FODMAP foods include low-lactose dairy (hard cheeses and Greek yogurt), bananas, gluten-free grains and cucumbers. After some time you can slowly reintroduce high-FODMAP foods to figure out what triggers your symptoms. But if you don't have IBD or IBS, this isn't a generalized cure for leaky gut.

2 PALEO
This "caveman" style of eating favors produce, pasture-raised meats, wild-caught fish, nuts and seeds, and nixes dairy, grains, processed food and refined sugar. Swapping junk food for fresh fare is a good move for anyone, but there's no scientific evidence that a Paleo diet addresses leaky gut.

"Leaky gut" = Intestinal permeability

Image source: Eating Well, July/August 2016 pg 27

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

The Big Picture

Trigger → intestinal permeability - aka “leaky gut”

↓

Leaky gut → Immune/Inflammatory response

↓

Immune/inflammatory response → Chronic disease

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Bischoff *et al. BMC Gastroenterology* 2014, **14**:189
http://www.biomedcentral.com/1471-230X/14/189

BMC Gastroenterology

REVIEW Open Access

Intestinal permeability – a new target for disease prevention and therapy

Stephan C Bischoff[1*], Giovanni Barbara[2], Wim Buurman[3], Theo Ockhuizen[4], Jörg-Dieter Schulzke[5], Matteo Serino[6], Herbert Tilg[7], Alastair Watson[8] and Jerry M Wells[9]

Table 1
Definitions

Intestinal barrier	*is a functional entity separating the gut lumen from the inner host, and consisting of mechanical elements (mucus, epithelial layer), humoral elements (defensins, IgA), immununological elements (lymphocytes, innate immune cells), muscular and neurological elements*
Intestinal permeability	*is defined as a functional feature of the intestinal barrier at given sites, measurable by analyzing flux rates across the intestinal wall as a whole or across wall components of defined molecules that are largely inert during the process and that can be adequately measured in these settings*
Normal intestinal permeability	*is defined as a stable permeability found in healthy individuals with no signs of intoxication, inflammation or impaired intestinal functions*
Impaired intestinal permeability	*is defined as a disturbed permeability being non-transiently changed compared to the normal permeability leading to a loss of intestinal homeostasis, functional impairments and disease*

Source: Bischoff, et al BMC Gastroenterology, 2014 (see previous slide)

Learning Objectives

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- Discuss the relationship between inflammation and the spectrum of chronic disease
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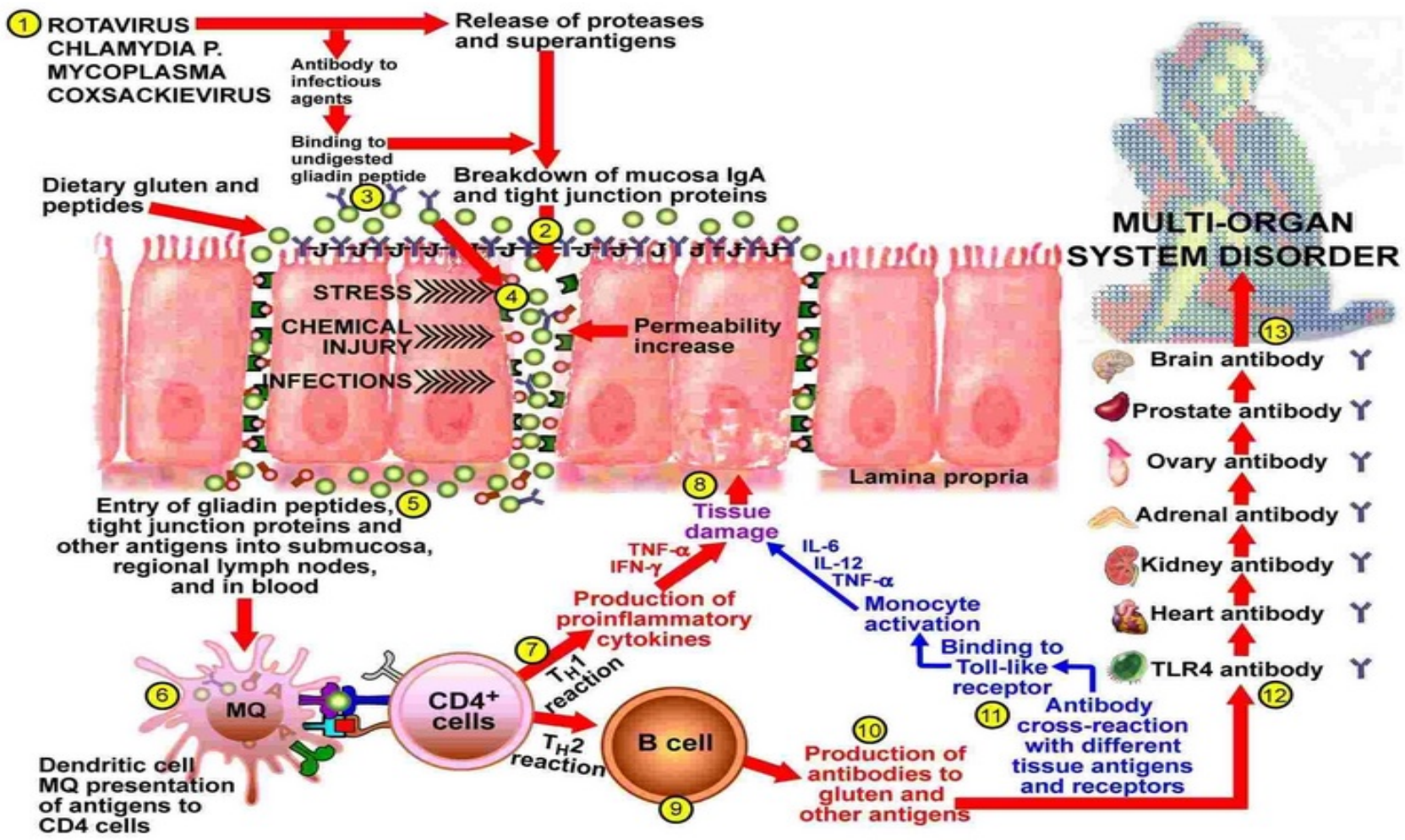


Depiction of immunological mechanisms underlying gluten intolerance and its immunopathological consequences.

Source: http://glutensensitivity.net/VojdaniDiagrams.htm#HG

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Recent advances in clinical practice

ALTERATIONS IN INTESTINAL PERMEABILITY

M C Arrieta, L Bistritz, J B Meddings

Gut 2006;**55**:1512–1520. doi: 10.1136/gut.2005.085373

The goal of this review is to describe barrier function of the intestine, the structure of the tight

We now recognise that the functional state of the tight junction, once considered a static parameter, is in reality incredibly dynamic. Epithelial tight junctions open and close all the time in response to a variety of stimuli. These include *dietary state*, humoral or neuronal signals, inflammatory mediators, mast cell products, and a variety of cellular pathways that can be usurped by *microbial or viral pathogens*.

Clin Rev Allergy Immunol. 2012 Feb;42(1):71-8. doi: 10.1007/s12016-011-8291-x.

Leaky gut and autoimmune diseases.

Fasano A[1].

Author information

Abstract

Autoimmune diseases are characterized by tissue damage and loss of function due to an immune response that is directed against specific organs. This review is focused on the role of impaired intestinal barrier function on autoimmune pathogenesis. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens. Zonulin is the only physiologic modulator of intercellular tight junctions described so far that is i in pathway is deregulated theories underlying the and environmental trigg ent clinical evidence suppo es.

Zonulin is the only physiologic modulator of intercellular tight junctions described so far that is involved in the trafficking of macromolecules and therefore in tolerance/immune response balance. When the zonulin pathway is deregulated in genetically susceptible individuals, autoimmune disorders can occur.

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

"TID" triggers of intestinal permeability

Toxins

Infection

Dietary proteins

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

InterdiscIp Toxicol. 2013; **Vol. 6**(4): 159–184.
doi: 10.2478/intox-2013-0026
Published online in:
www.intertox.sav.sk & www.versita.com/it

VERSITA

interdisciplinary toxicology

REVIEW ARTICLE

Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance

Anthony SAMSEL [1] and Stephanie SENEFF [2]

[1] Independent Scientist and Consultant, Deerfield, NH 03037, USA
[2] Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA, USA

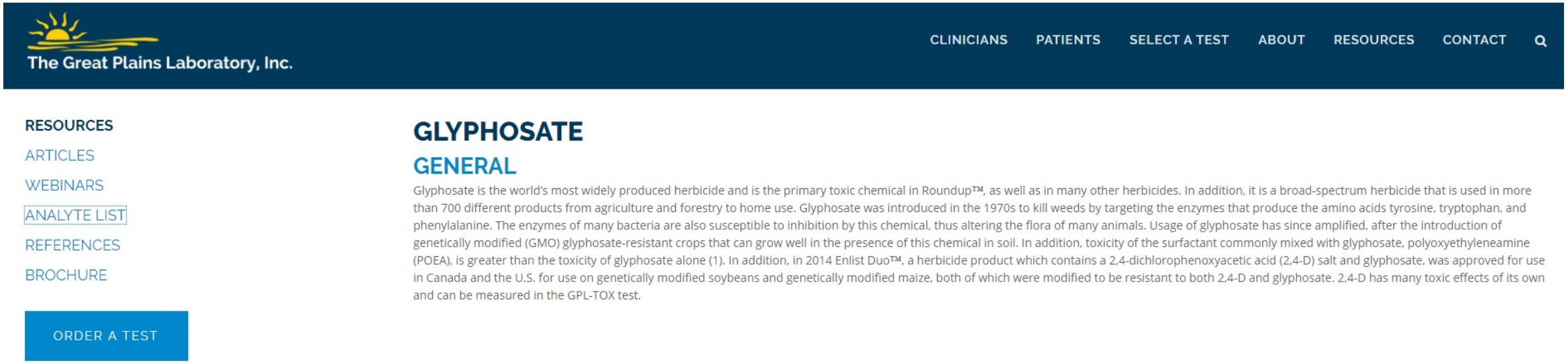
ITX060413R01 • Received: 24 September 2013 • Revised: 10 November 2013 • Accepted: 12 November 2013

ABSTRACT

Celiac disease, and, more generally, gluten intolerance, is a growing problem worldwide, but especially in North America and Europe, where an estimated 5% of the population now suffers from it. Symptoms include nausea, diarrhea, skin rashes, macrocytic anemia and depression. It is a multifactorial disease associated with numerous nutritional deficiencies as well as reproductive issues and increased risk to thyroid disease, kidney failure and cancer. Here, we propose that glyphosate, the active ingredient in the herbicide, Roundup®, is the most important causal factor in this epidemic. Fish exposed to glyphosate develop digestive problems that are reminiscent of celiac disease. Celiac disease is associated with imbalances in gut bacteria that can be fully explained by the known effects of glyphosate on gut bacteria. Characteristics of celiac disease point to impairment in many cytochrome P450 enzymes, which are involved with detoxifying environmental toxins, activating vitamin D3, catabolizing vitamin A, and maintaining bile acid production and sulfate supplies to the gut. Glyphosate is known to inhibit cytochrome P450 enzymes. Deficiencies in iron, cobalt, molybdenum, copper and other rare metals associated with celiac disease can be attributed to glyphosate's strong ability to chelate these elements. Deficiencies in tryptophan, tyrosine, methionine and selenomethionine associated with celiac disease match glyphosate's known depletion of these amino acids. Celiac disease patients have an increased risk to non-Hodgkin's lymphoma, which has also been implicated in glyphosate exposure. Reproductive issues associated with celiac disease, such as infertility, miscarriages, and birth defects, can also be explained by glyphosate. Glyphosate residues in wheat and other crops are likely increasing recently due to the growing practice of crop desiccation just prior to the harvest. We argue that the practice of "ripening" sugar cane with glyphosate may explain the recent surge in kidney failure among agricultural workers in Central America. We conclude with a plea to governments to reconsider policies regarding the safety of glyphosate residues in foods.

KEY WORDS: celiac disease; gluten; glyphosate; food; cytochrome P450; deficiency

Glyphosate Testing now available



INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

“TID” triggers of intestinal permeability

Toxins

Infection

Dietary proteins

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Acta Tropica

Volume 81, Issue 1, January 2002, Pages 1–5

Protozoon infections and intestinal permeability

Hande Dagci[a], Sebnem Ustun[b], Memduh S Taner[c], Galip Ersoz[b], Ferit Karacasu[a], Seza Budak[a]

"This finding supports the view that IP increases during the course of protozoan infections which cause damage to the intestinal wall while non-pathogenic protozoan infections have no effect on IP. The increase in IP in patients with *B. hominis* brings forth the idea that *B. hominis* can be a pathogenic protozoan."

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

The American Journal of Pathology, Vol. 182, No. 2, February 2013

The American Journal of
PATHOLOGY
ajp.amjpathol.org

EPITHELIAL AND MESENCHYMAL CELL BIOLOGY

Lipopolysaccharide Causes an Increase in Intestinal Tight Junction Permeability *in Vitro* and *in Vivo* by Inducing Enterocyte Membrane Expression and Localization of TLR-4 and CD14

Shuhong Guo,*† Rana Al-Sadi,*† Hamid M. Said,‡ and Thomas Y. Ma*†

From the Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico; the Albuquerque Veterans Affairs Medical Center,† Albuquerque, New Mexico; and the Department of Internal Medicine,‡ University of California, Irvine, California*

Accepted for publication October 15, 2012.

Address correspondence to Thomas Y. Ma, M.D., Ph.D., Internal Medicine-Gastroenterology, MSC10 5550, Universi Mexico, Albu 87131-0001. E salud.unm.edu

Bacterial-derived lipopolysaccharides (LPS) play an essential role in the inflammatory process of inflammatory bowel disease. A defective intestinal tight junction (TJ) barrier is an important pathogenic factor of inflammatory bowel disease and other inflammatory conditions of the gut. Despite its importance in mediating intestinal inflammation, the physiological effects of LPS on the intestinal epithelial barrier remain unclear. The major aims of this study were to determine the effects of physiologically relevant concentrations

..these studies show for the first time that LPS causes an increase in intestinal permeability..

associated protein CD14. In conclusion, these studies show for the first time that LPS causes an increase in intestinal permeability via an intracellular mechanism involving TLR-4–dependent up-regulation of CD14 membrane expression. *(Am J Pathol 2013, 182: 375–387; http://dx.doi.org/10.1016/j.ajpath.2012.10.014)*

Physiol Rev 91: 151–175, 2011
doi:10.1152/physrev.00003.2008

Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer

ALESSIO FASANO

Mucosal Biology Research Center and Center for Celiac Research, University of Maryland School of Medicine, Baltimore, Maryland

Fasano A. Zonulin and Its Regulation of In
Autoimmunity, and Cancer. *Physiol Rev* 91: 151

of the gastrointestinal tract have traditionally
nutrients and to electrolytes and water homeo
arrangement of the gastrointestinal tract, howev
is its ability to regulate the trafficking of macro
mechanism. Together with the gut-associated
epithelial barrier, with its intercellular tight junction
non-self antigens. Zonulin is the only physiological modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance. When the finely tuned zonulin pathway is deregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune, inflammatory, and neoplastic disorders can occur. This new paradigm subverts traditional theories underlying the development of these diseases and suggests that these processes can be arrested if the interplay between genes and environmental triggers is prevented by reestablishing the zonulin-dependent intestinal barrier function. This review is timely given the increased interest in the role of a "leaky gut" in the pathogenesis of several pathological conditions targeting both the intestine and extraintestinal organs.

When the finely tuned zonulin pathway is deregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune, inflammatory, and neoplastic disorders can occur.

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i45.17107

World J Gastroenterol 2014 December 7; 20(45): 17107-17114
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

CASE CONTROL STUDY

Increased circulating zonulin in children with biopsy-proven nonalcoholic fatty liver disease

Lucia Pacifico, Enea Bonci, Lidia Marandola, Sara Romaggioli, Stefano Bascetta, Claudio Chiesa

Lucia Pacifico, Sara Romaggioli, Stefano Bascetta, Department of Pediatrics and Child Neuropsychiatry, Sapienza University of Rome, 00161 Rome, Italy
Enea Bonci, Lidia Marandola, Department of Experimental

including zonulin, inflammatory and metabolic parameters, and MRI for measurement of HFF and visceral adipose tissue.

ONAL

Table 1 Characteristics of obese children by liver status

	No NAFLD (n = 40)	NAFLD (n = 40)	P value
Age, yr[1]	11.10 (3.1)	11.10 (3.1)	
Male gender[1]	25 (62.5)	25 (62.5)	
BMI-SD score	2.10 (0.32)	2.15 (0.50)	0.5600
Waist circumference, cm	92 (12)	97 (12)[a]	0.0270
Abdominal fat			
Visceral adipose tissue, cm^2	284 (217-502)	447 (337-676)	0.0040
Subcutaneous adipose tissue, cm^2	1648 (1301-2503)	1828 (1629-2471)	0.2200
Hepatic fat fraction	1.5% (1.0%-3.0%)	16.0% (10.0%-30.0%)	< 0.0001
Triglycerides, mg/dL	81 (52-114)	96 (68-149)	0.0490
Total cholesterol, mg/dL	154 (142-185)	149 (130-179)	0.1100
HDL-C, mg/dL	49 (43-54)	45 (37-53)	0.3100
Aspartate aminotransferase, U/L	25 (11)	34 (26)	0.0370
Alanine aminotransferase, U/L	26 (17)	50 (43)	< 0.0001
γ-glutamyl transferase, U/L	15 (8)	23 (12)	< 0.0001
Fasting glucose, mg/dL	85 (6)	83 (8)	0.3300
2-h glucose, mg/dL	94 (13)	93 (14)	0.8700
Fasting insulin, μU/mL	11 (8-15)	20 (15-28)	0.0010
2-h insulin, μU/mL	35 (23-63)	67 (29-107)	0.0070
Fasting C peptide, pmol/L	780 (576-887)	1075 (816-1302)	< 0.0001
HOMA-IR values	2.24 (1.80-3.17)	4.11 (2.95-6.67)	0.0030
WBISI	5.84 (3.16-6.87)	2.57 (1.58-5.36)	0.0020
HbA_{1c}	5.0% (0.32)	5.4% (0.47)	0.0170
HSCRP, μg/L	1800 (1000-3200)	3000 (1500-4325)	0.0490
Zonulin, ng/mL	3.31 (2.05-4.63)	4.23 (3.18-5.89)	0.0090

[1]Matched variables. Results are expressed as n (%), mean ± SD, or median (IQR). BMI-SDS: Body mass index-standard deviation score; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; WBISI: Whole-body insulin sensitivity index; HbA_{1c}: Haemoglobin A_{1c}; HSCRP: High-sensitive C reactive protein; NAFLD: Nonalcoholic fatty liver disease.

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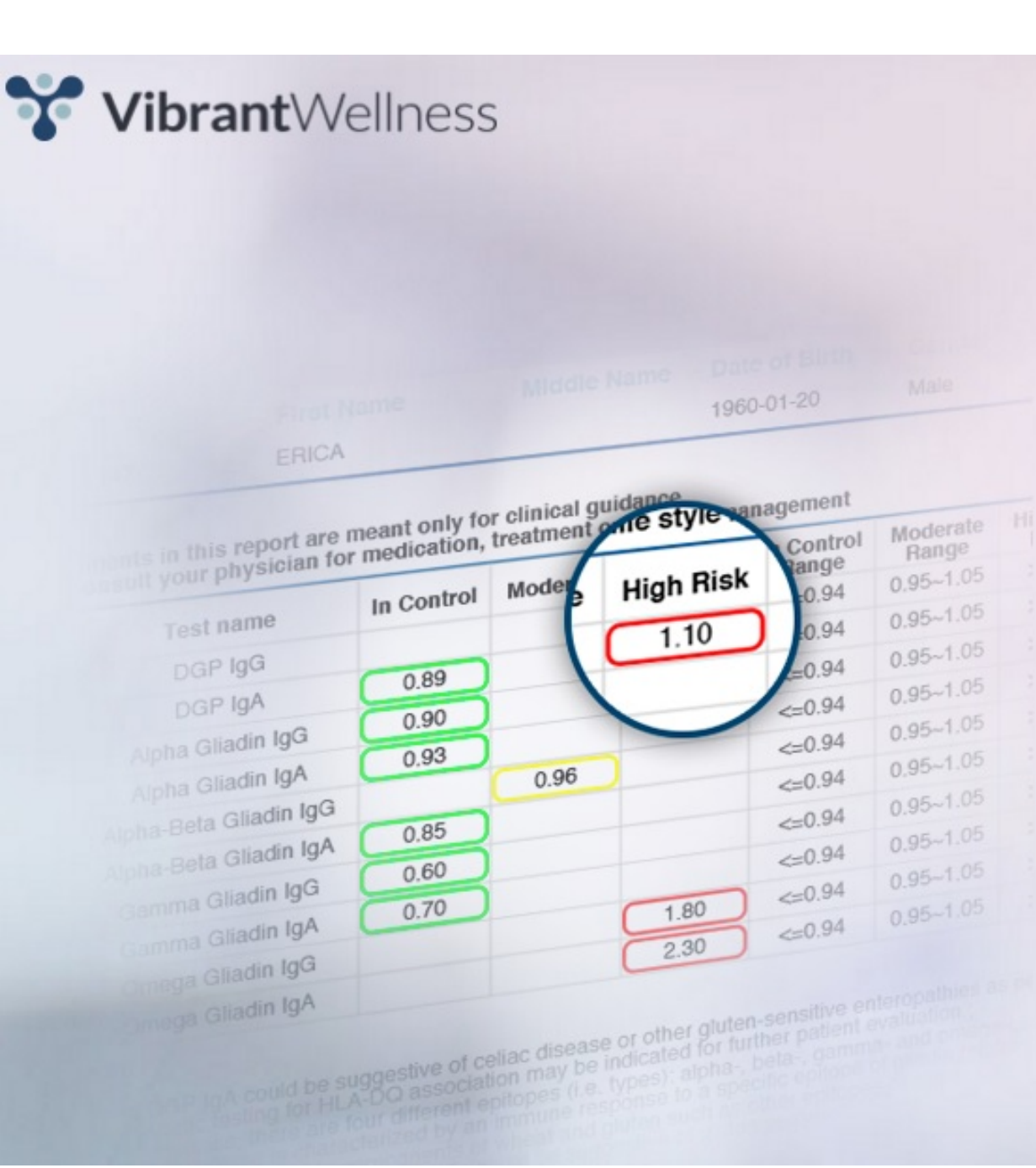

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Final Report Date:	05-06-2016 15:08	**Specimen Collected:**	11-30-2015
Accession ID:	1512010000	**Specimen Received:**	12-01-2015 00:00

Last Name	First Name	Middle Name	Date of Birth	Gender	Physician ID
TESTNAME	PATIENT	VIBRANT	1994-10-10	Female	999994

Celiac HLA Genetics

HLA Type Tested	Results	Comments
DQ2.2	NEGATIVE	Patient is at risk for developing celiac disease
DQ2.5	NEGATIVE	
DQ7	POSITIVE	
DQ8	POSITIVE	

Leaky Gut Panel

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
Zonulin (ng/mL)	<10.0			<=45.3	45.4~55.3	>=55.4	<10.0 08/20/2015
Anti-Zonulin IgG	0.60			<=0.94	0.95~1.05	>=1.06	0.77 08/20/2015
Anti-Zonulin IgA	0.05			<=0.94	0.95~1.05	>=1.06	0.20 08/20/2015
Anti-Actin IgG	0.31			<=0.94	0.95~1.05	>=1.06	0.67 08/20/2015
Anti-Actin IgA	0.73			<=0.94	0.95~1.05	>=1.06	0.09 08/20/2015
LPS IgG (U/ml)	<6.3			<=60.0	60.1~80.0	>=80.1	<6.3 08/20/2015
LPS IgM (U/ml)	<6.3			<=38.3		>=38.4	<6.3 08/20/2015

PATIENT NAME:	Sampley Fakerfield
REQUISITION ID:	R2005
DOB:	6/11/1974
SAMPLE DATE:	3/3/2016
RECEIVE DATE:	3/4/2016
REPORT DATE:	3/8/2016

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ADVANCED INTESTINAL BARRIER ASSESSMENT: PROFILE 5150 (PLASMA)

DAO (Diamine Oxidase)

PATIENT RESULT
46.0 ng/ml
REPORTABLE RANGE: 10.0–40.0 ng/ml

ABOVE REPORTABLE RANGE

Zonulin

PATIENT RESULT
0.92 ng/ml
REPORTABLE RANGE: <20 ng/ml

OPTIMAL

Histamine

PATIENT RESULT
1.62 ng/ml
REPORTABLE RANGE: 0.1–3.1 ng/ml

BORDERLINE

DAO: Histamine Ratio

28

A high DAO-to-Histamine ratio suggests that there is sufficient DAO present to degrade any free histamine. A low ratio, on the other hand, may be indicative of histamine intolerance. The lower the ratio, and particularly the closer it gets to 1, the stronger that indication.

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Metabolomic Profiles and Zonulin testing!

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Zonulin Test Summary

Description/Background Information

Zonulin - the "Gatekeeper" of Intestinal Permeability

Sample Type/Collection/Stability/ Shipping

It is recommended that patients refrain from taking probiotics for 14 days and antibiotics for 28 days prior to sample collection or as directed by the healthcare provider.

Stool samples should be refrigerated immediately after collection and shipped with cold icepacks to Salveo Diagnostics. Zonulin is stable for up to 4 days at room temperature.

Treatment Considerations

"TID" triggers of intestinal permeability

Toxins

Infection

Dietary proteins

Just the basics: What is gluten?

- Gluten is a mixture of proteins found in wheat and related grains, including all their species and hybrids. It is composed of two primary subfractions:
  - Prolamines
  - Glutelins

The Prolamine Fraction of Proteins in Grains

GRAIN	PROLAMINE	% TOTAL PROTEIN
Wheat	Gliadin	69
Rye	Secalinin	30-50
Oats	Avenin	16
Barley	Hordein	46-52
Millet	Panicin	40
Corn	Zien	55
Rice	Orzenin	5
Sorgum	Kafirin	52

Source: http://www.nutramed.com/celiac/gluten.htm

Spectrum of Gluten Related Disorders

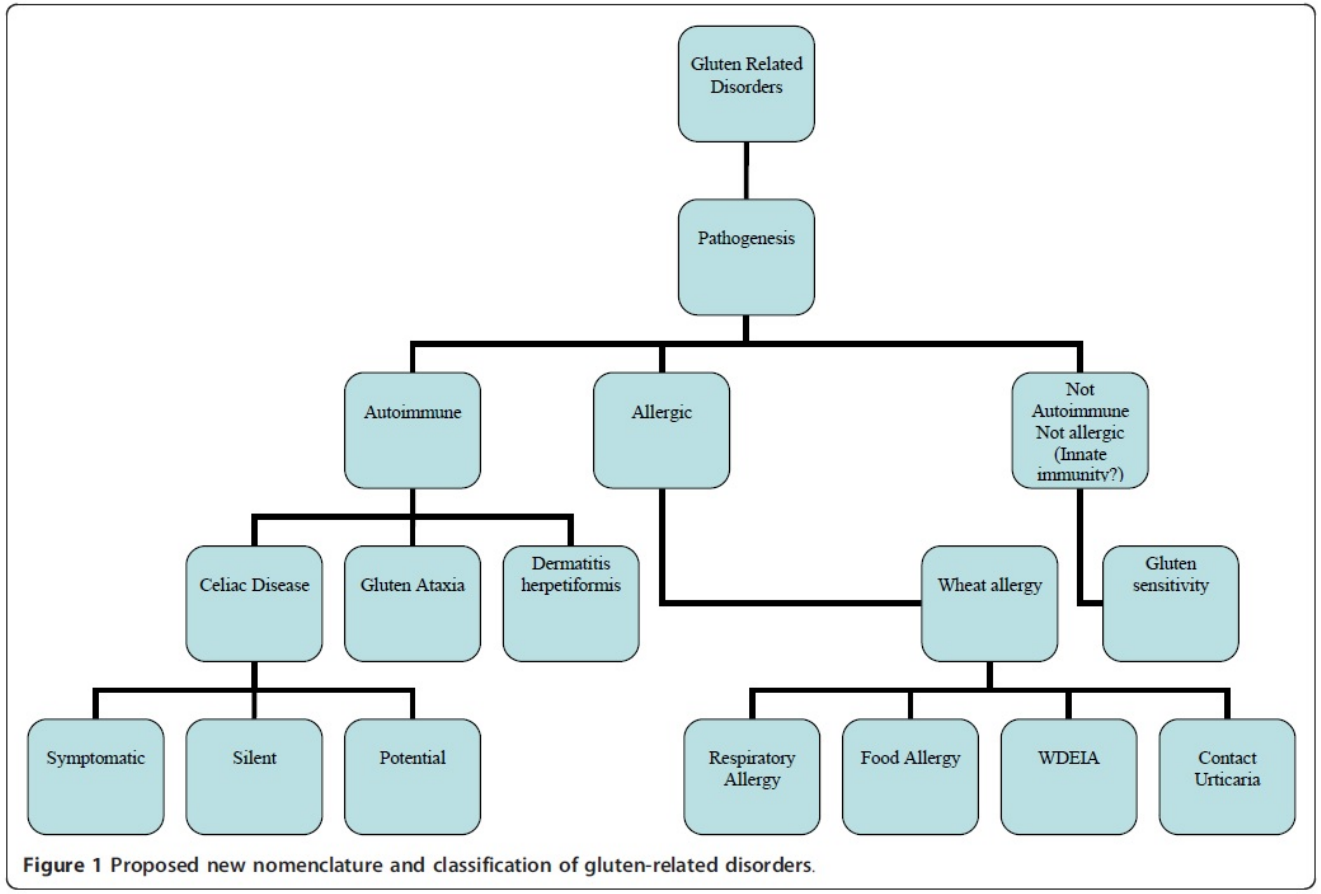

Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

Sapone A. et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Medicine*. 2012, 10:13.

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Scand J Gastroenterol. 2006 Apr;41(4):408-19.

Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines.

Drago S[1], El Asmar R, Di Pierro M, Grazia Clemente M, Tripathi A, Sapone A, Thakar M, Iacono G, Carroccio A, D'Agate C, Not T, Zampini L, Catassi C, Fasano A.

⊕ Author information

Abstract

OBJECTIVE: Little is known about the interaction of gliadin with intestinal epithelial cells and the mechanism(s) through which gliadin crosses the intestinal epithelial barrier. We investigated whether gliadin has any immediate effect on zonulin release and signaling.

MATERIAL AND METHODS: Both ex vivo human small intestines and intestinal cell monolayers were exposed to gliadin, and zonulin release and changes in paracellular permeability were monitored in the presence and absence of zonulin antagonism. Zonulin binding, cytoskeletal rearrangement, and zonula occludens-1 (ZO-1) redistribution were evaluated by immunofluorescence microscopy. Tight junction occludin and ZO-1 gene expression was evaluated by real-time polymerase chain reaction (PCR).

RESULTS: When exposed to gliadin, zonulin receptor-positive IEC6 and Caco2 cells released zonulin in the cell medium with subsequent zonulin binding to the cell surface, rearrangement of the cell cytoskeleton, loss of occludin-ZO1 protein-protein interaction, and increased monolayer permeability. Pretreatment with the zonulin antagonist FZI/0 blocked these changes without affecting zonulin release. When exposed to luminal gliadin, intestinal biopsies from celiac patients in remission expressed a sustained luminal zonulin release and increase in intestinal permeability that was blocked by FZI/0 pretreatment. Conversely, biopsies from non-celiac patients demonstrated a limited, transient zonulin release which was paralleled by an increase in intestinal permeability that never reached the level of permeability seen in celiac disease (CD) tissues. Chronic gliadin exposure caused down-regulation of both ZO-1 and occludin gene expression.

CONCLUSIONS: Based on our results, we concluded that gliadin activates zonulin signaling irrespective of the genetic expression of autoimmunity, leading to increased intestinal permeability to macromolecules.

PMID: 16635906 [PubMed - indexed for MEDLINE]

FUNCTIONAL ACADEMY

How many know or suspect a sensitivity to gluten?

A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care

Imran Aziz[a], Nina R. Lewis[a], Marios Hadji
Nathan Rugg[a], Alan Kelsall[a], Laurence N

Eur J of Gastro & Hepatology 2014, Vol 26 No 1

Background Reports suggest that gluten sensitivity (GS) exists in the absence of coeliac disease (CD). This clinical entity has been termed noncoeliac gluten sensitivity (NCGS).

Objectives To determine the population prevalence of self-reported GS and referral characteristics to secondary care.

Patients and methods A UK population-based

were found to have CD and 93% to have NCGS. All CD patients were human leucocyte antigen DQ2 or DQ8 positive compared with 53% of NCGS cases ($P=0.0003$). Nutritional deficiencies ($P \leq 0.003$), autoimmune disorders (23.1 vs. 9.7%, $P=0.0001$) and a lower mean BMI (23.7 vs. 25.8, $P=0.001$) were significantly associated with CD compared with NCGS.

Conclusion GS is commonly self-reported with symptoms

There is an emerging problem encountered in clinical practice of patients complaining of gluten-related symptoms despite the absence of diagnostic markers for CD, such as negative coeliac serology and normal duodenal biopsies.

Introduction

Coeliac disease (CD) is a chronic inflammatory disorder of the small bowel, which affects 1% of the population [1,2]. The condition can be defined as a state of heightened immunological responsiveness to ingested gluten (from wheat, barley or rye) in genetically susceptible individuals [2,3]. The diagnosis of CD is based on the demonstration of histological abnormalities on duodenal biopsies in accordance with the modified Marsh classification [4,5]. Corroborative evidence used to support the diagnosis comes from positive coeliac serology in the form of endomysial antibody (EMA) and tissue transglutaminase antibody (TTG) [3,6]. The cornerstone of treatment for CD is lifelong adherence to a strict gluten-free diet (GFD), which in the majority leads to an improved clinical outcome, psychological well-being and quality of life [3,7].

However, the consumption of a GFD seems greatly out of proportion to the projected number of patients with CD. Marketers have estimated that 15–25% of North American consumers want gluten-free foods [8,9], although recently published data would suggest this to be an overestimation [10,11]. A National Health and Nutrition Examination Survey in the USA, involving 7798 people aged 6 years or older, suggests that 0.63% of the American public consume a GFD, although the majority of these do not have CD [10]. The prevalence of serologically diagnosed CD in this study was found to be 0.71%, yet up to 80% were previously unaware of the diagnosis of CD and not taking a GFD. Elsewhere, work from New Zealand has found that CD affects 1% of children, yet 5% report gluten avoidance [11]. Consistent with these findings is the emerging problem encountered in clinical practice of patients complaining of gluten-related symptoms despite the absence of diagnostic markers for CD, such as negative coeliac serology and normal duodenal biopsies. These patients pose a clinical dilemma to healthcare professionals and in the past have

DOI: 10.1097/01.meg.0000435546.87251.f7

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care

Imran Aziz[a], Nina R. Lewis[a], Marios H
Nathan Rugg[a], Alan Kelsall[a], Laurence Newrick[a] and David S. Sanders[a]

Eur J of Gastro & Hepatology 2014, Vol 26 No 1

Background Reports suggest that gluten sensitivity (GS) exists in the absence of coeliac disease (CD). This clinical entity has been termed noncoeliac gluten sensitivity (NCGS).

Objectives To determine the population prevalence of self-reported GS and referral characteristics to secondary care.

Patients and methods A UK population-based questionnaire screened for GS and related symptoms. Diagnostic outcomes were also analyzed in patients

with those without GS (20 vs. 3.89%, odds ratio 6.23, $P<0.0001$). In secondary care 200 GS patients (female 84%, mean age 39.6 years) were investigated, in whom 7% were found to have CD and 93% to have NCGS. All CD patients were human leucocyte antigen DQ2 or DQ8 positive compared with 53% of NCGS cases ($P=0.0003$). Nutritional deficiencies ($P \leq 0.003$), autoimmune disorders (23.1 vs. 9.7%, $P=0.0001$) and a lower mean BMI (23.7 vs. 25.8, $P=0.001$) were significantly associated with CD compared with NCGS.

Conclusion GS is commonly self-reported with symptoms suggesting an association with irritable bowel syndrome. The majority of patients have NCGS, an entity which

Received 26 July 2013 Accepted 3 September 2013

These patients pose a clinical dilemma to healthcare professionals and in the past have been described as belonging to a 'no man's land' due to the diagnostic uncertainty.

Introduction

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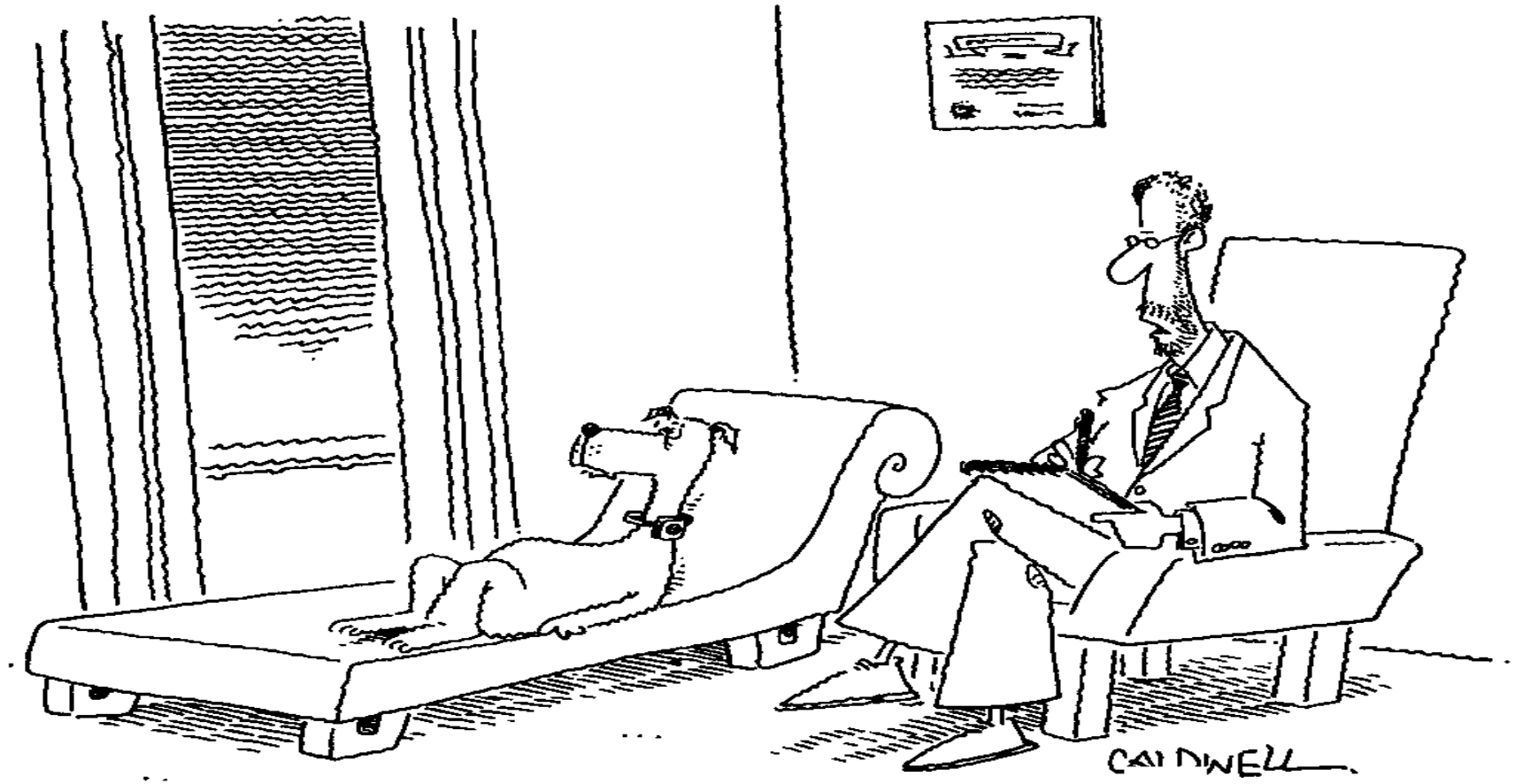
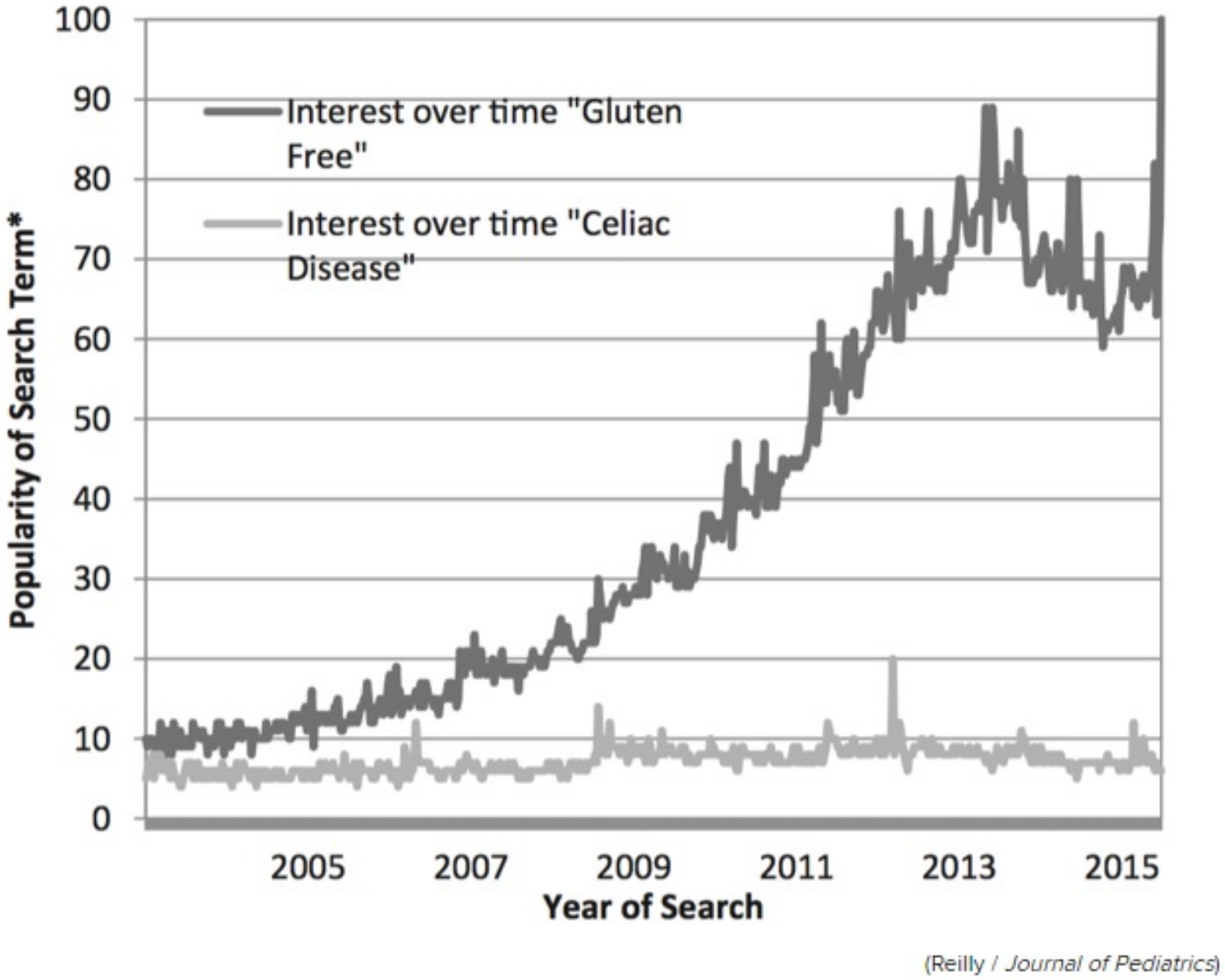
DOI: 10.1097/01.meg.0000435546.87251.f7



"Please...tell me more about this imaginary fence."

Ok, so should I go gluten free?

Google Search Term Popularity: "Celiac Disease" Versus "Gluten Free"



(Reilly / *Journal of Pediatrics*)

Source: Reilly N. The Gluten Free Diet: Recognizing Fact, Fiction and Fad. *Journal of Pediatrics.* 2016.
DOI: http://dx.doi.org/10.1016/j.jpeds.2016.04.014

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

British Journal of Nutrition (2010), 104, 773

British Journal of Nutrition (2010), **104**, 773

Letter to the Editor

Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects – comment by Jackson

Frank W. Jackson
Jackson GI Medical
1460 Raven Hill Road

A paper in the *British Journal of Nutrition* by De Palma *et al.*[1] noted that healthy adult human subjects fed a gluten-free diet (GFD) developed significant changes in their

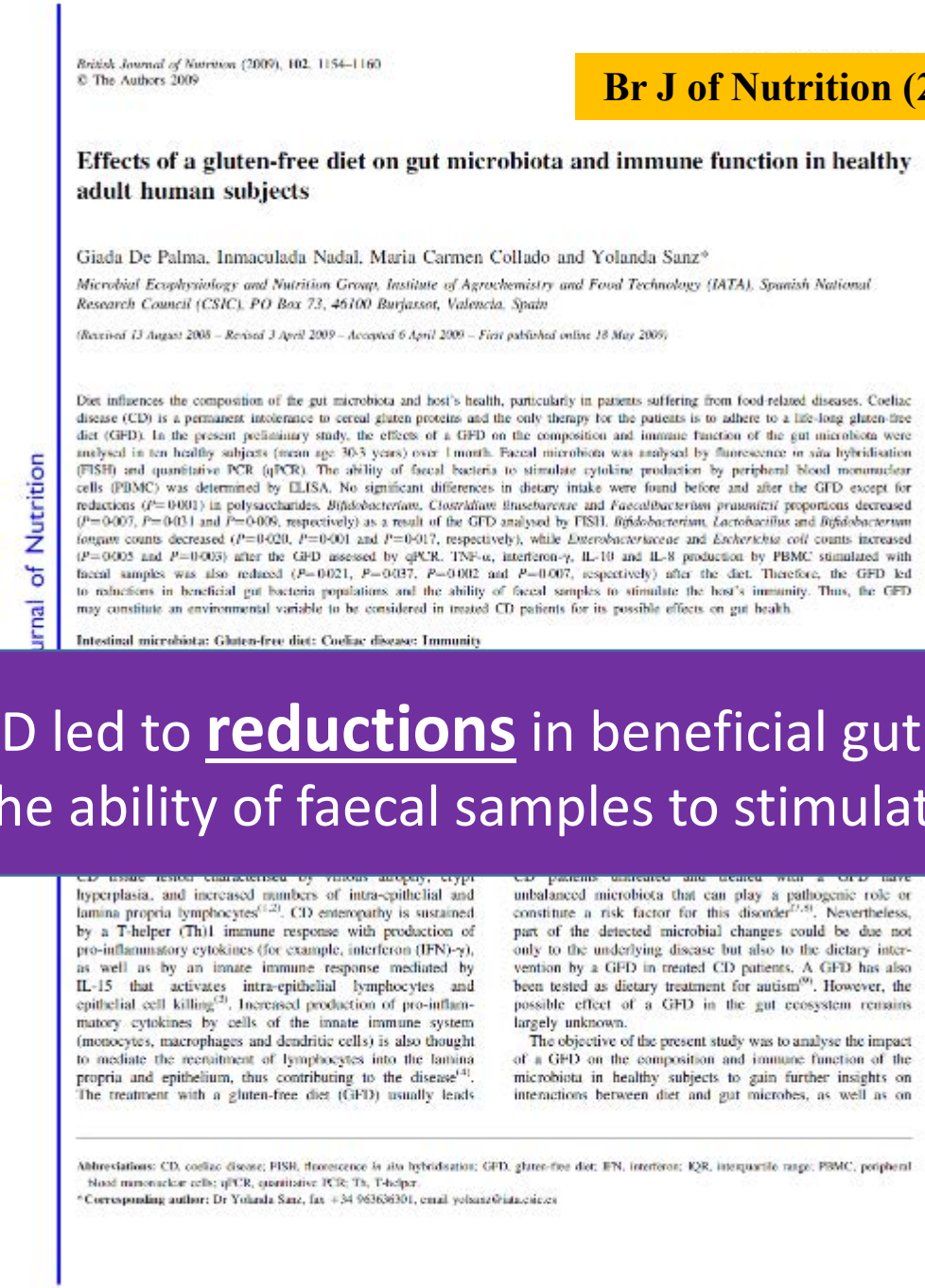
It appears that a GFD in both coeliac and non-coeliac subjects could produce similar, potentially adverse changes in the microbiota solely on the basis of a marked **reduction in intake** of naturally occurring fructans which have prebiotic action.

that a GFD in both coeliac and non-coeliac subjects could produce similar, potentially adverse, changes in the microbiota solely on the basis of a marked reduction in intake of naturally occurring fructans which have prebiotic action. Provision of gluten-free but prebiotic-rich foods and/or a supplement of fructan-type prebiotics could avoid this situation and, in so doing, provide important support to the intestinal microbiota as well as important nutritional guidance for the coeliac patient.

F. W. J. is the president of Jackson GI Medical which markets a prebiotic supplement.

healthy adult human subjects. *Br J Nutr* **102**, 1154–1160.
2. Collado M, Calabuig M & Sanz Y (2007) Differences between the faecal microbiota of coeliac infants and healthy controls. *Curr Issues Intest Microbiol* **8**, 9–14.
3. Gibson GR (2008) Prebiotics as gut microflora management tools. *J Clin Gastroenterol* **42**, Suppl. 2, S75–S79.
4. Van Loos J, Coussement P, De Leenheer L, *et al.* (1995) On the presence of inulin and oligofructose as natural ingredients in the Western diet. *Crit Rev Food Sci Nutr* **35**, 525–552.
5. Moshfegh AJ, Friday JE, Goldman JP, *et al.* (1999) Presence of inulin and oligofructose in the diets of Americans. *J Nutr* **129**, 1407S–1411S.

NS British Journal



British Journal of Nutrition (2009), 102, 1154–1160
© The Authors 2009

Br J of Nutrition (2009), 102, 1154–1160

Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects

Giada De Palma, Inmaculada Nadal, Maria Carmen Collado and Yolanda Sanz*

Microbial Ecophysiology and Nutrition Group, Institute of Agrochemistry and Food Technology (IATA), Spanish National Research Council (CSIC), PO Box 73, 46100 Burjassot, Valencia, Spain

(Received 13 August 2008 – Revised 3 April 2009 – Accepted 6 April 2009 – First published online 18 May 2009)

Diet influences the composition of the gut microbiota and host's health, particularly in patients suffering from food-related diseases. Coeliac disease (CD) is a permanent intolerance to cereal gluten proteins and the only therapy for the patients is to adhere to a life-long gluten-free diet (GFD). In the present preliminary study, the effects of a GFD on the composition and immune function of the gut microbiota were analysed in ten healthy subjects (mean age 30·5 years) over 1 month. Faecal microbiota was analysed by fluorescence in situ hybridisation (FISH) and quantitative PCR (qPCR). The ability of faecal bacteria to stimulate cytokine production by peripheral blood mononuclear cells (PBMC) was determined by ELISA. No significant differences in dietary intake were found before and after the GFD except for reductions ($P=0·001$) in polysaccharides. *Bifidobacterium*, *Clostridium litusebarense* and *Faecalibacterium prausnitzii* proportions decreased ($P=0·007$, $P=0·031$ and $P=0·008$, respectively) as a result of the GFD analysed by FISH. *Bifidobacterium*, *Lactobacillus* and *Bifidobacterium longum* counts decreased ($P=0·020$, $P=0·001$ and $P=0·017$, respectively), while *Enterobacteriaceae* and *Escherichia coli* counts increased ($P=0·005$ and $P=0·003$) after the GFD assessed by qPCR. TNF-α, interferon-γ, IL-10 and IL-8 production by PBMC stimulated with faecal samples was also reduced ($P=0·021$, $P=0·037$, $P=0·002$ and $P=0·007$, respectively) after the diet. Therefore, the GFD led to reductions in beneficial gut bacteria populations and the ability of faecal samples to stimulate the host's immunity. Thus, the GFD may constitute an environmental variable to be considered in treated CD patients for its possible effects on gut health.

Intestinal microbiota: Gluten-free diet: Coeliac disease: Immunity

Therefore, the GFD led to **reductions** in beneficial gut bacteria populations and reductions in the ability of faecal samples to stimulate the host's immunity.

Abbreviations: CD, coeliac disease; FISH, fluorescence in situ hybridisation; GFD, gluten-free diet; IFN, interferon; IQR, interquartile range; PBMC, peripheral blood mononuclear cells; qPCR, quantitative PCR; Th, T-helper.

***Corresponding author:** Dr Yolanda Sanz, fax +34 963636301, email yolsanz@iata.csic.es

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

British Journal of Nutrition (2010), 104, 773

British Journal of Nutrition (2010), **104**, 773

Letter to the Editor

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Frank W. Jackson
Jackson GI Medical
1460 Raven Hill Road
Mechanicsburg
PA 17055
USA

A paper in the *British Journal of Nutrition* by De Palma *et al.*[1] noted that healthy adult human subjects fed a gluten-free diet (GFD) developed significant changes in their gut microbiota. Similar results were observed by Collado *et al.*[2] in coeliac-affected infants on a GFD compared with healthy controls. Naturally occurring fructan-type resist-

Provision of gluten-free but prebiotic-rich foods and/or a supplement of fructan-type prebiotics could avoid this situation and, in so doing, provide important support to the intestinal microbiota as well as important nutritional guidance for the coeliac patient.

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Br J Nutr. 2010 Aug;104 Suppl 2:S1-63. doi: 10.1017/S0007114510003363.

Prebiotic effects: metabolic and health benefits.

Roberfroid M[1], Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A.

Author information

A large number of human intervention studies have been performed that have demonstrated that dietary consumption of certain food products can result in statistically significant changes in the composition of the gut microbiota in line with the prebiotic concept. Thus the prebiotic effect is now a well-established scientific fact.

As a result of the research activity that followed the publication of the prebiotic concept 15 years ago, it has become clear that products that cause a selective modification in the gut microbiota's composition and/or activity(ies) and thus strengthens normobiosis could either induce beneficial physiological effects in the colon and also in extra-intestinal compartments or contribute towards reducing the risk of dysbiosis and associated intestinal and systemic pathologies.

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Abstract

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Dig Dis Sci. 2016 Jan 2. [Epub ahead of print]

Gut Microbiota and Celiac Disease.

Marasco G[1], Di Biase AR[2], Schiumerini R[3], Eusebi LH[4], Iughetti L[5], Ravaioli F[6], Scaioli E[7], Colecchia A[8], Festi D[9].

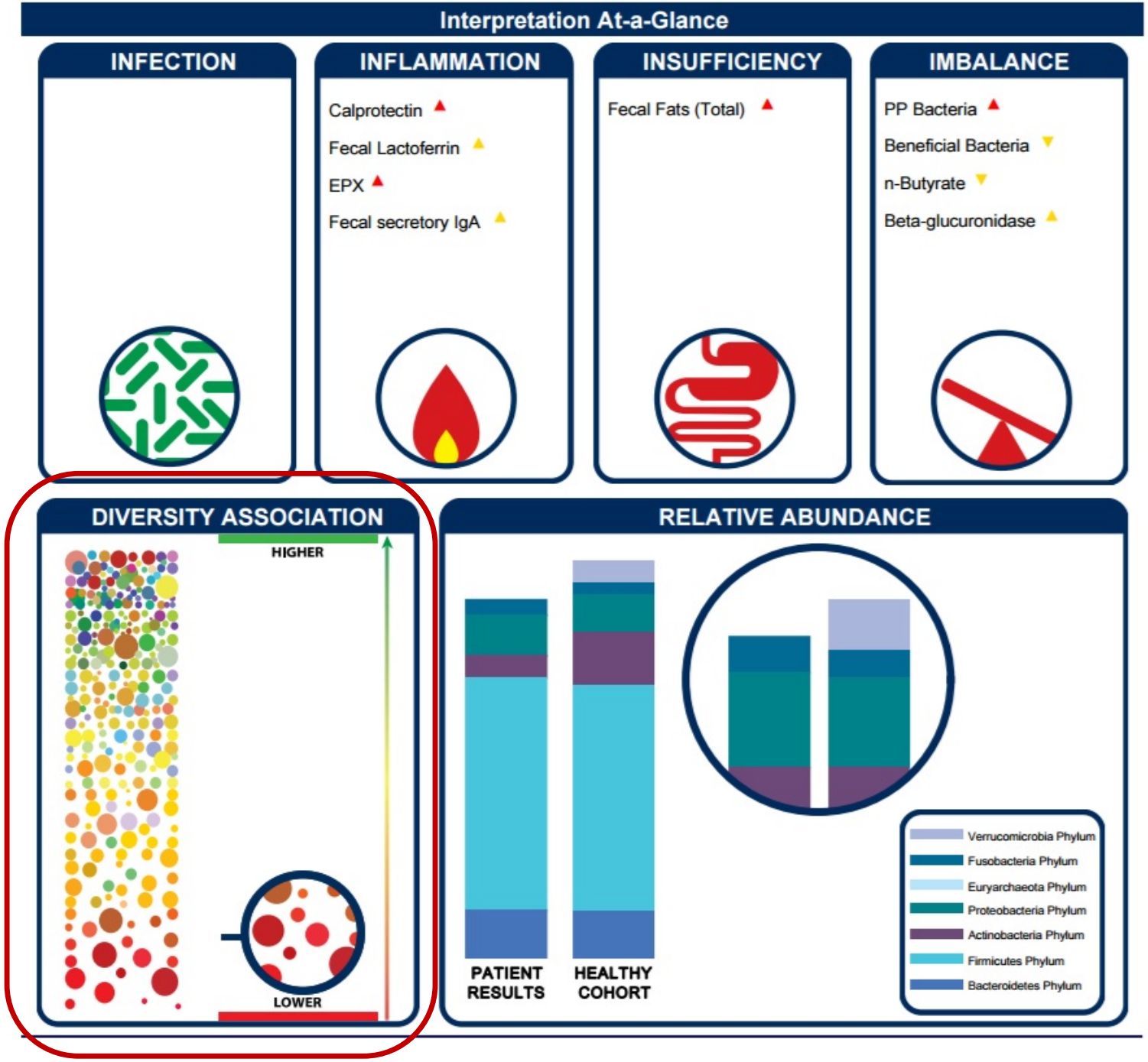
Author information

Abstract

Recent evidence regarding celiac disease has increasingly shown the role of innate immunity in triggering the immune response by stimulating the adaptive immune response and by mucosal damage. The interaction between the gut microbiota and the mucosal wall is mediated by the same receptors paper is a review e have a reducti ed, but might sti ibed by studies w nse and restore a normal proportion of beneficial bacteria in the gastrointestinal tract. Additional evidence is needed in order to better understand the role of gut microbiota in the pathogenesis of celiac disease, and the clinical impact and therapeutic use of probiotics in this setting.

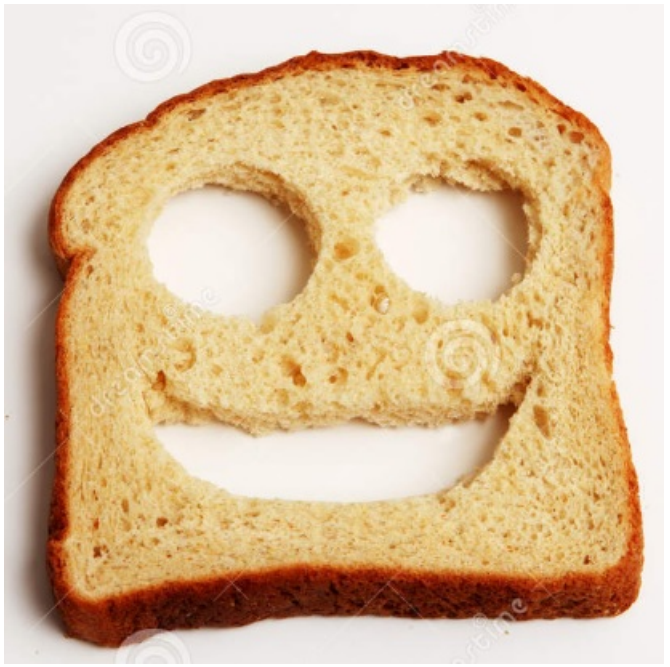
The use of probiotics seems to reduce the inflammatory response and restore a normal proportion of beneficial bacteria in the gastrointestinal tract.

KEYWORDS: Celiac disease; Dysbiosis; Gluten-free diet; Gut microbiota; Probiotic



INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

The grain with two faces



Nutrients **2015**, *7*, 1565-1576; doi:10.3390/nu7031565

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nutrients

ISSN 2072-6643

www.mdpi.com/journal/nutrients

Article

Effect of Gliadin on Permeability of Intestinal Biopsy Explants from Celiac Disease Patients and Patients with Non-Celiac Gluten Sensitivity

Justin Hollon [1,*], Elaine Leonard Puppa [2], Bruce Greenwald [3], Eric Goldberg [3], Anthony Guerrerio [4] and Alessio Fasano [5]

[1] Department of Pediatric Gastroenterology, Naval Medical Center Portsmouth, 620 John Paul Jones Circle, Portsmouth, VA 23708, USA

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Medicine, Baltimore, MD 21205, USA; E-Mail: aguerrerio@jhmi.edu

[5] Center for Celiac Research, Massachusetts General Hospital and Division of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston, MA 02114,

"Conclusions: Increased intestinal permeability after gliadin exposure occurs in ALL individuals."

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Food and Energy Security
Open Access

REVIEW

The contribution of wheat to human diet and health

Peter R. Shewry[1,2] & Sandra J. Hey[1]

[1]Rothamsted Research, Harpenden, Hertfordshire AL5 2JQ, UK
[2]University of Reading, Whiteknights, Reading Berkshire RG6 6AH, UK

Keywords
Diet and health, dietary fiber, grain composition, phytochemicals, wheatwheat

Correspondence
Peter R. Shewry, Rothamsted Research, Harpenden, Hertfordshire AL5 2JQ, UK.
Tel: +44 (0) 1582 763133; Fax: +44 (0) 1582 763010; E-mail: peter.shewry@rothamsted.ac.uk

Funding In
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Biotechnological and Biological Sciences Research Council (BBSRC) of the UK.

Abstract

Wheat is the most important staple crop in temperate zones and is in increasing demand in countries undergoing urbanization and industrialization. In addition to being a major source of starch and energy, wheat also provides substantial amounts of a number of components which are essential or beneficial for health, notably protein, vitamins (notably B vitamins), dietary fiber, and phytochemicals. Of these, wheat is a particularly important source of dietary fiber, with bread

..wheat also provides substantial amounts of a number of components which are essential or beneficial for health, notably protein, vitamins (notably B vitamins), dietary fiber, and phytochemicals..

Learning Objectives

- Describe the relationship between food exposure (i.e. gluten) and intestinal permeability
- Explain the relationship between intestinal permeability and inflammation
- Discuss the relationship between inflammation and the spectrum of chronic disease
- Identify a medical nutrition therapy (MNT) based treatment plan

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Abstract

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Shock. 2009 Oct;32(4):374-8. doi: 10.1097/SHK.0b013e3181a2bcd6.

Systemic inflammation increases intestinal permeability during experimental human endotoxemia.

Hietbrink F[1], Besselink MG, Renooij W, de Smet MB, Draisma A, van der Hoeven H, Pickkers P.

Author information

Abstract

Although the gut is often considered the motor of sepsis, the relation between systemic inflammation and intestinal permeability in humans is not clear. We analyzed intestinal permeability during experimental endotoxemia in humans. Before and during experimental endotoxemia (Escherichia coli LPS, 2 ng/kg), using polyethylene glycol (PEG) as a permeability marker, intestinal permeability was analyzed in 14 healthy subjects. Enterocyte damage was determined by intestinal fatty acid binding protein. Endotoxemia induced an inflammatory response. Urinary PEGs 1,500 and 4,000 recovery increased from 38.8 +/- 6.3 to 63.1 +/- 12.5 and from 0.58 +/- 0.31 to 3.11 +/- 0.93 mg, respectively ($P < 0.05$). Intestinal fatty acid binding protein ex
recovery ($r = 0.48$, $P =$
most likely caused by

PMID: 19295480 [PubMed

The increase in intestinal permeability is most likely caused by inflammation-induced paracellular permeability, rather than ischemia-mediated enterocyte damage.

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Abstract

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Mol Cell Biochem. 2014 Mar;388(1-2):203-10. doi: 10.1007/s11010-013-1911-4. Epub 2013 Dec 18.

Increased circulatory levels of lipopolysaccharide (LPS) and zonulin signify novel biomarkers of proinflammation in patients with type 2 diabetes.

Jayashree B[1], Bibin YS, Prabhu D, Shanthirani CS, Gokulakrishnan K, Lakshmi BS, Mohan V, Balasubramanyam M.

Author information

Abstract

Emerging data indicate that gut-derived endotoxin (metabolic endotoxemia) may contribute to low-grade systemic inflammation in insulin-resistant states. Specific gut bacteria seem to serve as lipopolysaccharide (LPS) sources and several reports claim a role for increased intestinal permeabil
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Specific gut bacteria seem to serve as lipopolysaccharide (LPS) sources and several reports claim a role for increased intestinal permeability in the genesis of metabolic disorders…. In Asian Indians who are considered highly insulin resistant, the circulatory LPS levels, LPS activity, and ZO-1 were significantly increased in patients with type 2 diabetes and showed positive correlation with inflammatory markers and poor glycemic/lipid control.

PMID: 24347174 [PubMed - indexed for MEDLINE]

Obes Rev. 2011 Jun;12(6):449-58. doi: 10.1111/j.1467-789X.2010.00845.x. Epub 2011 Mar 8.

Leaky gut and diabetes mellitus: what is the link?

de Kort S[1], Keszthelyi D, Masclee AA.

Author information

Abstract

Diabetes mellitus is a chronic disease requiring lifelong medical attention. With hundreds of millions suffering worldwide, and a rapidly rising incidence, diabetes mellitus poses a great burden on healthcare systems. Recent studies investigating the underlying mechanisms involved in disease development in diabetes point to the role of the dys-regulation of the intestinal barrier. Via alterations in the intestinal permeability, intestinal

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Recent studies investigating the underlying mechanisms involved in disease development in diabetes point to the role of the dysregulation of the intestinal barrier. Via alterations in the intestinal permeability, intestinal barrier function becomes compromised whereby access of infectious agents and dietary antigens to mucosal immune elements is facilitated, which may eventually lead to immune reactions with damage to pancreatic beta cells and can lead to increased cytokine production with consequent insulin resistance.

Diabetes Research and Clinical Practice

Volume 105, Issue 2, August 2014, Pages 141–150

Invited Review

Inflammation as a link between obesity, metabolic syndrome and type 2 diabete

Nathalie Esser[a, b], Syl

Abstract

It is recognized that a chronic low-grade inflammation and an activation of the immune system are involved in the pathogenesis of obesity-related insulin resistance and type 2 diabetes. Systemic inflammatory markers are risk factors for the development of type 2 diabetes and its macrovascular complications. Adipose tissue, liver, muscle and pancreas are themselves sites of inflammation in presence of obesity. An infiltration of macrophages and other immune
population shift from an anti-infla
crucial for the production of pro-i
paracrine manner to interfere wit
dysfunction and subsequent insu
interleukin-1β is implicated in the
of the NLRP3 inflammasome. Th
supporting the role of the immune
type 2 diabetes and to examine various mechanisms underlying this relationship. If type 2 diabetes is an inflammatory disease, anti-inflammatory therapies could have a place in prevention and treatment of type 2 diabetes.

It is recognized that a chronic low-grade inflammation and an activation of the immune system are involved in the pathogenesis of obesity-related insulin resistance and type 2 diabetes.

Psychiatr. Pol. 2016; 50(4): 747–760
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: http://dx.doi.org/10.12740/PP/OnlineFirst/45053

The brain-gut axis dysfunctions and hypersensitivity to food antigens in the etiopathogenesis of schizophrenia

Hanna Karakuła-Juchnowicz[1, 2], Michał Dzikowski[1],
Agnieszka Pelczarska[3], Izabela Dzikowska[4], Dariusz Juchnowicz[5]

Medical University of Lublin
ersity of Lublin
ca
atology, Lublin, Poland
ersity in Bialystok

"Research results seem to be very promising and indicate the possibility of improved clinical outcomes in some patients with schizophrenia by modifying diet, use of probiotics, and the implementation of antibiotic therapy of specific treatment groups."

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Learning Objectives

- Describe the relationship between food exposure (i.e. gluten) and intestinal permeability
- Explain the relationship between intestinal permeability and inflammation
- Discuss the relationship between inflammation and the spectrum of chronic disease
- Identify a medical nutrition therapy (MNT) based treatment plan

Healing Leaky Gut with the 4R GI Restoration Protocol

Source: Institute for Functional Medicine

1. Remove
   a. Toxins
   b. Infection
   c. Dietary triggers
2. Replace
   a. HCL
   b. Digestive enzymes
3. Reinoculate
   a. probiotics
4. Repair
   a. Glutamine/SCFAs
   b. Fish oils
   c. curcumin

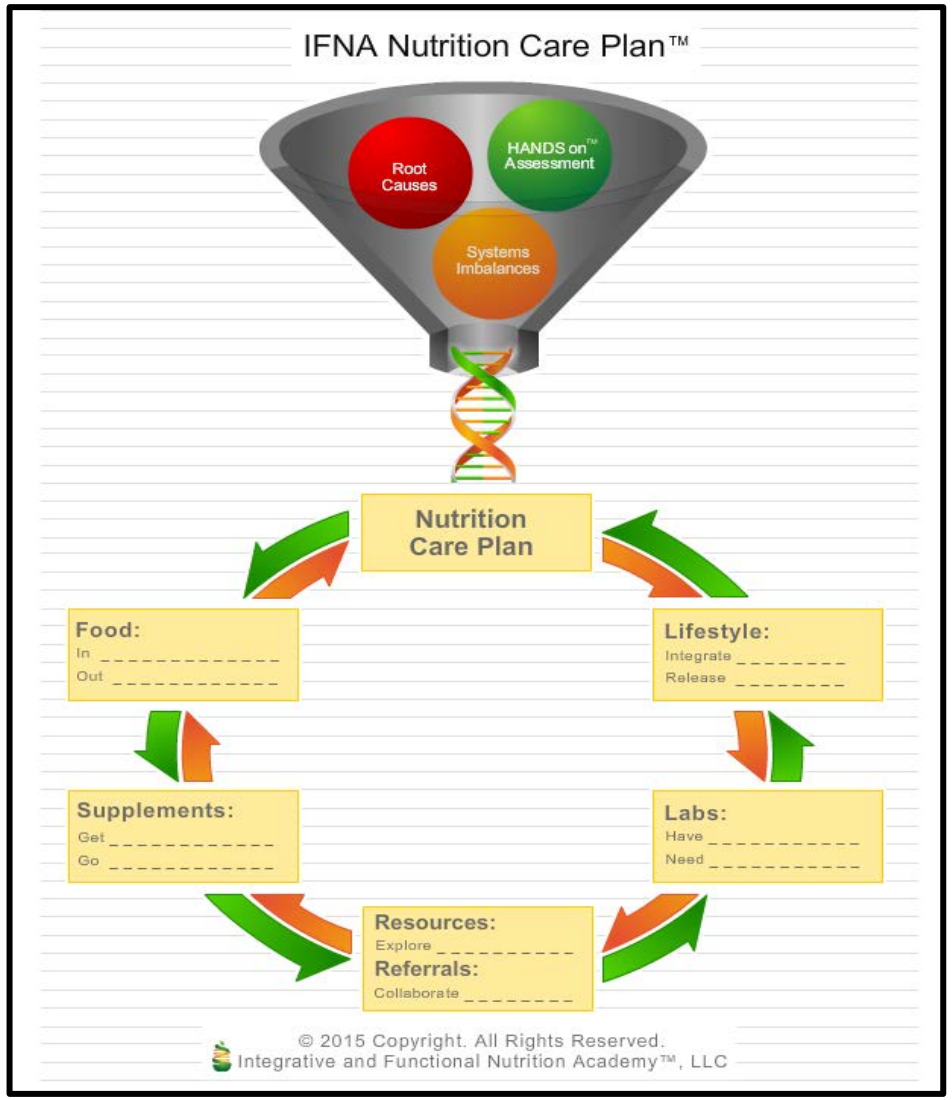
INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

What to consider eliminating:

- Gluten (r/o celiac disease first, if possible)
- Dairy
- Corn? Soy? Grains? animal protein?
- Refined sugar
- Infection
- Toxins (alcohol, preservatives, smoking, *stress*)

What to consider adding:

- Betaine HCL, broad spectrum digestive enzymes
- Probiotics/prebiotics/fermented foods
- Glutamine (dose low and go slow)/zinc carnosine
- Methylated nutrients (B2, B6, folate, B12, CoQ10)
- Omega-3 fish oils
- Fiber rich foods/prebiotics
- Antioxidant/phytochemical rich foods (i.e. fresh fruits and vegetables, seeds, nuts, legumes, etc.)



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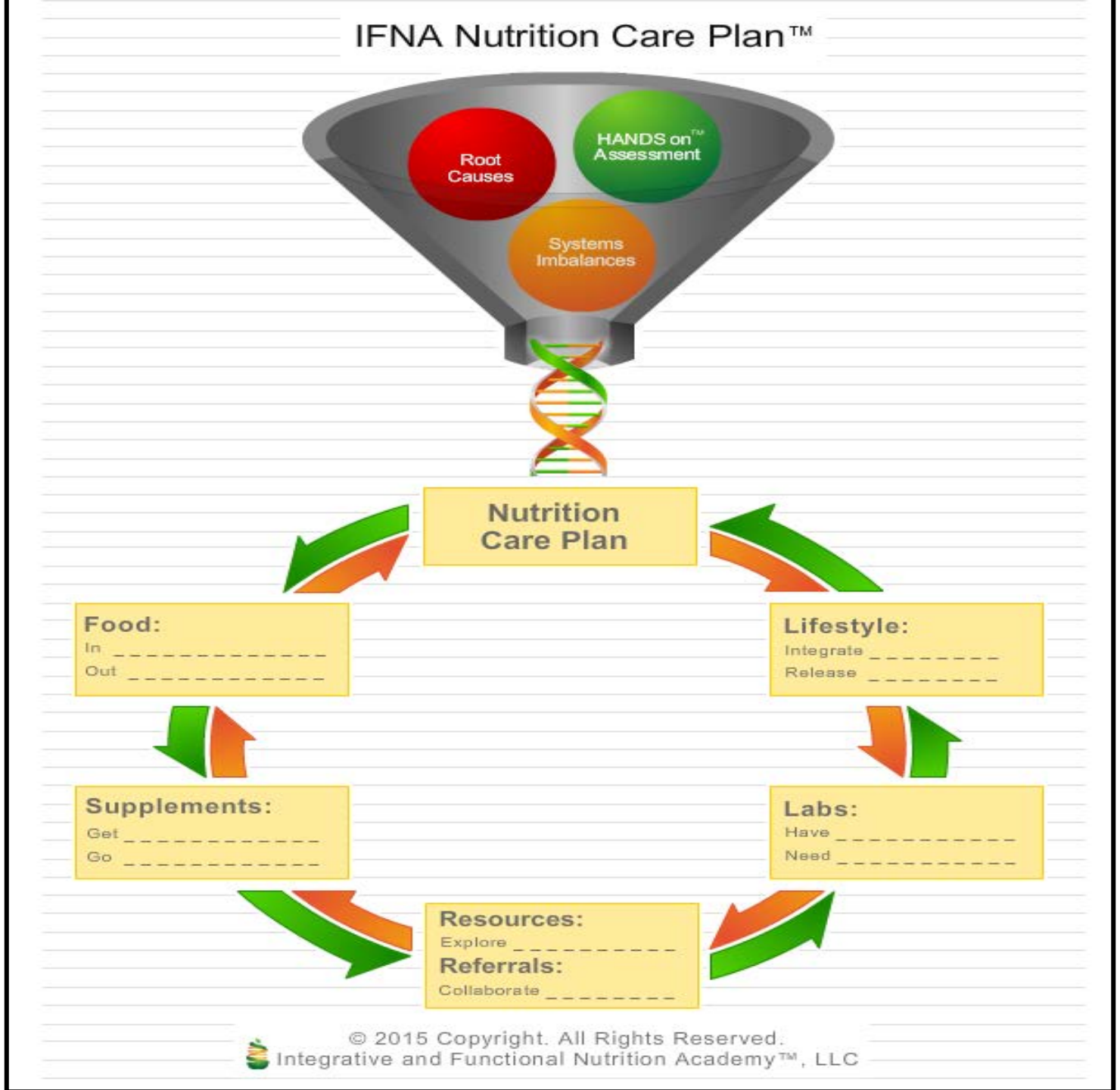

Once you have a good history, test results etc., you can formulate the rest of your Nutrition Care Plan

Image source: www.IFNAcademy.com

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Key Takeaways

- Impaired intestinal permeability is real phenomenon that is part of the “3 legged stool” that leads to autoimmunity
- Triggers can include toxins, infection, diet (TID)
- Impaired intestinal permeability can be healed using the 4R protocol

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

Presenters from left to right: Alessio Fasano, MD; Sheila Dean, DSc, RDN, Andrea Scaramuzza, MD
76th ADA Annual Symposium - June 12, 2016

INTEGRATIVE AND FUNCTIONAL NUTRITION ACADEMY

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More questions?
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Mind, Mood & Food

Optimal Nutrition for Body & Brain

April 15-20, 2018
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