Microbiome And Leaky Gut

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Lecture Objectives

Genes, Nutrition and the Gut Mucosa Functions:
How to Connect the Dots
The Epidemics of Immune-Mediated Diseases In The Western Hemisphere: The Hygiene Hypothesis
The Epidemics of Celiac Disease

- CD prevalence (%)
- Year (1960-2010)
- Celiac incidence (1990-2010)

- CD prevalence:
  - 0.21% (1960)
  - 0.45% (1970)
  - 0.93% (1980-2000)

- Incidence (thousands): 27-77

- World map showing prevalence rates:
  - North America: 1:100-1:200
  - South America: 1:67-1:681
  - Europe: 1:88-1:262
  - Middle East: 1:87-1:156
  - Africa: 1:18-1:355
  - Asia (except N/A): 1:100-1:310
  - Australia: 1:82-1:251
Immune-Mediated Diseases
Epidemics: Autism
We Are Not Born With The Destiny to Develop Chronic Inflammatory Diseases
The Yin and Yang Between Tolerance and Immune Response Leading To Chronic Inflammatory Diseases

- Human Genome
- Environmental Factors
- Increased Gut Permeability
- Immune Response
- Microbiome
- Clinic Outcome
Loss of Mucosal Immune Homeostasis

Chronic Inflammation-Allergy

1. Normal/physiologically controlled permeability
   - Defensins
   - Mucus Synthesis & Quality
   - SIgA

2. Minor barrier defect
   - Dietary/microbial Ag influx
   - Mucosal Tolerance Homeostasis
   - Anergy
   - Regulatory DC’s
   - Macrophages
   - Tregs
   - IL-10/TGF-β

3. Increased permeability
   - Inflammation - Allergy
   - Innate or immuno-regulatory defect
   - Proinflammatory Allergic cytokines

4. Massive dietary and microbial antigen influx
   - Break of Tolerance
   - Apoptosis resistant T cells
   - Tissue damage
   - Chronic inflammation
   - Allergy

Adapted from P. Brandtzaeg, Beneficial Microbes 2010
The Paracellular Pathway

Tight junctions are a ‘dark horse’ implicated in a host of disease states, ranging from acute injury to chronic inflammation and autoimmune diseases.

Zonulin Genetics and Diagnostics
Zonulin Characterization in Sera of CD Patients

Fasano A Physiol Rev 2011;91:151-175
Identification of human zonulin, a physiological modulator of tight junctions, as prehaptoglobin-2

Amit Tripathi, Karen M. Lammers, Simeon Goldblum, Terez Shea-Donohue, Sarah Netzel-Arnett, Marguerite S. Buzz, Toni M. Antalis, Stefanie N. Vogel, Aiping Zhao, Shiqi Yang, Marie-Claire Arrietta, Jon B. Meddings, and Alessio Fasano

Mucosal Biology Research Center, Center for Vascular and Inflammatory Diseases and Department of Physiology, and Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, MD 20201; and Department of Medicine, University of Alberta, Edmonton, Alberta, Canada T6G 2V2

Siamangs (Hylobates syndactylus)  Orangutans (Pongo pygmaeus)  Gorillas (Gorilla gorilla)  Humans (Homo sapiens)  Common chimpanzees (Pan troglodytes)  Pygmy chimpanzees (Bonobos) (Pan paniscus)

Present

2.5

5

10

15

20

25

30

35

40

45

50

55

60

65

70

75

80

85

90

95

100

105

110

Millions of years ago

200

300

400

500

Haptoglobin 1

Haptoglobin 2 (Zonulin)

A

B

C

D

E
The Zonulin Transgenic Mouse As A Model To Study Gut-Brain Axis Miscommunication

**C57Bl/6** wild type mouse

HP 1-1 (no zonulin gene)

**C57Bl/6** mouse transfected with human HP2 gene

HP 1-2 (1 zonulin gene)

**Transgenic C57Bl/6** mouse engineered by duplicating α chain (α1 → α2)

HP 2-2 (2 zonulin genes)

**WB**

α2 →

α1 →
Experimental Design

Daily Body Weight after 7 days all mice are put on Normal drinking water

Zonulin transgenic Hp2 mice are phenotypically normal despite increased small intestinal permeability

*p<0.05

Sturgeon C et al. NY Am Acad Sci USA (in press)
DSS Treatment Causes Increased Morbidity And Mortality In Ztm

A

Male Percent survival

Day

B

Female Percent survival

Day

C

Male % Body Weight

Day

Sturgeon C et al. NY Am Acad Sci USA (in press)
Ztm treated with DSS show increased small intestinal permeability and increased expression of the HP2 gene.

* p<0.05  ** p<0.01  *** p<0.001

Sturgeon C et al. NY Am Acad Sci USA (in press)
AT1001 (Larazotide Acetate) Treatment Ameliorates Increased DSS Induced Morbidity and Mortality in Ztm

Sturgeon C et al. NY Am Acad Sci USA (in press)
Zonulin Characterization and Signaling

Zonulin signaling

Freeze-Fracture

Following Pathway Activation

Resting State

Zonulin Gene Is Located on Chromosome 16

Chromosome 16 contains about 98 million bases, or some 3\% of the human genome, encoding for \(~1,300\) genes.
<table>
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<tr>
<th>Disease</th>
<th>Model</th>
<th>Zonulin Shown to be Involved</th>
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<tbody>
<tr>
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<tr>
<td>Autism</td>
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<tr>
<td>Celiac Disease</td>
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<tr>
<td>Colitis/IBD (Crohn’s disease)</td>
<td>Human</td>
<td>YES</td>
</tr>
<tr>
<td>Colitis</td>
<td>Mouse</td>
<td>YES</td>
</tr>
<tr>
<td>Fe metabolism in heart transplant</td>
<td>Human</td>
<td>NO</td>
</tr>
<tr>
<td>Glioma</td>
<td>Human</td>
<td>YES</td>
</tr>
<tr>
<td>Glioma Cell</td>
<td>Cell</td>
<td>YES</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Human</td>
<td>YES</td>
</tr>
<tr>
<td>HIV</td>
<td>Human</td>
<td>YES</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Mouse</td>
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<tr>
<td>Necrotizing Enterocolitis (NEC)</td>
<td>Rat</td>
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<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>Human</td>
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<tr>
<td>Non-Celiac Gluten Sensitivity</td>
<td>Human</td>
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<tr>
<td>Obesity/Insulin resistance</td>
<td>Human</td>
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<td>Post-surgery Sepsis</td>
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<tr>
<td>Type 2 diabetes</td>
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</table>
Serum Zonulin Levels and Their Correlation With Intestinal Permeability In Celiac Disease and Type 1 Diabetes

Celiac Disease

Type 1 Diabetes

Zonulin-LA/MA

multiple R=0.36; intercept p=1.71E-10; X variable 1 p=0.0004
Environmental Triggers Causing Zonulin Release

Gluten

Gut Microbiome
Mechanisms of Zonulin Release: Gliadin

- CXCR-3 is a seven-transmembrane G couple protein receptor that is preferentially expressed on activated T lymphocytes and subset of B and NK cells.
- Three known CXCR3 ligands CXCL-9, -10, -11 are produced at the site of inflammation and elicit migration of pathological Th1 cells.
- CXCR3 has been implicated as a potential target for impeding T-cell-mediated destruction in autoimmune diseases such as multiple sclerosis and type 1 diabetes.

Mapping of α-gliadin motifs exerting cytotoxic activity (red), immunomodulatory activity (light green), zonulin release and gut permeating activity (blue) and CXCR3-dependent IL8 release in CD patients (dark green).
Proximal Bowel Contamination Activates the Zonulin Pathway

Zonulin Release

Changes in Tissue Resistance

Changes in Tissue Resistance Is Prevented by the Zonulin Inhibitor AT1001

El Asmar et al Gastroenterology 2002;123:1607-15
Dysbiosis is one of the key factors causing zonulin release and subsequent loss of barrier function.

The Microbiome as Possible Transducer of All Environmental Factors Affecting Onset of CID in Genetically Susceptible Individuals.
The changing face of gut microbes

- The human gut harbors $10^{11} - 10^{12}$ bacteria per gram colonic content ($>10^{14}$ total bacteria);
- Total bacteria outnumber human cells 10:1;
- Total bacterial genes outnumber human genes $>150:1$;
- $>10,000$ different species of bacteria are resident in the human intestinal microbiota (400-500 per person).
• The human gut harbors $10^{11}$-$10^{12}$ bacteria per gram colonic content ($>10^{14}$ total bacteria)
• Total bacteria outnumber human cells 10:1
• Total bacterial genes outnumber human genes >150:1
• >10,000 different species of bacteria are resident in the human intestinal microbiota (400-500 per person)
Is Microbiome Science Ready For Primetime Clinical Applicability?

Classification of Organisms

- **Domain**: Bacteria
- **Phylum**: Firmicutes
- **Class**: Clostridia
- **Order**: Clostridiales
- **Family**: Ruminococcaceae
- **Genus**: Anaerotruncus
- **Species**: Anaerotruncus_sp

The “Omics” Revolution

**Microbiome (Who is there):** A powerful tool used to analyze microbial communities (commensal, symbiotic, and pathogenic microorganisms) regardless of the ability of member organisms to be cultured in the laboratory.

**Metagenomics/Metatranscriptomic (What language do they speak and what are they talking about):** Genomic and transcriptome analysis of microbial DNA extracted directly from communities present in a specific environment, for example the human gut.
Why The First 1000 Days Of Life Are Instrumental For Clinical Destiny

- **Vaginal Delivery**
  - Proper Nutrition
  - No infections
  - No Antibiotic treatments

- **C section**
  - Inappropriate Nutrition
  - Multiple infections
  - Antibiotic treatments

**Microbiome Composition**

**Balanced Microbiome**

**Appropriate GALT Maturation**

**Tolerogenic Response to Food Antigens - State of Health**

**Dysbiosis**

**Inappropriate GALT Maturation**

**Pro-inflammatory Response to Food Antigens - CID**

**Probiotics, Prebiotics, Symbiotics**
Role of Breastmilk

Impact of human milk glycobiome on the infant intestinal microbiota

Maternal Milk:
- Antigen
  - Free
  - Complexed to IgA
  - Complexed to IgG
- Tolerogenic immune mediators
  - TGF-β, IL10, Vit A, ...
- Microbiota modulating factors
  - Prebiotics (oligosaccharides, glycoproteins)
  - Antimicrobial (lysozyme, lactoferrin, IgA, ...)
- Gut growth factors (EGF, TGF-β, ...)
The Yin and Yang Between Tolerance and Immune Response Leading To Chronic Inflammatory Diseases

- Human Genome
- Environmental Factors
- Increased Gut Permeability
- Immune Response
- Microbiome
- Clinic Outcome
The Mediterranean Diet
When Did It Start, When It Was Abandoned?

- Diet:
  - Fruits, nuts, tubers
  - Occasional meat

- Change from nomadic to settled lifestyle:
  - 10,000 years ago
  - Advent of agriculture
  - Development of gluten-containing grains

The Mediterranean Diet Pyramid

- Every Day:
  - Water

- In Moderation:
  - Wine

- Less Often:
  - Meats and Sweets

- Weekly:
  - Moderate Portions:
    - Poultry, Eggs, Cheese, and Yogurt

- Often:
  - at least twice each week:
    - Fish and Seafood

- Every Day:
  - Base Each Meal Around these Foods:
  - Be Physically Active; Enjoy Meals with Others
How The Mediterranean Diet Can Affect Clinical Outcome

Direct Effects

✓ A balanced diet is crucial to maintain and improve health

✓ Phytochemicals and other bioactive compounds possess demonstrated healthy benefits

✓ These compounds are widely abundant in Mediterranean foods:
  • Citrus (Flavanones)
  • Grape (Anthocyanins)
  • Apples (Procyanidins)
  • Legumes (Flavonoids)
  • Dairy products (Bioactive peptides)
  • Vegetables (Vitamins, Minerals, Glucosinolates)
  • Blue Fish (Ω-3 Fatty acids)

Indirect Effect Through Microbiome Composition

Ley et al, Science 2008;320:1647-1651
Microbiota in Immunity & Inflammation

Y Belkaid & TW Hand, Cell 2014;157:121-141
Gut Dysbiosis
Reduced bacterial diversity (dysbiosis): an emerging theme across diseases

• Microbiota affected by:
  - Infections
  - Antibiotics
  - Xenobiotics
• Diabetes mellitus
• Obesity
• Cancers: gastric, colonic
• Inflammatory bowel diseases
• Necrotizing enterocolitis
• Irritable bowel syndrome, colic

Scientific American
June 2012

Correlation Between Dysbiosis And Human Diseases

Gut microbiota (Dysbiosis)

- Metabolites
- Inflammatory cytokines
- PAMPS

- Heart diseases
- Liver infection cancer
- Brain Parkinson's disease, Alzheimer's disease
- Prostate Cancer
- Kidney Infection
- Lung Allergy (Asthma) Infection (TB)
- Islet Obesity Diabetes

Metabolites: secondary bile acids, SFAC, vitamin, etc
PAMPS: LPS, flagelin, peptidglycan, etc
Proinflammatory cytokines: IL-6, TNF-α, etc
?: mutual interactions
EXTENDED REPORT

Dysbiosis and zonulin upregulation alter gut epithelial and vascular barriers in patients with ankylosing spondylitis

Francesco Ciccia,1 Giuliana Guggino,1 Aroldo Rizzo,2 Riccardo Alessandro,3 Michele Maria Luchetti,4 Simon Milling,5 Laura Saieva,3 Heleen Cypers,6,7 Tommaso Stampone,2 Paola Di Benedetto,8 Armando Gabrielli,3 Alessio Fasano,9 Dirk Elewaut,6,7 Giovanni Triolo1

Handling editor Tore K Kvien

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2016-210000).

For numbered affiliations see end of article.

ABSTRACT

Background Dysbiosis has been recently demonstrated in patients with ankylosing spondylitis (AS) but its implications in the modulation of intestinal immune responses have never been studied. The aim of this study was to investigate the role of ileal bacteria in modulating local and systemic immune responses in AS.

Methods Ileal biopsies were obtained from 50 HLA-B27+ patients with AS and 20 normal subjects. Silver stain was used to visualise bacteria. Ileal expression of microbial flora in the gut is essential for intestinal health and its altered balance, termed dysbiosis, may influence intestinal permeability through the release of zonulin,4 a protein that modulates the permeability of epithelial tight junctions of the digestive tract.

Dysbiosis has been recently demonstrated in the terminal ileum of patients with ankylosing spondylitis (AS) together with the presence of subclinical gut inflammation.5,6 It is unclear however
Invasive And Adherent bacteria Are Present in AS Ileum and Are Associated to Down-Regulation of TJ Proteins

Ciccia et al Ann Rheum Dis 2017
Occludin, Claudin 4, and Zonulin Tissue Expression is Altered in AS Patients And Modulated By Intestinal Bacteria
Gut Vascular Barrier Is Affected in AS Patients

A. VE Cadherin

<table>
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<th>AS chronic</th>
<th>HCs</th>
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B. JAM1

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C. PV1

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D. Occludin

E. CD31

F. Merge

G. Occludin

H. CD31

I. Merge

J. PV1

K. CD31

L. GFAP

M. Merge

N. PV1

O. CD31

P. GFAP

Q. Merge

Ciccia et al Ann Rheum Dis 2017
Serum Zonulin Levels In AS Patients and In Vitro Effect of Zonulin on Endothelial Cells and Monocytes
Role of Gut Microbiota In Metabolic Disorders

- Allergy
- Autism
- Minimal hepatic encephalopathy
- Familial Mediterranean fever
- Atherosclerosis
- Pancreatitis
- Diabetes
- Obesity/NAFLD
- Liver disease
- Fibromyalgia
- Burn injury
Low diversity (less modular) gut microbiota in IBD and in obesity

124 Danish & Spanish adults
42 BMI >30
25 IBD

S Greenblum et al., PNAS 2012;109:594-599
Core microbiome in obese and lean twins: Missouri Adolescent Female Twin Study


with restoration after gastric bypass: H Zhang et al. PNAS 2009;106:2365-70
Why A Leaky Gut Together With Dysbiosis Can Make Us Fat
An increase in intestinal permeability is considered to be associated with gut inflammatory tone and development of obesity, fatty liver (typical of obese subjects) and type 2 diabetes
Microbes and Host Metabolism

A. Lipopolysaccharide
- LPS
- TLR4
- \(\uparrow\) Inflammation
- \(\uparrow\)lipogenesis
- \(\uparrow\)gluconeogenesis

B. Short-chain fatty acids
- Dietary fibres
- Butyrate
- Acetate
- Propionate
- GPR41
- GPR43
- \(\uparrow\)GLP1 and PYY
- \(\downarrow\)Inflammation

C. Bile acids
- Primary bile acids
- Secondary bile acids
- TGR5
- \(\uparrow\)Energy expenditure
- \(\uparrow\)GLP1

Factors Influencing Bacterial Translocation (BT) - Endotoxemia

- Stress hormones e.g. SNS
- Etiology stage cirrhosis
- Metabolic factors?
- Environmental factors
- Genetic susceptibility
- Cytokines ROS/NO, chemokines
- Gut flora
- Intestinal barrier
- Pathological BT
- GALT immune response
Gut microbiota, intestinal permeability, obesity-induced inflammation, and liver injury.

Frazier TH, DiBaise JK, McClain CJ.
Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Louisville School of Medicine, Louisville, Kentucky 40202, USA. thfraz01@louisville.edu

Abstract
Obesity and its metabolic complications are major health problems in the United States and worldwide, and increasing evidence implicates the microbiota in these important health issues. Indeed, it appears that the microbiota function much like a metabolic "organ," influencing nutrient acquisition, energy homeostasis, and, ultimately, the control of body weight. Moreover, alterations in gut microbiota, increased intestinal permeability, and metabolic endotoxemia likely play a role in the development of a chronic low-grade inflammatory state in the host that contributes to the development of obesity and associated chronic metabolic diseases such as nonalcoholic fatty liver disease. Supporting these concepts are the observations that increased gut permeability, low-grade endotoxemia, and fatty liver are observed in animal models of obesity caused by either high-fat or high-fructose feeding. Consistent with these observations, germ-free mice are protected from obesity and many forms of liver injury. Last, many agents that affect gut flora/permeability, such as probiotics/prebiotics, also appear to affect obesity and certain forms of liver injury in animal model systems. Here the authors review the role of the gut microbiota and metabolic endotoxemia-induced inflammation in the development of obesity and liver injury, with special reference to the intensive care unit setting.

PMID: 21807932 [PubMed - indexed for MEDLINE]
Nutrition, Intestinal Permeability, and Blood Ethanol Levels Are Altered in Patients with Nonalcoholic Fatty Liver Disease (NAFLD).

Department of Nutritional Medicine (180a), University of Hohenheim, Fruwirthstraße 12, 70599 Stuttgart, Germany, volynets@uni-hohenheim.de.

Abstract

BACKGROUND: A role of an altered dietary pattern (e.g., a diet rich in sugar) but also alterations at the level of the intestinal barrier have repeatedly been discussed to be involved in the development and progression of nonalcoholic fatty liver disease (NAFLD).

AIMS: To determine if the nutritional intake, intestinal flora, and permeability and the development of NAFLD are related in humans.

METHODS: Ten controls and 20 patients with NAFLD ranging from simple steatosis to steatohepatitis were included in the study. Bacterial overgrowth, orocecal transit time, and intestinal permeability were assessed. Alcohol, endotoxin, and plasminogen activator inhibitor (PAI-) 1 concentration were determined in plasma. Nutritional intake was assessed using a dietary history.

RESULTS: Despite no differences in the prevalence of bacterial overgrowth and in the orocecal transit time, intestinal permeability, alcohol, and endotoxin levels in plasma were significantly higher in patients with NAFLD than in controls. Similar results were also found for PAI-1 plasma concentrations. Patients with NAFLD had a significantly higher intake of protein, total carbohydrates, and mono- as well as disaccharides than controls. PAI-1, endotoxin, and ALT plasma levels were positively related to total protein and carbohydrate intake.

CONCLUSIONS: Taken together, our results indicate that intestinal permeability, endogenous alcohol synthesis, and nutritional intake are markedly altered in patients with NAFLD.

PMID: 22427130 [PubMed - as supplied by publisher]

Gut permeability is related to body weight, fatty liver disease, and insulin resistance in obese individuals undergoing weight reduction.

Damm-Machado A¹, Louis S¹, Schnitzer A¹, Volynets V¹, Rings A¹, Basrai M¹, Bischoff SC².

Abstract

BACKGROUND: Obesity and associated metabolic disorders are related to impairments of the intestinal barrier.

OBJECTIVE: We examined lactulose:mannitol (Lac:Man) permeability in obese individuals with and without liver steatosis undergoing a weight-reduction program to test whether an effective weight-loss program improves gut barrier function and whether obese patients with or without liver steatosis differ in this function.

DESIGN: Twenty-seven adult, nondiabetic individuals [mean ± SD body mass index (BMI; in kg/m²): 43.7 ± 5.2; 78% with moderate or severe liver steatosis] were included in the follow-up intervention study (n = 13 by month 12). All patients reduced their weight to a mean ± SD BMI of 36.4 ± 5.1 within 12 mo. We assessed barrier functions by the oral Lac:Man and the fecal zonulin tests. Insulin resistance was assessed by the homeostatic model assessment index (HOMA), and liver steatosis by sonography and the fatty liver index (FLI).

RESULTS: The Lac:Man ratio and circulating interleukin (IL) 6 concentration decreased during intervention from 0.080 (95% CI: 0.073, 0.093) to 0.027 (95% CI: 0.024, 0.034; P < 0.001) and from 4.2 ± 1.4 to 2.8 ± 1.6 pg/mL (P < 0.01), respectively. At study start, the Lac:Man ratio was higher in patients with moderate or severe steatosis than in those without any steatosis (P < 0.001). The Lac:Man ratio tended to correlate with HOMA (ρ = 0.55, P = 0.052), which correlated with FLI (ρ = 0.75, P < 0.01). A multiple-regression analysis led to a final model explaining FLI best through BMI, waist circumference, and the Lac:Man ratio.

CONCLUSIONS: Intestinal permeability is increased in obese patients with steatosis compared with obese patients without. The increased permeability fell to within the previously reported normal range after weight reduction. The data suggest that a leaky gut barrier is linked with liver steatosis and could be a new target for future steatosis therapies. This trial was registered at clinicaltrials.gov as NCT01344525.

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Loss of Mucosal Immune Homeostasis

Leading to NAFLD

1. Normal/physiologically controlled permeability
2. Minor barrier defect: dietary/microbial Ag influx
3. Increased permeability
4. Massive dietary and microbial antigen influx

Mucosal Tolerance Homeostasis
Anergy (HEALTH)

Defensins
Mucus Synthesis & Quality
SIgA

Inflammation

Vicious circle

Regulatory DC’s
Macrophages
Tregs IL-10/TGF-β

Proinflammatory
Allergic/Th1 cytokines

The Spectrum of NAFLD

Fatty Liver
NASH
Cirrhosis

Fat accumulates in the liver
Fat plus inflammation and scarring
Scar tissue replaces liver cells
Circulating Zonulin, a Marker of Intestinal Permeability, Is Increased in Association with Obesity-Associated Insulin Resistance

José María Moreno-Navarrete, Mònica Sabater, Francisco Ortega, Wifredo Ricart, José Manuel Fernández-Real*

Department of Diabetes, Endocrinology and Nutrition, Institut d'Investigació Biomèdica de Girona (IdIBGI), CIBEROBN (CB06/03/010) and Instituto de Salud Carlos III (ISCIII), Girona, Spain

Abstract

Zonulin is the only physiological mediator known to regulate intestinal permeability reversibly by modulating intercellular tight junctions. To investigate the relationship between intestinal permeability and obesity-associated metabolic disturbances in humans, we aimed to study circulating zonulin according to obesity and insulin resistance. Circulating zonulin (ELISA) was measured in 123 caucasian men in association with inflammatory and metabolic parameters (including minimal model-measured insulin sensitivity). Circulating zonulin increased with body mass index (BMI), waist to hip ratio (WHR), fasting insulin, fasting triglycerides, uric acid and IL-6, and negatively correlated with HDL-cholesterol and insulin sensitivity. In multiple regression analysis, insulin sensitivity (p = 0.002) contributed independently to circulating zonulin variance, after controlling for the effects of BMI, fasting triglycerides and age. When circulating IL-6 was added to this model, only BMI (p = 0.01) contributed independently to circulating zonulin variance. In conclusion, the relationship between insulin sensitivity and circulating zonulin might be mediated through the obesity-related circulating IL-6 increase.


Editor: Massimo Federici, University of Tor Vergata, Italy
The Relationship of Serum Zonulin Level with Clinical and Laboratory Parameters in Childhood Obesity.

Küme T, Acar S, Tuhan H, Çatlı G, Anik A, Gürsoy Çalan Ö, Böber E, Abacı A.

Abstract

OBJECTIVE: The aim of this study was to investigate the relationship between zonulin and clinical laboratory parameters in childhood obesity.

METHODS: The study included obese children with a body mass index >95th percentile and healthy children who were similar age and gender distribution. Clinical (body mass index, waist circumferences, mid arm circumference, triceps skin fold, percentage of body fat, systolic blood pressure, diastolic blood pressure) and biochemical (glucose, insulin, lipids, thyroid function tests, cortisol, zonulin and leptin levels) parameters were measured.

RESULTS: A total of 43 obese subjects (23 males, mean age: 11.1±3.1 yrs) and 37 healthy subjects (18 males, mean age: 11.5±3.5 yrs) were included in this study. Obese children had significantly higher insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, zonulin and leptin levels than those of the healthy children (p < 0.05), while glucose levels were not different (p > 0.05). Comparison of the obese children regarding the insulin resistance showed no statistically significant differences for zonulin levels (p > 0.05).

CONCLUSION: To the best of our knowledge, the present study is the first study to compare serum zonulin levels between obese and non-obese children. The results of the study showed that zonulin was significantly higher in obese children when compared to healthy children, which is indicating a potential role of zonulin in the obesity etiopathogenesis and related disturbances.

PMID: 28008865 DOI: 10.4274/jcrpe.3682
The correlation between insulin sensitivity and circulating zonulin in participants with normal glucose tolerance (NGT, n=82) and with glucose intolerance (GI, n=41).
Increased circulating zonulin in children with biopsy-proven nonalcoholic fatty liver disease

Zonulin levels for obese children. A: Zonulin levels for obese children with and without nonalcoholic fatty liver disease (NAFLD); B: Zonulin levels for obese children with NAFLD according to severity of steatosis.

Probiotic With or Without Fiber Controls Body Fat Mass, Associated With Serum Zonulin, in Overweight and Obese Adults: Randomized Controlled Trial.

Correlation between serum zonulin, serum hsCRP and trunk fat mass. Evolution of zonulin (a) and hsCRP (c), and correlations between zonulin (b) and hsCRP (d) with trunk fat mass as changes from baseline to end-of-intervention (6 months) in the Per Protocol population. Panels a) and c) display changes from baseline as mean ± 95% confidence intervals at each time point. Placebo n=35–36, LU n=35–36, B420 n=24–25, LU+B420 n=36–37.

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