The Role of the Microbiome in Cardiovascular Disease

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Flatiron Functional Medicine
Louisville, CO

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NA/Non-Clinical

Status of off-label use of devices, drugs or other materials that constitute the subject of this presentation
NA/Non-Clinical

Dr. Jill

Jill Carnahan. MD ABIHM, ABoIM, IFMCP

OBJECTIVES

1. Review how the microbiome induces Cardiovascular disease and inflammation and importance of Diversity
2. Discuss how the microbiome may influence metabolic endotoxemia
3. Identify which organism are associated with cardiovascular disease and metabolic syndrome
4. Learn how to assess the microbiome.
5. Discuss treatments to improve microbiome health

What would you do with this patient?

- 55y/o male with strong FH of CVD
- Father died 58 y/o of MI
- PMHx: Hyperlipidemia, Hypothyroid, DM
- Social: smoker 2ppd, divorced
- Poor diet – dines on fast food 3-5 X weekly
- High stress job, working in factory 40 hours per week
- Symptoms: gas, bloating, heartburn, fatigue and shortness of breath with exertion


Microbial Diversity
is Key!

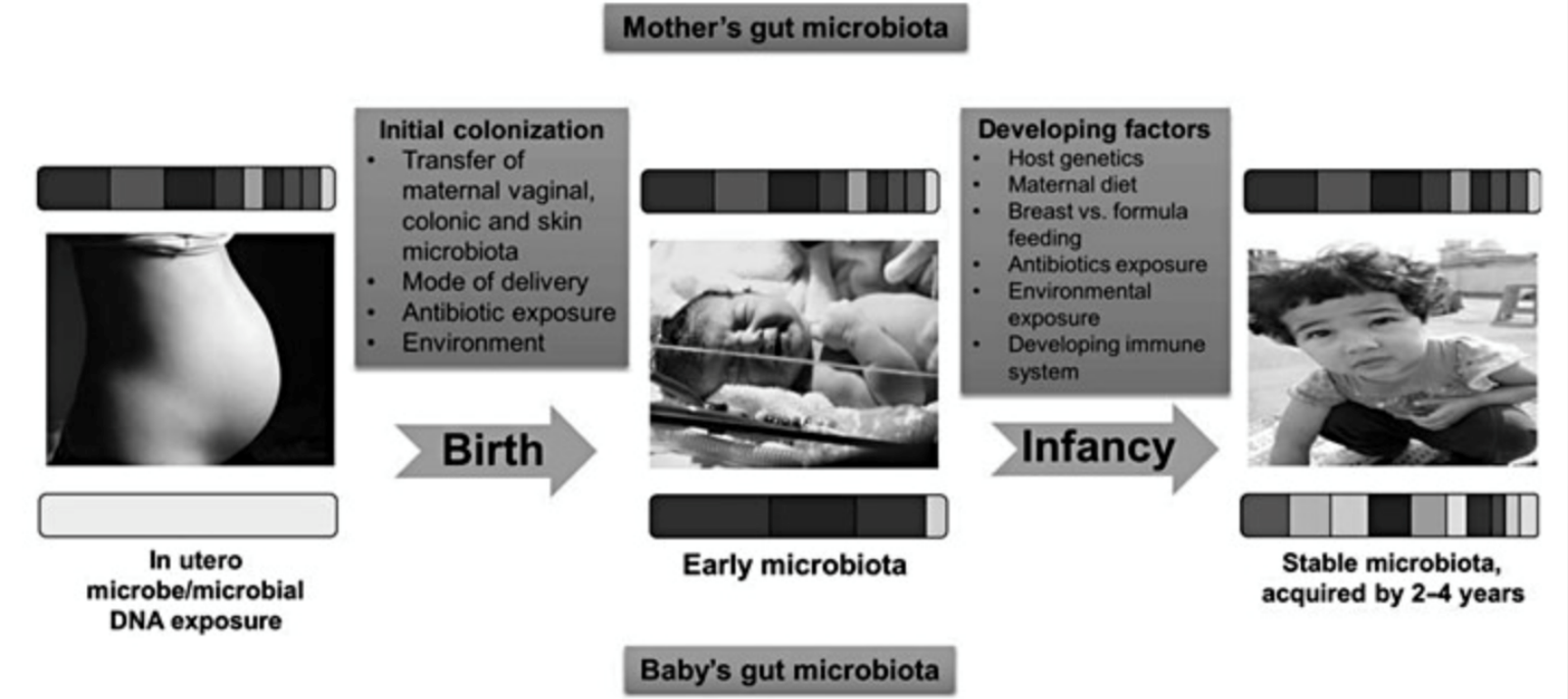
Importance of microbial biodiversity

- Greater microbial diversity associated with body's ability to deal with stressors, such as opportunistic pathogens or dietary perturbations
- Individuals with disease more likely to have alterations in gut microbiome compared to healthy controls
- Associations between reduced microbial diversity and illness

Diversity begins at birth…

- Bacterial colonization during birth plays a major role in the formation of gut microbiota.
- Factors affecting microbiota include:
  - Premature birth,
  - Caesarean section versus vaginal birth
  - Breast milk versus commercial formula
- Infants born vaginally were colonized similar to their mother's vaginal microbiota,
  - Lactobacillus, Prevotella, or Sneathia spp,
- Caesarean section born infants colonized by bacteria found on the skin surface
  - Staphylococcus, Corynebacterium, and Propionibacterium species.

Development of Neonate Microbiota



http://www.karger.com/Article/FullText/354902

J Allergy Clin Immunol. 2011 Sep;128(3):646-52.e1-5. doi: 10.1016/j.jaci.2011.04.060. Epub 2011 Jul 22.

Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age.

Bisgaard H[1], Li N, Bonnelykke K, Chawes BL, Skov T, Paludan-Müller G, Stokholm J, Smith B, Krogfelt KA.

Author information

Abstract

BACKGROUND: Changes in the human microbiome have been suggested as a risk factor for a number of lifestyle-related disorders, such as atopic diseases, possibly through a modifying influence on immune maturation in infancy.

OBJECTIVES: We aimed to explore the association between neonatal fecal flora and the development of atopic disorders until age 6 years, hypothesizing that the diversity of the intestinal microbiota influences disease development.

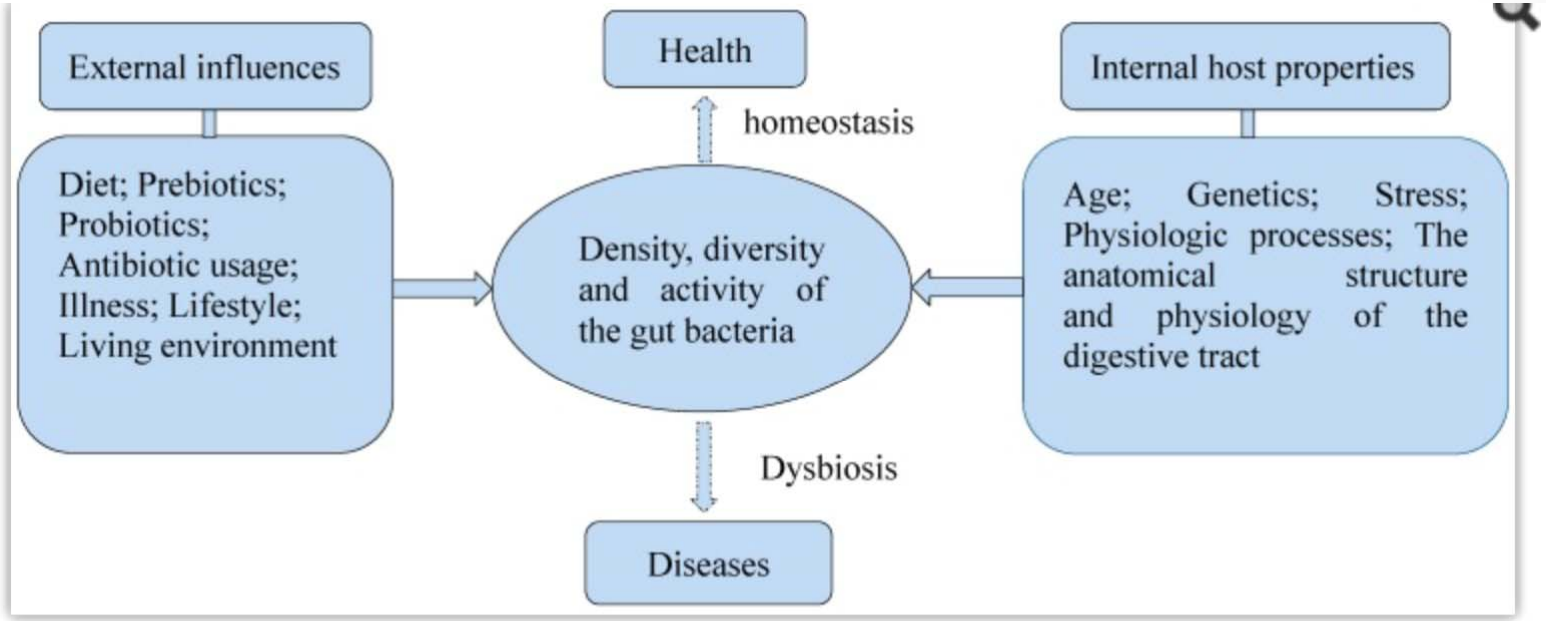
METHODS: We studied the intestinal microbiota in infants in the Copenhagen Prospective Study on Asthma in Childhood, a clinical study of a birth cohort of 411 high-risk children followed for 6 years by clinical assessments at 6-month intervals, as well as at acute symptom exacerbations. Bacterial flora was analyzed at 1 and 12 months of age by using molecular techniques based on 16S rRNA PCR combined with denaturing gradient gel electrophoresis, as well as conventional culturing. The main outcome measures were the development of allergic sensitization (skin test and specific serum IgE), allergic rhinitis, peripheral blood eosinophil counts, asthma, and atopic dermatitis during the first 6 years of life.

RESULTS: We found that bacterial diversity in the early intestinal flora 1 and 12 months after birth was inversely associated with the risk of allergic sensitization (serum specific IgE P = .003; skin prick test P = .017), peripheral blood eosinophils (P = .034), and allergic rhinitis (P = .007). There was no association with the development of asthma or atopic dermatitis.

CONCLUSI ...hinitis, and periphe ...hat an imbalance ir

Reduced bacterial diversity of the infant's intestinal flora was associated with increased risk of allergic sensitization, allergic rhinitis, and peripheral blood eosinophilia

Many factors influence diversity…



Several factors influence the density, diversity, and activity of the gut

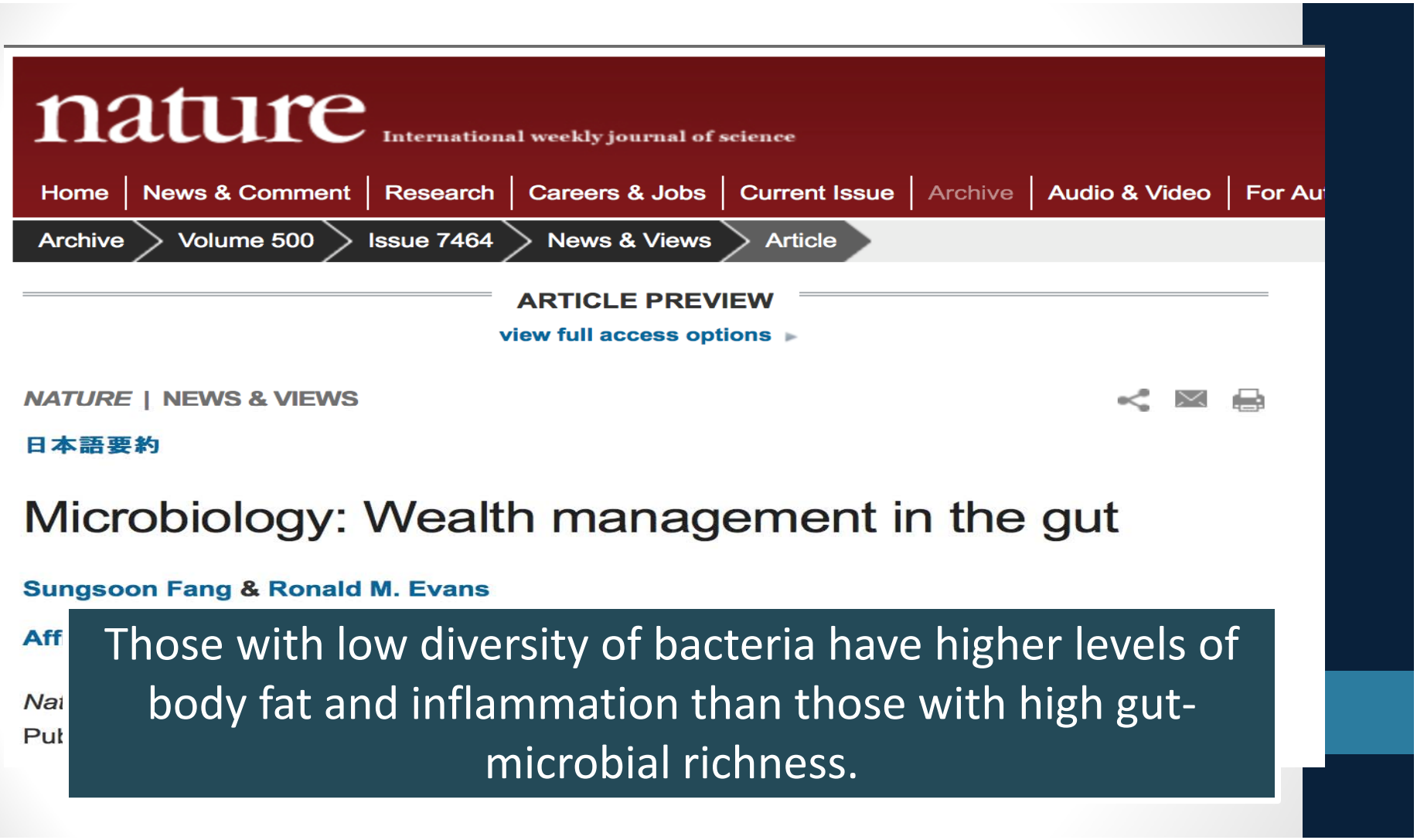
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425030/#!po=16.6667

Examples of Dysbiosis in Disease

Ulcerative colitis	Mice	↓*Lactobacilli* ↑*Clostridiales*	Colonic	[56]
	Mice	↑*E. coli*	Colonic	[57]
	Humans	↓*R.* hominis ↓*F. prausnitzii*	Fecal	[58]
Crohn's disease	Humans	↓*Bacteroides* ↓*Bifidobacteria*	Fecal	[61]
Obesity	Mice	↓*Bacteroides* ↑*Firmicutes* ↑*Proteobacteria*	Fecal	[67]
Type-1diabetes	Humans (children)	↓*Lactobacillus* ↓*Bifidobacterium* ↓*Blautia coccoides* ↓*Eubacterium rectal* ↓*Prevotella* ↑*Clostridium* ↑*Bacteroides* ↑*Veillonella*	Fecal	[87]
Type-2 diabetes	Humans	↓*Clostridia* ↓*Firmicutes* ↑*Betaproteobacteria*	Fecal	[88]

Examples of Dysbiosis in Disease

Nonalcoholic steatohepatitis	Rats	↑*E. coli*	Proximal small intestine	[92]
Colorectal cancer	Humans	↓*Prevotella* ↓*Ruminococcus* spp. ↓*Pseudobutyrivibrio ruminis* ↑*Acidaminobacter*, ↑*Phascolarctobacterium*, ↑*Citrobacter farmer* ↑*Akkermansia muciniphila*	Fecal	[104]
HIV	Humans	↑*Erysipelotrichaceae* ↑*Proteobacteria* ↑*Enterobacteriaceae* ↓*Clostridia* ↓*Bacteroidia*	Proctosigmoid	[112]
HIV	Humans	↓*Lactobacilli* ↓*Bifidobacteria* ↑*Candida albicans* ↑*Pseudomonas aeruginosa*	Fecal	[113,114]
Autistic	Humans (children)	↑*Bacteroides vulgates* ↑*Desulfovibrio* ↓*Firmicutes* ↓*Actinobacteria*	Fecal	[122]
Rheumatic arthritis	Humans	↓*Bifidobacteria* ↓*Bacteroides fragilis*	Fecal	[127]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NATURE | NEWS & VIEWS
日本語要約
Microbiology: Wealth management in the gut
Sungsoon Fang & Ronald M. Evans
Those with low diversity of bacteria have higher levels of body fat and inflammation than those with high gut-microbial richness.

Richness of human gut microbiome correlates with metabolic markers

Emmanuelle Le Chatelier, Trine Nielsen, Junjie Qin, Edi Prifti, Falk Hildebrand, Gwen Falony, Mathieu Almeida, Manimozhiyan Arumugam, Jean-Michel Batto, Sean Kennedy, Pierre Leonard, Junhua Li, Kristoffer Burgdorf, Niels Grarup, Torben Jørgensen, Ivan Brandslund, Henrik Bjørn Nielsen, Agnieszka S. Juncker, Marcelo Bertalan, Florence Levenez, Nicolas Pons, Simon Rasmussen, Shinichi Sunagawa, Julien Tap, Sebastian Tims + ***et al.***

Affiliations | **Contributions** | **Corresponding authors**

Nature **500**, 541–546 (29 August 2013) | doi:10.1038/nature12506
Received 10 April 2012 | Accepted 26 July 2013 | Published online 28 August 2013

Le Chatelier Study

- Study participants (n=292) characterized into two groups by the number of gut microbial genes (gut bacterial richness) with an average 40% difference between low gene count (LGC) individuals and high gene count (HCG) individuals.
- **Individuals with low bacterial gene richness (23% of study population) characterized by increase in adiposity, insulin resistance, and dyslipidaemia.**
- Low-bacterial-richness individuals showed a more pronounced inflammatory phenotype when compared with high-bacterial-richness individuals.

Dietary intervention impact on gut microbial gene richness

Aurélie Cotillard, Sean P. Kennedy, Ling Chun Kong, Edi Prifti, Nicolas Pons, Emmanuelle Le Chatelier, Mathieu Almeida, Benoit Quinquis, Florence Levenez, Nathalie Galleron, Sophie Gougis, Salwa Rizkalla, Jean-Michel Batto, Pierre Renault, ANR MicroObes consortium, Joel Doré, Jean-Daniel Zucker, Karine Clément, Stanislav Dusko Ehrlich, Hervé Blottière, Marion Leclerc, Catherine Juste, Tomas de Wouters, Patricia Lepage, Charlene Fouqueray + *et al.*

Affiliations | Contributions | Corresponding authors

Natur
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Consumption of high-fiber foods, such as fruit and vegetables, led to increase in bacterial richness and improved clinical symptoms associated with obesity.

Support previous work linking diet to the composition of gut microbe populations, and suggests that a permanent change might be achieved by appropriate diet

NATURE | LETTER

Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David, Corinne F. Maurice, Rachel N. Carmody, David B. Gootenberg, Julie E. Button, Benjamin E. Wolfe, Alisha V. Ling, A. Sloan Devlin, Yug Varma, Michael A. Fischbach, Sudha B. Biddinger, Rachel J. Dutton & Peter J. Turnbaugh

Affiliations | Contributions | Corresponding author

Nature (2013) | doi:10.1038/nature12820

Received 18

Short-term consumption of diets composed entirely of animal or plant products alters microbial community structure and overwhelms inter-individual differences in microbial gene expression

http://www.nature.com/nature/journal/vaop/ncurrent/full/nature12820.html

Science translational medicine
Author Manuscript NIH Public Access

The Effect of Diet on the Human Gut Microbiome: A Metagenomic Analysis in Humanized Gnotobiotic Mice

Peter J. Turnbaugh, Vanessa K. Ridaura, [...], and Jeffrey I. Gordon

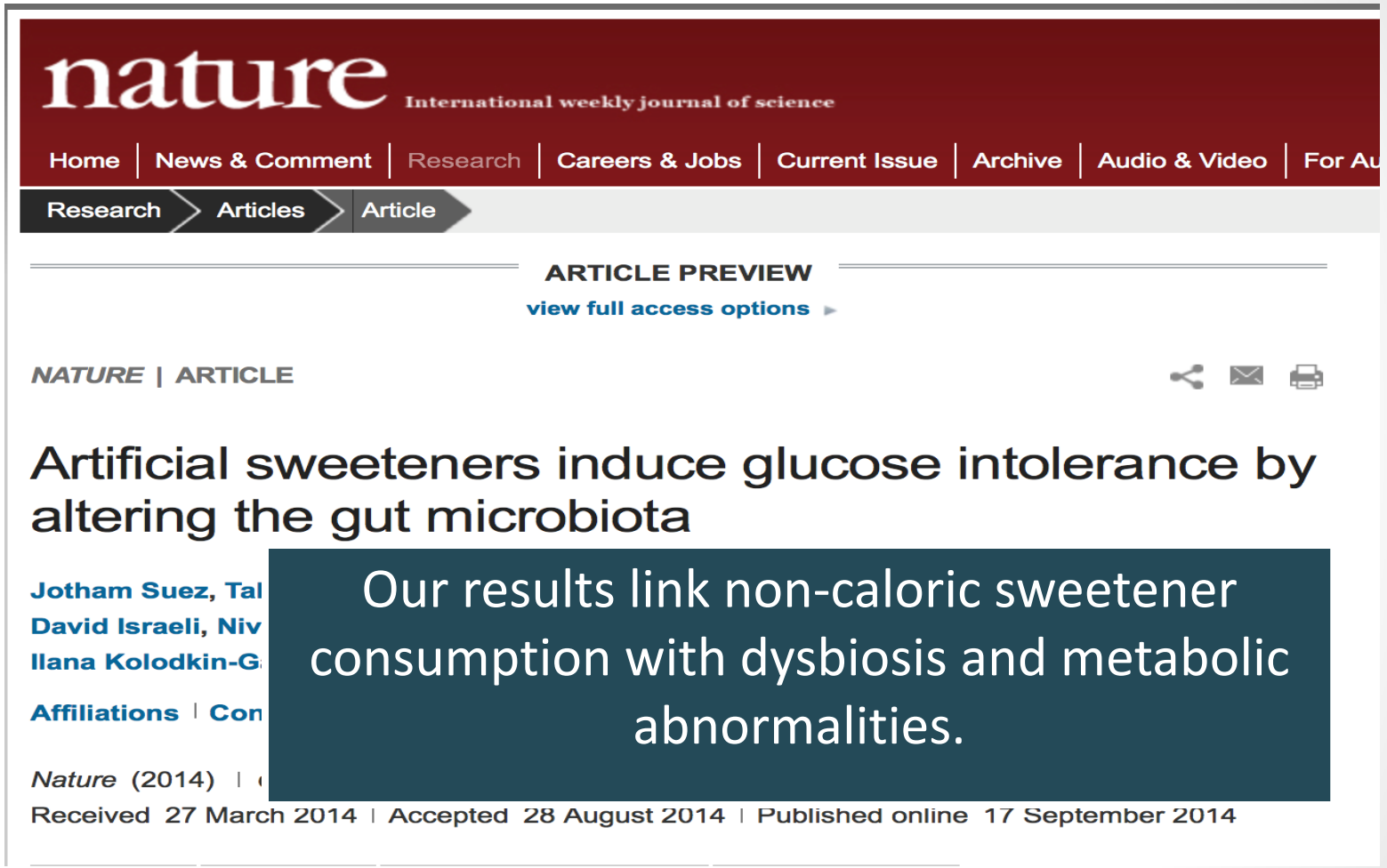
Additional article informatio

Going from a low fat, plant polysaccharide rich diet to a high fat, high sugar Western diet changed the microbiota in one day in GF mice

Abstract

Diet and nutritional sta
determinants of human health. The nutritional value of food is influenced in part by a person's gut microbial community (microbiota) and its component genes (microbiome). Unraveling the interrelationships between diet, the structure and operations of the gut microbiota, and nutrient and energy harvest is confounded by variations in human environmental exposures, microbial ecology and

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2894525/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NATURE | ARTICLE
Artificial sweeteners induce glucose intolerance by altering the gut microbiota
Jotham Suez, Tal
David Israeli, Niv
Ilana Kolodkin-G
Affiliations | Con
Nature (2014) |
Received 27 March 2014 | Accepted 28 August 2014 | Published online 17 September 2014
Our results link non-caloric sweetener consumption with dysbiosis and metabolic abnormalities.

Coffee Consumption Affects Microbiome

on gut microbiota and serum metabolomics☆☆☆

Theresa E. Cowan, Marie S.A. Palmnäs, Jaeun Yang, Marc R. Bomhof, Kendra L. Ardell, Raylene A. Reimer, Hans J. Vogel, Jane Shearer

Received 15 October 2013; received in revised form 19 December 2013; accepted 23 December 2013. published online 03 February 2014.

Abstract | Full Text | PDF | Images | References | Supplemental Materials

Abstract

Epidemic
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Coffee consumption attenuated the increase in Firmicutes to Bacteroidetes ratio and normally associated with high-fat feeding ....

Coffee increased levels of short-chain fatty acids while lowering levels of branched-chain amino acids.

J Proteome Res. 2012 Oct 5;11(10):4781-90. doi: 10.1021/pr300581s. Epub 2012 Sep 6.

Metabolomics view on gut microbiome modulation by polyphenol-rich foods.

Moco S[1], Martin FP, Rezzi S.

Author information

Abstract

Health is influenced by genetic, lifestyle, and diet determinants; therefore, nutrition plays an essential role in health management. Still, the substantiation of nutritional health benefits is challenged by the intrinsic macro- and micronutrient complexity of foods and individual responses. Evidence of healthy effects of food requires new strategies not only to stratify populations according to their metabolic requirements but also to predict and measure individual responses to dietary intakes. The influence of the gut microbiome and its interaction with the host is pivotal to understand nutrition and metabolism. Thus, the modulation of the gut microbiome composition by alteration of food habits has potentialities in health improvement or even disease prevention. Dietary polyphenols are naturally occurring constituents in vegetables and fruits, including coffee and cocoa. They are commonly associated to health benefits, although mechanistic evidence in vivo is not yet fully understood. Polyphenols are extensively metabolized by

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PM

Modulation of the gut microbiome by alteration of food habits has potential for disease prevention. Dietary polyphenols naturally occurring in coffee and cocoa… are extensively metabolized by gut bacteria into anti-inflammatory end-products

Published on March 27th, 2014 | *By: April Gocha, PhD* 0

Thank your microbiome—gut microbes are behind chocolate's health benefits

The good microbes, such as *Bifidobacterium* and lactic acid bacteria, feast on chocolate. When you eat dark chocolate, they grow and ferment it, producing compounds that are anti-inflammatory…

http://www.acs.org/content/acs/en/pressroom/newsreleases/2014/march/the-precise-reason-for-the-health-benefits-of-dark-chocolate-mystery-solved.html

Current Cardiology Reports
Springer

Far from the Eyes, Close to the Heart: Dysbiosis of Gut Microbiota and Cardiovascular Consequences

Ma

Adc

Dysbiosis associated with multiple diseases, including type 2 diabetes and obesity, each distinguishable by a unique gut microbiota profile.

Microbiota typically found in the blood of diabetic patients also has been observed in atherosclerotic plaque.

http://www.ncbi.nlm.nih.gov/pubmed/26699388

Practical Application

- Gut microbiota important player in atherogenesis
- Metabolism by the intestinal flora linked to deleterious association between egg yolk consumption (a major dietary source of choline) and the development of atherosclerotic plaque
- Mediterranean style diet recommended
  - lean protein (fish, poultry), nuts, vegetables and fruit, together with regular physical activity, to maintain cardiovascular health.
- Targeting the gut microbiota or related metabolic pathways, may offer potential therapeutic benefit.

But there are still controversies…

- Fish is beneficial for heart disease risk despite containing TMAOs
- L-carnitine may ameliorate metabolic diseases by increasing insulin sensitivity of the skeletal muscle and may reduce ischemic heart disease.
- Complex ecology of the gut microbiota and its metabolic behavior must be considered

Pre and Probiotics are Essential

Proc Nutr Soc. 2014 May;73(2):172-85. doi: 10.1017/S0029665113003911. Epub 2014 Feb 4.

'The way to a man's heart is through his gut microbiota'--dietary pro- and prebiotics for the management of cardiovascular risk.

Tuohy KM[1], Fava F[1], Viola R[1].

Author information

Abstract

Open/close author information list

The human gut microbiota has been identified as a possible novel CVD risk factor. This review aims to summarise recent insights connecting human gut microbiome activities with CVD and how such activities may be modulated by diet. Aberrant gut microbiota profiles have been associated with obesity, type 1 and type 2 diabetes and non-alcoholic fatty liver disease. Transfer of microbiota from obese animals induces metabolic disease and obesity

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Diet, especially high intake of fermentable fiber and plant polyphenols, appears to regulate microbial activities within the gut.

Supports increased consumption of whole-plant foods and providing the scientific rationale for the design of efficacious prebiotics

http://www.ncbi.nlm.nih.gov/pubmed/24495527

The FASEB Journal
The Journal of the Federation of American Societies for Experimental Biology

Intestinal microbiota determine severity of myocardial infarction in rats

Vy

Lactobacillus plantarum 299v (Goodbelly) resulted in decreased circulating leptin levels by 41%, smaller myocardial infarcts (29% reduction), and greater recovery of postischemic mechanical function (23%). Pretreatment with leptin (0.12 µg/kg i.v.) abolished cardioprotection produced by Goodbelly.

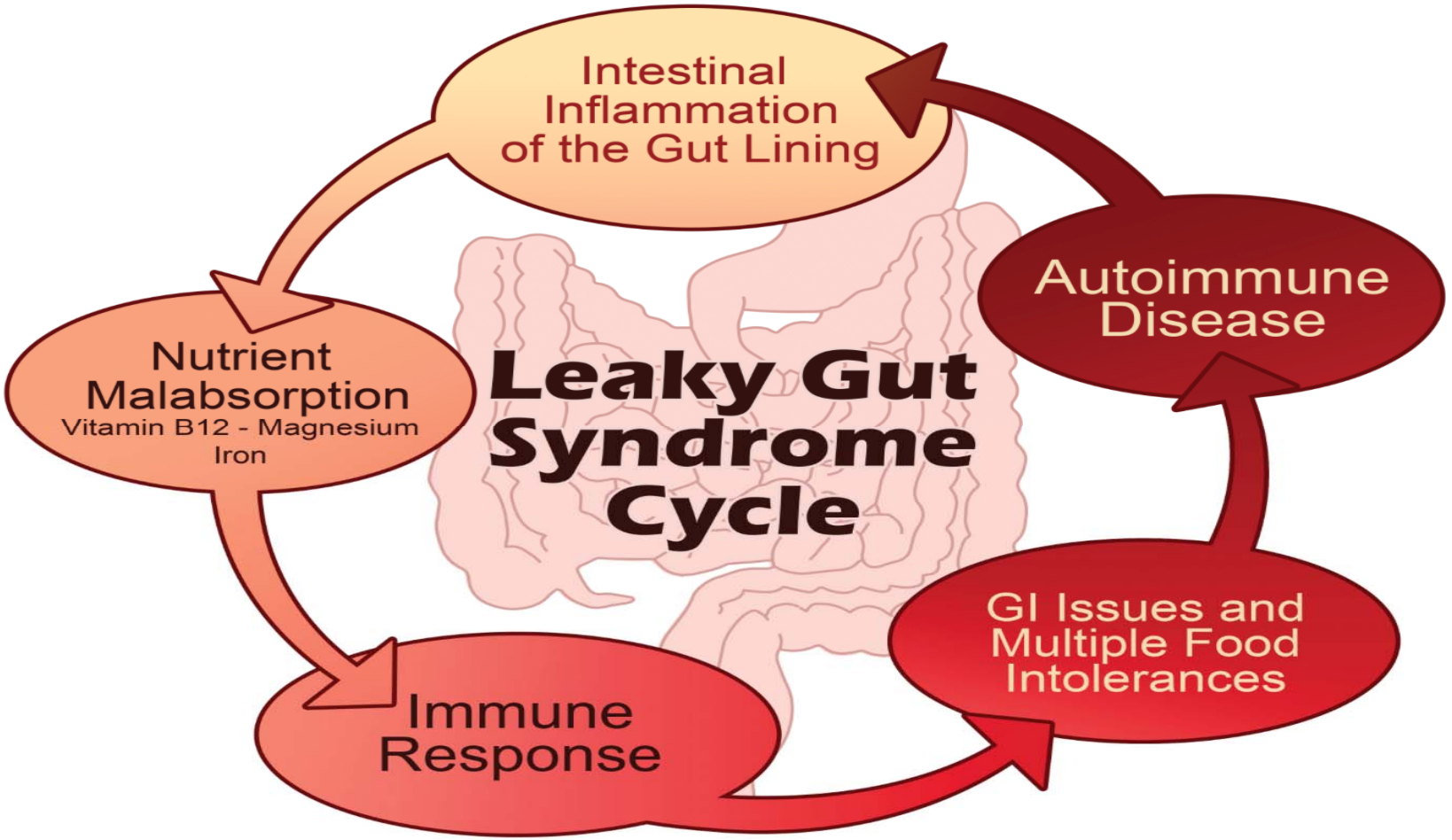
http://www.ncbi.nlm.nih.gov/pubmed/22247331

Lipopolysaccharides (LPS) are endotoxins

THE LPS STORY

Lipopolysaccharide

- Lipopolysaccharides (LPS) are large molecules found in gram-negative bacteria. They are endotoxins, and if absorbed, elicit a strong immune response.
- The detection of antibodies against LPS reveals macromolecule-sized endotoxin infiltration through the intestinal barrier into the systemic circulation.
- Intestinal permeability can cause systemic inflammation through translocation of LPS


Intestinal Inflammation of the Gut Lining
Autoimmune Disease
Nutrient Malabsorption
Vitamin B12 - Magnesium
Iron
Leaky Gut Syndrome Cycle
GI Issues and Multiple Food Intolerances
Immune Response

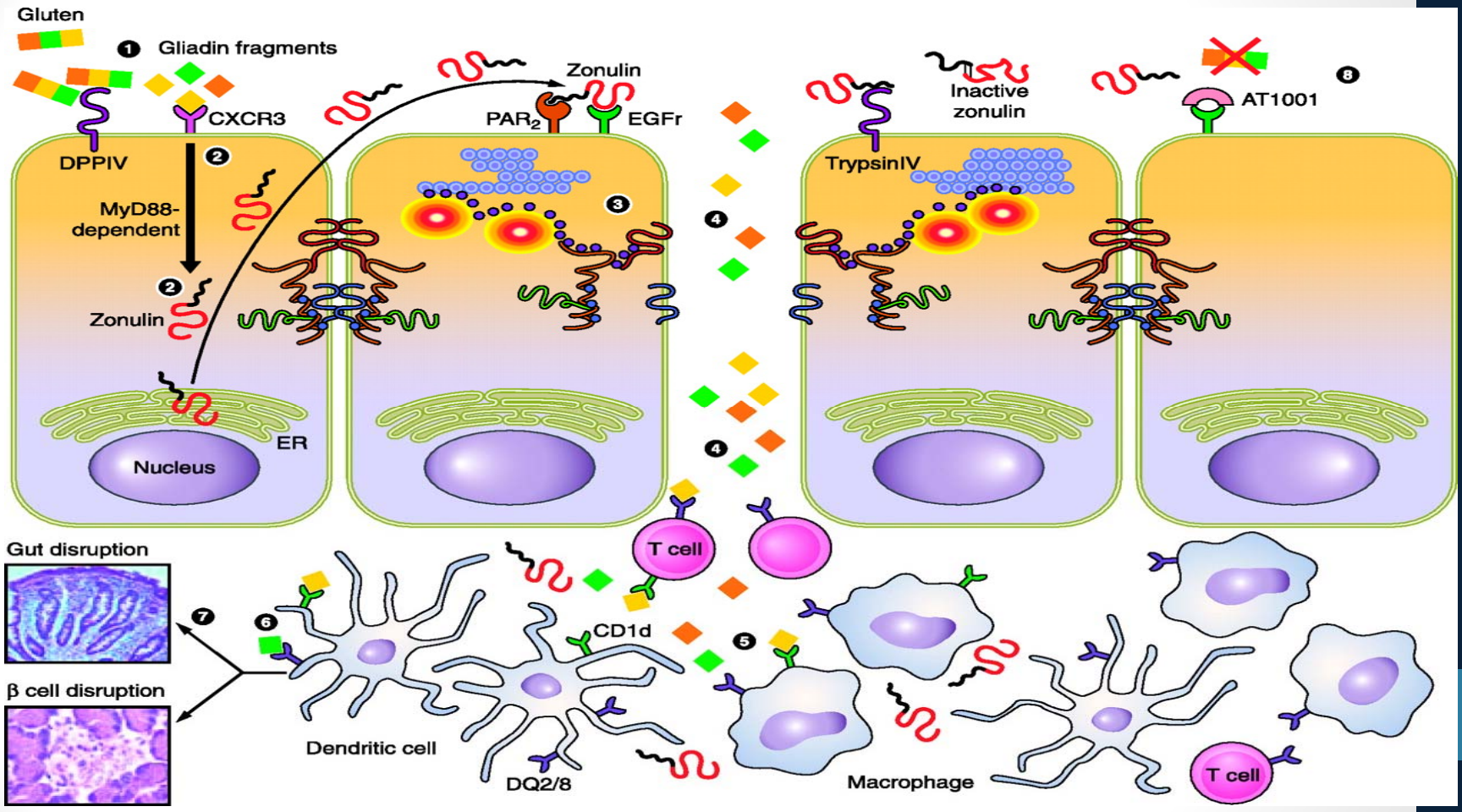
Dr. Josh Axe

Occludin

- Occludin is part of the main component of proteins holding together the tight junctions.
- The detection of antibodies to occludin indicates that the tight junctions are breaking down.
- This is a measure of a mechanism involved in damaging the intestinal barrier membrane.

Zonulin

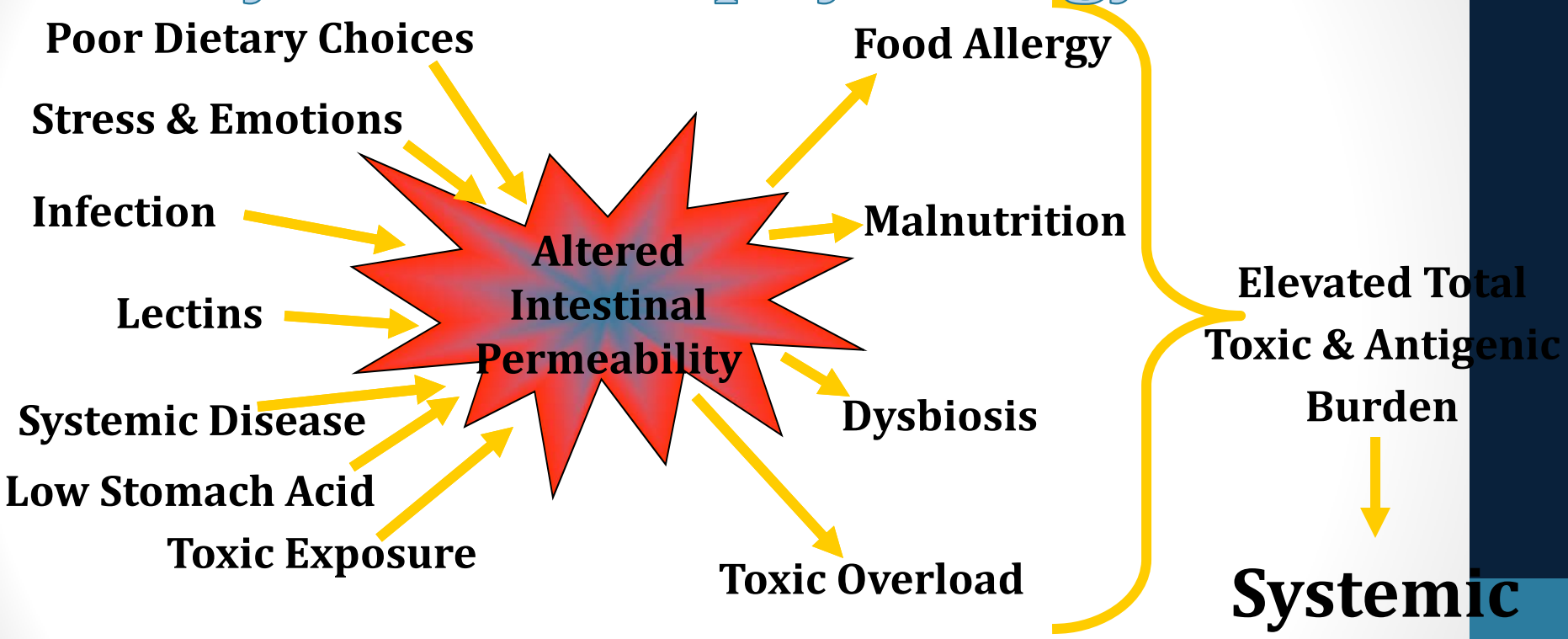
- Zonulin, a protein, regulates the permeability of the intestine.
- The detection of antibodies against zonulin indicates that the normal regulation of tight junctions is compromised.
- Clue to presence of an ongoing mechanism involved in damaging the intestinal barrier.

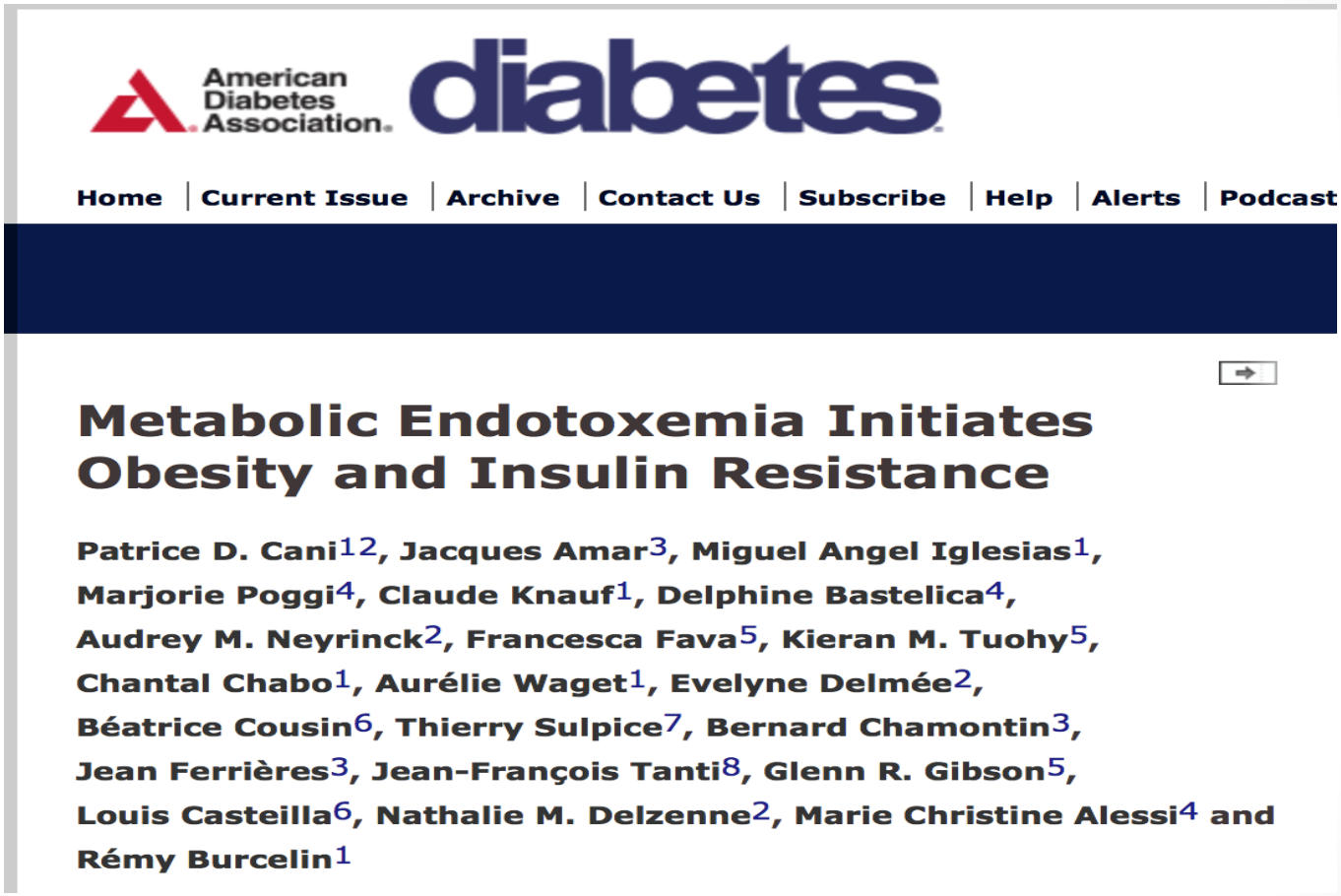

Gluten
1 Gliadin fragments
CXCR3
DPPIV
2
MyD88-dependent
2
Zonulin
ER
Nucleus
Zonulin
PAR2
EGFr
3
4
4
Inactive zonulin
TrypsinIV
8
AT1001
Gut disruption
β cell disruption
7
6
T cell
CD1d
5
Dendritic cell
DQ2/8
Macrophage
T cell

Causes of Increased Intestinal Permeability

- Inflammatory Bowel disease
- NSAID therapy
- Small Intestinal Bacterial Overgrowth (SIBO)
- Celiac disease
- Protozoal infections
- Toxic Exposure
- Food allergy
- Chronic Alcoholism
- Diarrhea
- Strenuous exercise
- Increasing age
- Nutritional Depletions

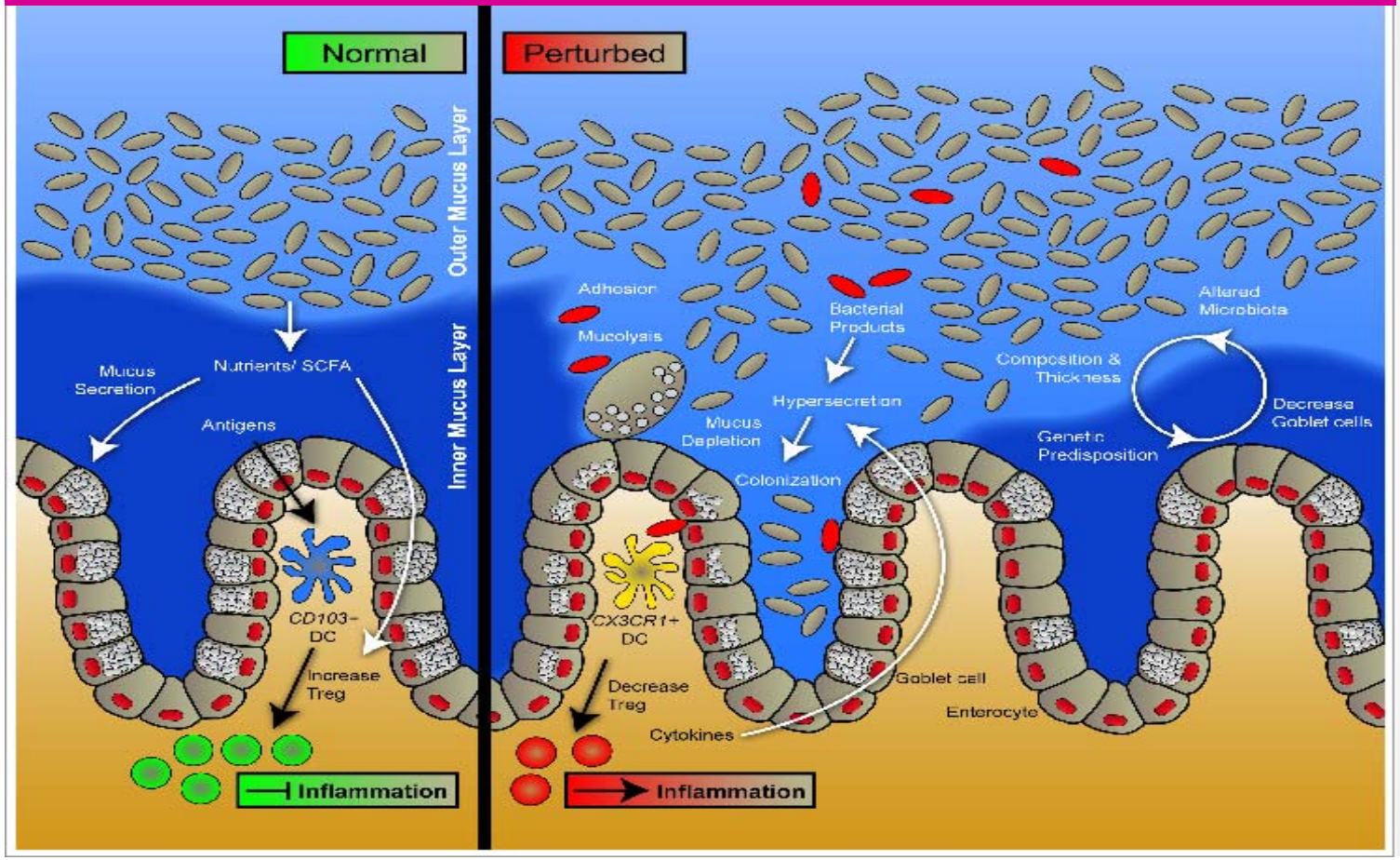
Leaky Gut Pathophysiology





http://diabetes.diabetesjournals.org/content/56/7/1761.long

MICROBIAL-IMMUNE-METABOLIC AXIS OF COMMUNICATION



Tissue Barriers. 2015; 3(1-2): e982426. Published online 2015 Jan 15. doi: 10.4161/21688370.2014.982426

Metabolic Endotoxemia

- Diabetes and characterized by insulin resistance and a low-grade inflammation.
- LPS is common trigger to of insulin resistance, obesity, and diabetes
- Endotoxemia increased during the fed and decreased during fasted state
- LPS concentration 2-3X threshold defines metabolic endotoxemia.
- High-fat diet increased the proportion of an LPS-containing microbiota in the gut.

Metabolic Endotoxemia

- Metabolic endotoxemia was induced for 4 weeks in mice by continuous infusion of LPS
  - Increased weight gain
  - Increased markers of inflammation
  - Increased Triglyceride production by liver
  - Increase insulin resistance
- Metabolic endotoxemia dysregulates the inflammatory tone and triggers body weight gain and diabetes.
- Lowering plasma LPS concentration could be a potent strategy for the control of metabolic diseases.

Select Interventions to reduce LPS inflammation

- Physical Exercise
- Quercetin
- Curcumin
- Sulphorophane
- Resveritrol
- EPA DHA
- Bifidobacteria
- MegaSpore

Physical Exercise Reduces Circulating Lipopolysaccharide and TLR4 Activation and Improves Insulin Signaling in Tissues of DIO Rats

Alexandre G. Oliveira, Bruno M. Carvalho, Natália Tobar, Eduardo R. Ropelle, José R. Pauli, Renata A. Bagarolli, Dioze Guadagnini, José B.C. Carvalheira and Mario J.A. Saad

+ Author Affiliations

Correspondi

Physical exercise induces an important suppression in the TLR4 signaling pathway in the liver, muscle, and adipose tissue, reduces LPS serum levels, and improves insulin signaling and sensitivity.

Abstract

OBJECTIVE

with a chro

(TLR4) plays an important role in the link among insulin resistance, inflammation, and obesity. The current study aimed to analyze the effect of exercise on TLR4 expression and activation in obese rats and its consequences on insulin sensitivity and signaling.

http://diabetes.diabetesjournals.org/content/60/3/784.full

Quercetin Reduces Inflammatory Responses in LPS-Stimulated Cardiomyoblasts

Cristina Angeloni and Silvana Hrelia

Department of Biochemistry "G. Moruzzi", University of Bologna, Via Irnerio 48, 40126 Bologna, Italy

Received 10 February 2012; Accepted 22 March 2012

Academic Editor: Tullia Maraldi

Abstract

Flavonoids posse
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caspase 3 and caspase 3 activity. Q also inhibited the LPS-induced phosphorylation of the stress-activated protein kinases (JNK/SAPK) and p38 MAP kinase that are involved in the inhibition of cell growth as well as the induction of apoptosis. In conclusion, these results suggest that Q might serve as a valuable protective agent in cardiovascular inflammatory diseases.

Quercetin, a naturally occurring flavonoid, has been shown to downregulate inflammatory responses and provide cardioprotection by inhibiting the LPS-induced phosphorylation of the stress-activated protein kinases (JNK/SAPK) and p38 MAP kinase

http://www.hindawi.com/journals/omcl/2012/837104/

Research Article

Curcumin Attenuation of Lipopolysaccharide Induced Cardiac Hypertrophy in Rodents

Rupak Chowdhury,[1] Ramadevi Nimmanapalli,[2] Thomas Graham,[1] and Gopal Reddy[1]

[1]College of Veterinary Medicine, Nursing and Allied Health, Tuskegee University, Tuskegee, AL 36088, USA
[2]Philadelphia College of Osteopathic Medicine, School of Pharmacy, Suwanee, GA, USA

Received 11 July 2013; Accepted 4 September 2013

Academic Editors: B. Kim and D. Szukiewicz

We can conclude from our study that curcumin attenuated LPS induced cardiac hypertrophy in vivo.

http://www.hindawi.com/journals/isrn/2013/539305/

Int Immunopharmacol. 2007 Dec 15;7(13):1776-83. Epub 2007 Oct 5.

Sulforaphane suppresses lipopolysaccharide-induced cyclooxygenase-2 (COX-2) expression through the modulation of multiple targets in COX-2 gene promoter.

Woo KJ[1], Kwon TK.

Author information

Abstract

Sulforaphane is a natural, biologically active compound extracted from cruciferous vegetables such as broccoli and cabbage. It possesses potent anti-inflammation and anti-cancer properties. The mechanism by which sulforaphane suppresses COX-2 expression remains poorly understood. In the present report, we investigated the effect of sulforaphane on the expression of COX-2 in lipopolysaccharide (LPS)-activated Raw 264.7 cells. Sulforaphane significantly suppressed the LPS-induced COX-2 protein and mRNA expression in a dose-dependent manner. The ability of sulforaphane to suppress the expression of the COX-2 was investigated using luciferase reporters controlled by various cis-elements in COX-2 promoter region. Electrophoretic mobility shift assay (EMSA) verified that NF-kappaB, C/EBP, CREB and AP-1 were identified as responsible for the sulforaphane-mediated COX-2 down-regulation. In addition, we demonstrated the signal transduction pathway of mitogen-activated protein kinase (MAP kinase) in
induced COX-2 p
regulation. These

Sulforaphane is a natural, biologically active compound extracted from cruciferous vegetables such as broccoli and cabbage. It possesses potent anti-inflammation and anti-cancer properties. Sulforaphane significantly suppressed the LPS-induced COX-2 protein and mRNA expression in a dose-dependent manner.

http://www.ncbi.nlm.nih.gov/pubmed/17996688

Int J Mol Med. 2016 Jan;37(1):182-8. doi: 10.3892/ijmm.2015.2396. Epub 2015 Oct 27.

Sulforaphane exerts anti-inflammatory effects against lipopolysaccharide-induced acute lung injury in mice through the Nrf2/ARE pathway.

Qi T[1], Xu F[2], Yan X[1], Li S[1], Li H[1].

Author information

Abstract

Sulforaphane (1-isothiocyanate-4-methyl sulfonyl butane) is a plant extract (obtained from cruciferous vegetables, such as broccoli and cabbage) and is known to exert anticancer, antioxidant and anti-inflammatory effects. It stimulates the generation of human or animal cells, which is beneficial to the body. The aim of the current study was to determine whether sulforaphane protects against lipopolysaccharide (LPS)-induced acute lung injury (ALI) through its anti-inflammatory effects, and to investigate the signaling pathways involved. For this purpose, male BALB/c mice were treated with sulforaphane (50 mg/kg) and 3 days later, ALI was induced by the administration of LPS (5 mg/kg) and we thus established the model of ALI. Our results revealed that sulforaphane significantly decreased lactate dehydrogenase (LDH) activity (as shown by LDH assay), the wet-to-dry ratio of the lungs and the serum levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (measured by ELISA), as well as nuclear factor-κB protein expression in mice with LPS-induced ALI. Moreover, treatment with sulforaphane significantly inhibited prostaglandin E2 (PGE2) production, and cyclooxygenase-2 (COX-2), matrix metalloproteinase-9 (MMP-9) protein expression (as shown by western blot analysis), as well as inducible nitric oxide synthase (iNOS) activity in mice with LPS-induced ALI. Lastly, we noted that pre-treatment with sulforaphane activated the nuclear factor-E2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway in the mice with LPS-induced ALI. These findings demonstrate that sulforaphane exerts protective effects against LPS-induced ALI through the Nrf2/ARE pathway. Thus, sulforaphane may be a potential a candidate for use in the treatment of ALI.

Pre-treatment with sulforaphane activated the nuclear factor-E2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway in the mice with LPS-induced injury

http://www.ncbi.nlm.nih.gov/pubmed/26531002

The FASEB Journal • FJ Express

Resveratrol, an extract of red wine, inhibits lipopolysaccharide induced airway neutrophilia and inflammatory mediators through an NF-κB-independent mechanism

M. A. Birrell, K. McCluskie, S. Wong, L. E. Donnelly,* P. J. Barnes,* and M. G. Belvisi[1]

Respiratory Pharmacology, *Thoracic Medicine, National Heart and Lung Institute, Imperial College London, London, UK

To read the full text of this article, go to http://www.fasebj.org/cgi/doi/10.1096/fj.04-2691fje; doi: 10.1096/fj.04-2691fje

Kidney Int. 2005 Mar;67(3):867-74.

EPA and DHA reduce LPS-induced inflammation responses in HK-2 cells: evidence for a PPAR-gamma-dependent mechanism.

Li H[1], Ruan XZ, Powis SH, Fernando R, Mon WY, Wheeler DC, Moorhead JF, Varghese Z.

Author information

Abstract

BACKGROUND: Recent studies have shown that fish oil, containing omega-3 polyunsaturated fatty acids (omega-3 PUFAs) eicosapentaenoic acid (EPA) (C20:5 omega 3), and docosahexaenoic acid (DHA) (C22:6 omega 3) retard the progression of renal disease, especially in IgA nephropathy (IgAN). Despite increasing knowledge of the beneficial effects of fish oils, little is known about the mechanisms of action of omega-3 PUFAs. It has been reported that activation of peroxisome proliferator-activated receptors (PPARs) inhibits production of proinflammatory cytokines. Both EPA and DHA have been shown to activate PPARs. The aim of this study was to examine if omega-3 PUFAs have anti-inflammatory effects via activation of PPARs in human renal tubular cells.

METHODS: An immortalized human proximal tubular cell line [human kidney 2 (HK-2) cells] was used in all experiments. Conditioned media was collected from c from the above cells for ctor activation assay

RESULTS: Both uclear factor-kappaB (-gamma mRNA and protein activity (two- to threefold) in HK-2 cells. A dose of 100 micromol/L bisphenol A diglycidyl ether (BADGE) abolished the PPAR-gamma activation induced by both EPA and DHA and removed the inhibitory effect of EPA and DHA on LPS-induced NF-kappaB activation in HK-2 cells. Overexpression of PPAR-gamma further inhibited NF-kappaB activation compared to the control cells in the presence of EPA and DHA.

CONCLUSION: Our data demonstrate that both EPA and DHA down-regulate LPS-induced activation of NF-kappaB via a PPAR-gamma-dependent pathway in HK-2 cells. These results suggest that PPAR-gamma activation by EPA and DHA may be one of the underlying mechanisms for the beneficial effects of fish oil.

Our data demonstrate that both EPA and DHA down-regulate LPS-induced activation of NF-kappaB

http://www.ncbi.nlm.nih.gov/pubmed/15698426

World Journal of Gastroenterology

World J Gastroenterol. 2006 Jun 21; 12(23): 3729–3735.
Published online 2006 Jun 21. doi: 10.3748/wjg.v12.i23.3729

PMCID: PMC4087466

Anti-inflammatory effects of bifidobacteria by inhibition of LPS-induced NF-κB activation

Christi

Author

Strains of bifidobacteria are effective in inhibiting LPS-induced inflammation….
And could be intervention in chronic intestinal inflammation.

Byproducts associated with the fermentation of the prebiotics by Bifidobacterium, such as short-chain fatty acids (butyrate, propionate and lactate) positively effect gut barrier (reduce leaking) and improve tight junctions between gut epithelial cells.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4087466/

Bifidobacter may reduce endotoxemia

Inflammatory bowel disease

Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability

OPEN ACCESS

P D Ca
D Nasl
+ Au

Obese and diabetic mice display enhanced intestinal permeability and metabolic endotoxaemia.
Increase of *Bifidobacterium* spp. reduces the impact of high-fat diet-induced metabolic endotoxaemia and inflammatory disorders.

Dr P D Cani, UCL, Unit PMNT-7369, Av E Mounier, 73/69, B-1200 Brussels, Belgium;
patrice.cani@uclouvain.be; or Professor NM Delzenne, UCL, Unit PMNT-7369, Av R Mounier,

http://gut.bmj.com/content/58/8/1091

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Link to Publisher's site

Sports (Basel). 2018 Mar; 6(1): 12.
Published online 2018 Feb 6. doi: 10.3390/sports6010012

PMCID: PMC5969196
PMID: 29910316

Nutrition and Supplementation Considerations to Limit Endotoxemia When Exercising in the Heat

Joshua H. Guy[1,*] and Grace E. Vin

Author information ▶ Article notes ▶ Co

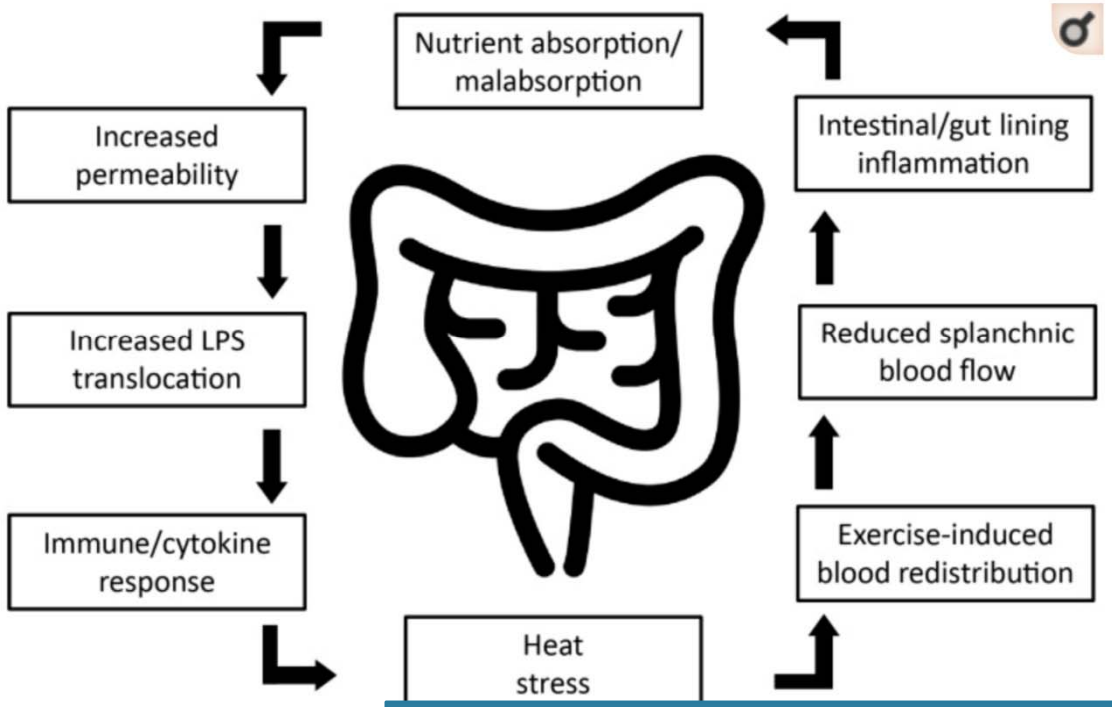
Following an Ironman distance triathlon, 68% of athletes exhibited an at least 150% increase in LPS… Furthermore, individuals with lower aerobic fitness typically have a higher post-exercise plasma LPS concentration than more highly trained individuals when undertaking the same work

Abstract

Exercise-induced heat producti
subsequently impact inflammat
supplementation strategies unde
inflammatory response, GI perm
brief review is to explore athlet
(LPS), and interleukin-6 (IL-6),
exercising in hot conditions. Th
preserve GI integrity, which ma
consumed with water, before ar
integrity, and reduce the incidence of GI disturbances compared with water alone. The use of non-steroidal anti-inflammatory drugs (NSAIDs) may compromise GI integrity and this may result in greater leakage of endotoxins during long duration exercise in the heat. Further work is required to elucidate the impact of nutrition and supplementation strategies, in particular the use of NSAIDs, when exercising in the heat.

Keywords: heat stress, inflammation, cytokines, hydration, gastrointestinal permeability

https://www.ncbi.nlm.nih.gov/pubmed/29910316



Strenuous physical exercise leads to redistribution of blood, shunting blood away from the splanchnic area, thereby significantly reducing splanchnic blood flow and resulting in mucosal damage and loss of integrity to the gut wall.

Gastrointestinal permeability and inflammatory cytokine response to exercise following nutrition and supplementation interventions.

Author	Oxygen Uptake ($mL \cdot kg^{-1} \cdot min^{-1}$) and Sample Size (n)	Experimental Conditions	Exercise and Nutrition/Supplementation Intervention	Biomarker Response
Ashton et al., (2003) [31]	49 ± 3, $n = 10$	Laboratory (temperate)	1000 mg of L-ascorbic acid (vitamin C) 2 h before exercise. Incremental cycle test to exhaustion.	L-ascorbic acid: ↓ LPS
Bishop et al., (2001) [36]	49 ± 3, $n = 7$	Laboratory (22 °C, 56% RH)	3 day Low-CHO or High-CHO diet. 60 min cycle at 60% Wmax and TT	High-CHO: ↓ IL-6 Low-CHO: ↑ IL-6
Buckley et al., (2009) [23]	53 ± 2, $n = 30$	Laboratory (temperate)	8 week daily supplementation 60 g Bovine Colostrum. Running 3 times per week for 45 min at lactate threshold.	Bovine Colostrum: ↑ L:R
Cox et al., (2010) [37]	65 ± 5, $n = 16$	Laboratory (temperate)	28 day Moderate-CHO or High-CHO diet. 100 min steady state cycling at 70% VO_2 max and ~30 min TT.	Moderate-CHO: ↑ IL-6 High-CHO: ↑ IL-6,
Moncada-Jiménez et al., (2010) [24]	57 ± 7, $n = 11$	Laboratory (temperate)	48 h Low-CHO or High-CHO. Duathlon, 5 km run, 30 min stationary cycle, 10 km run.	Low-CHO: ↑ IL-6 and LPS-LPB High-CHO: ↑ IL-6 and LPS-LPB
Morrison et al., (2014) [19]	64 ± 4, $n = 7$ 46 ± 4, $n = 8$	30 °C, 50% RH	1 week daily supplementation 1.7 $g \cdot kg^{-1}$ Bovine Colostrum. 30 min cycling at 50% HRR, 30 min running at 80% HRR	Bovine Colostrum: ↑ IL-6 and I-AFBP
Shing et al., (2014) [22]	63 ± 6, $n = 10$	35 °C, 40% RH	4 weeks daily supplementation probiotics capsule. Running at to exhaustion at 80% of ventilatory threshold	Probiotic: ↓ L:R and LPS Probiotic and Placebo: ↑ IL-6
Pugh et al., (2017) [21]	52 ± 5, $n = 10$	30 °C, 40–45% RH	0.25, 0.5 or 0.9 $g \cdot kg^{-1}$ glutamine 2 h before exercise. 60 min treadmill run at 70% of VO_2 max	0.25, 0.5 and 0.9 $g.kg^{-1}$ ↓ L:R 0.5 and 0.9 $g.kg^{-1}$ ↓ I-AFBP
Snipe et al., (2017) [20]	54 ± 6, $n = 11$	35 °C, 27% RH	Water or CHO (15 g) or energy-matched PRO before and every 20 min during 2 h running at 60% VO_2 max	CHO and PRO: ↓ I-AFBP and L:R CHO: ↓ IL-6 and LPS
Van Wijck et al., (2012) [13]	Well trained, $n = 9$	Laboratory (temperate)	400 mg ibuprofen 1 h before exercise. Cycling at 70% Wmax, ↓ by 25 W until exhaustion.	Ibuprofen: ↑ I-AFBP and L:R

Summary of interventions in study

- **Vitamin C** supplementation with ascorbic acid can reduce post-exercise LPS concentration by ~12 fold
- **Probiotic supplementation** has been shown to reduce post-exercise LPS concentrations after running in hot conditions (35–40 °C)
- **Glutamine** - Previous research has demonstrated that acute oral glutamine consumption can attenuate GI permeability relative to placebo during a 60 min treadmill run at 70% VO2 max in hot environmental conditions
- **Serum Derived Bovine Immune globulin**
- ***Avoid NSAIDs***

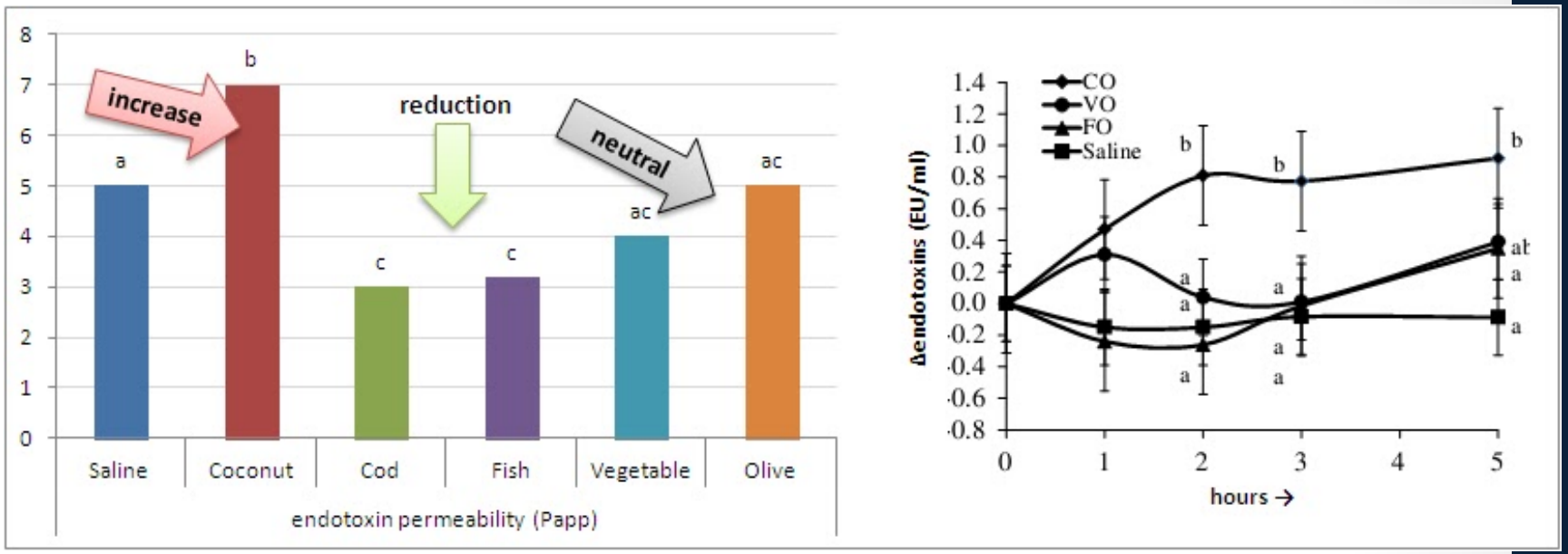
Dietary Interventions to to Decrease Endotoxemia

- Increase low-mercury fish consumption
- Increase in whole plant food
- Avoid sugar and processed foods
- Increase dietary fiber and prebiotics to increase production of SCFAs
  - From foods like onion, leek, garlic, and dandelion greens (prebiotics are the non digestible oligofructose, inulin, galactooligosaccharides within these plants).
- Intermittent fasting

Importance of Soluble and Insoluble Fibers

- Soluble fibers are digested by enzymes into short chain fatty acids (SCFAs)
- SCFAs constitute approximately 5–10% of the energy source in healthy people.
- Fiber-enriched diets improve insulin sensitivity in lean and obese diabetic subjects

TYPES OF DIETARY FATS AND ENDOTOXEMIA



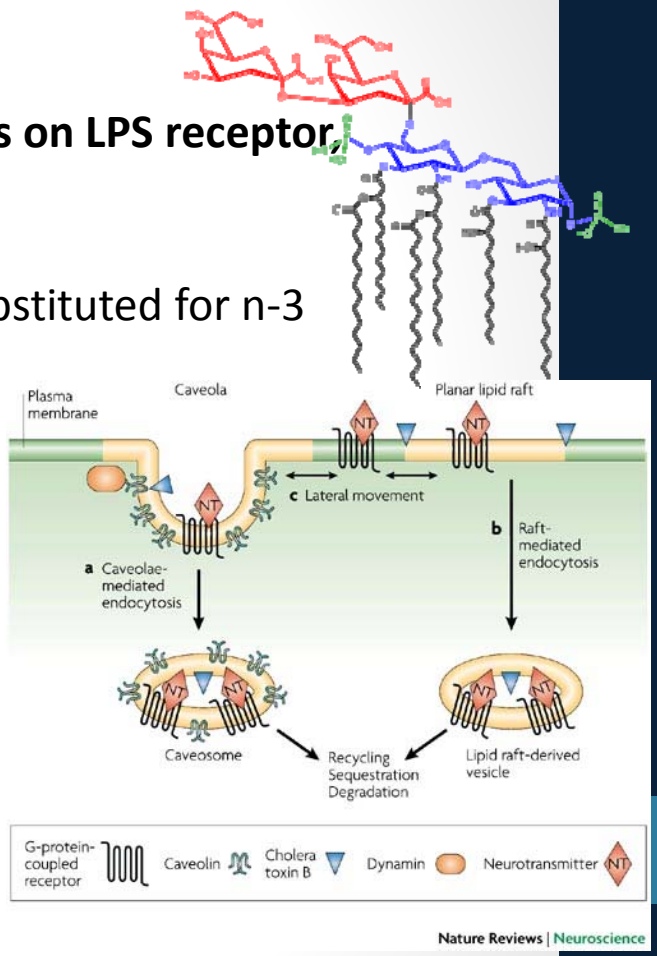
Endotoxin permeability and changes in serum endotoxin levels in the hours subsequent to the ingestion of a test meal containing either 50ml coconut (CO), vegetable (VO) and fish oil (FO) in otherwise healthy pigs (Mani. 2013).

Why does the type of fat matter?

Saturated fat (SFA) and n-3 PUFAs have opposite effects on LPS receptor, TLR4, and lipid rafts

- Lipid-A component of LPS is composed of SFA
- Endotoxin toxicity is reduced when SFA in lipid-A is substituted for n-3 PUFAs

Lee, et al. J Biol Chem. 2004;279:16971-16979



How does endotoxin enter the blood?

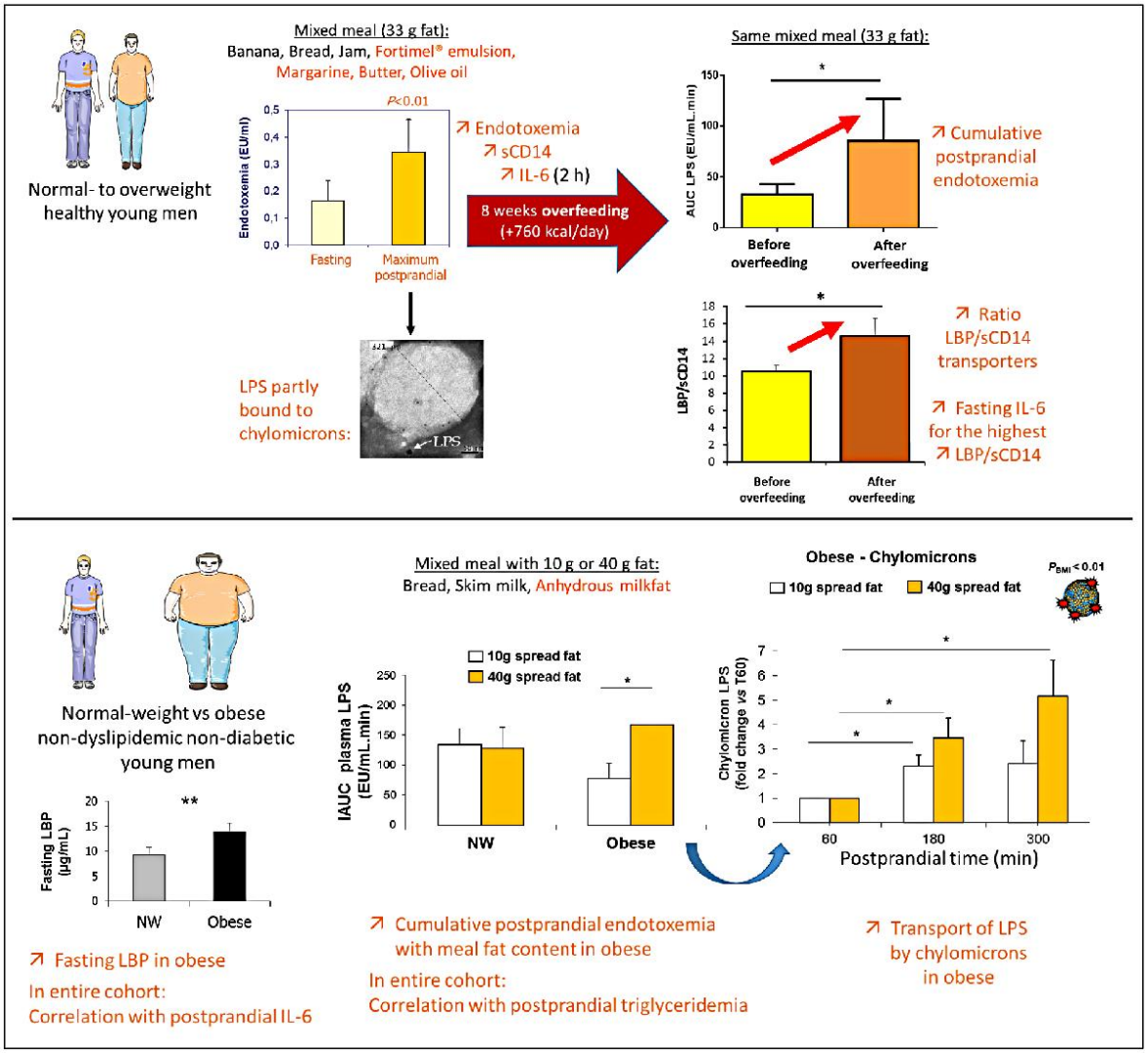
Paracellular pathways

- Via tight junctions

Transcellular pathways

- Via lipid rafts (endocytosis)
  - Rigid portion of membrane
  - Composed of cholesterol, SFA
  - Important in cell signaling

Triantafilou, et al. J Cell Sci. 2002;115:2603-2611;

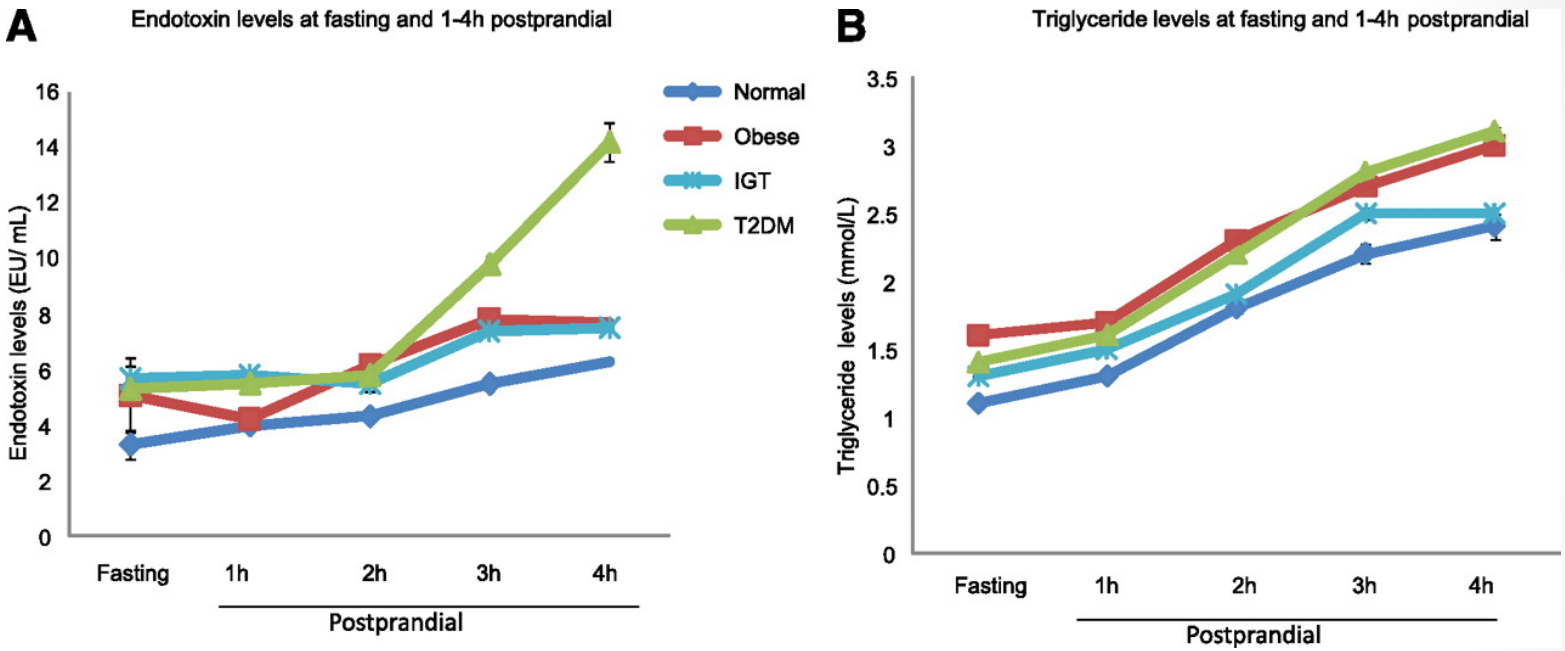


Summary of recent studies about postprandial endotoxemia in lean, overweight or obese men (Laugerette *et al.*, 2011, 2014; Vors *et al.*, 2015).

Upper panel: lean to overweight subjects were submitted to the same postprandial test before and after 8 weeks of overfeeding.

Lower panel: lean and obese subjects were submitted to two different postprandial tests varying by the amount of fat in the meal.

Changes in circulating endotoxin levels (A) and triglyceride levels (B) in NOC, IGT, obese, and type 2 diabetic (T2DM) subjects.

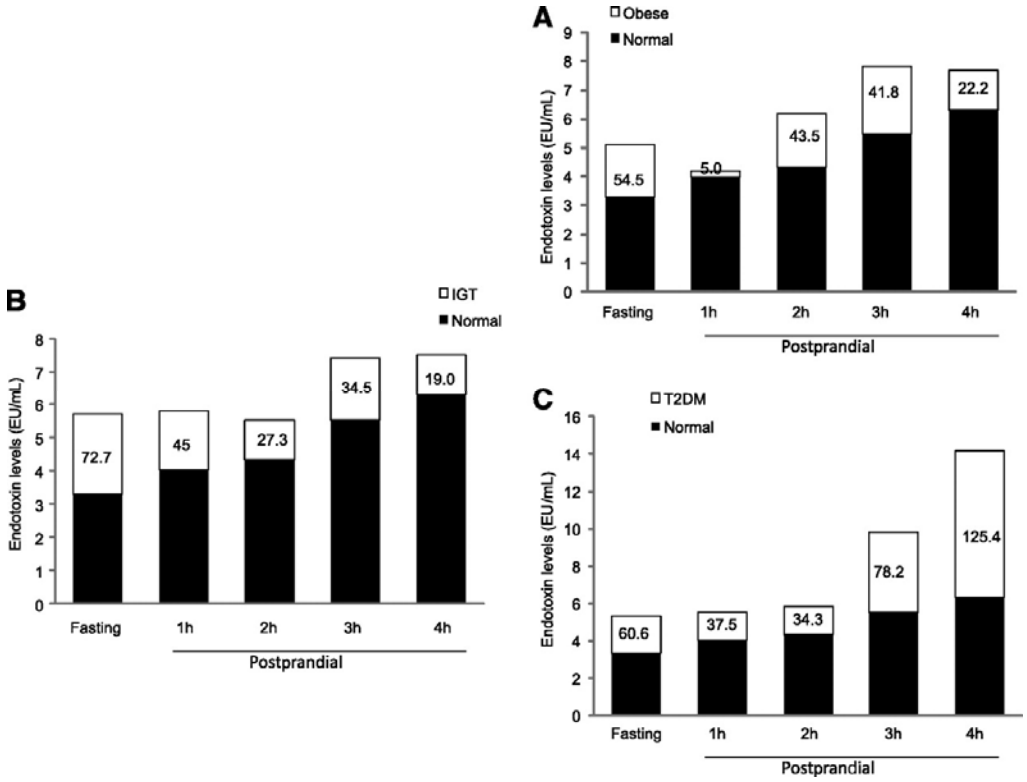


changes in circulating endotoxin levels (*A*) and triglyceride levels (*B*) in NOC, IGT (impaired glucose tolerance), obese, and type 2 diabetic (T2DM) subjects. Endotoxin and triglyceride levels were measured at baseline and then, after a high-SFA meal, at each hour postprandially over a 4-h duration. Each point on the graph represents the mean value for each cohort (± SEM).

Alison L. Harte et al. Dia Care 2012;35:375-382

American Diabetes Association.

Increase in endotoxin levels between the NOC subjects and the obese (A), IGT (B), and type 2 diabetic (T2DM) (C) subjects from baseline to 4 h after a high-fat meal.

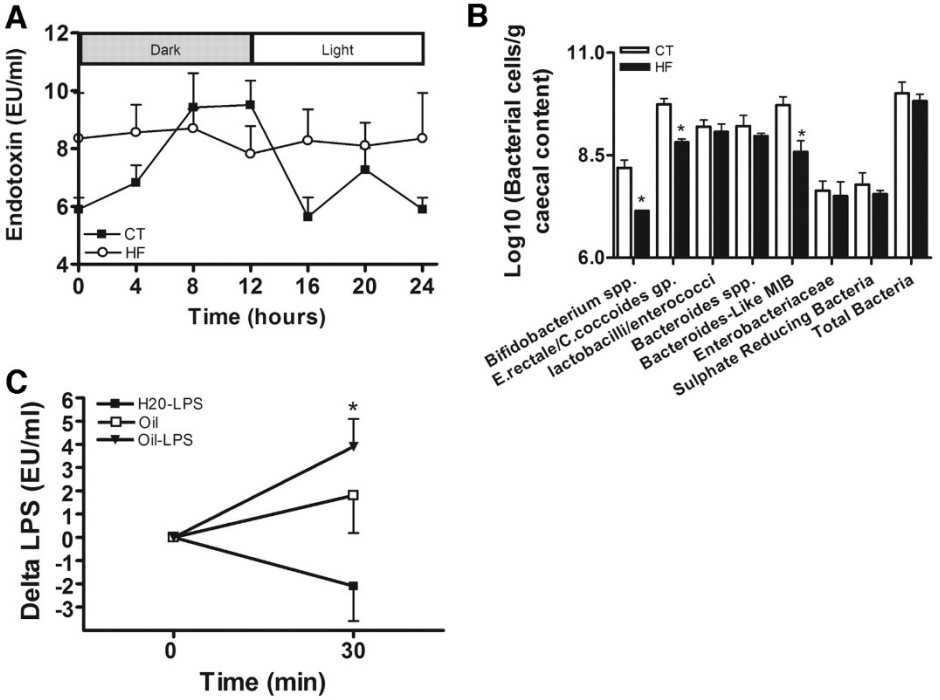


Alison L. Harte et al. Dia Care 2012;35:375-382

American Diabetes Association.

High-fat feeding increased endotoxemia and changed intestinal microbiota.

Chronic experimental metabolic endotoxemia induces obesity and diabetes.



Patrice D. Cani et al. Diabetes 2007;56:1761-1772

American Diabetes Association.

CONDITION	MECHANISM
Leptin Resistance	LPS enters and causes inflammation in the enteric nervous system leading to a disruption in the gut-brain axis of communication.
Chronic Constipation	LPS enters the enteric nervous system and causes disruption in signals for gastric emptying and bowel motility.
Mood and Appetite Disorders	LPS disrupts ghrelin function which has a direct impact on appetite and mood,
Depression	LPS can migrate to the blood-brain barrier and cause inflammation along with inhibition of dopamine receptors.
Cognitive Decline	Inflammation in the blood brain barrier leads to cognitive decline
Loss of Memory and Recall	LPS can get into the amygdala and hippocampus which disrupts memory function
Depression	LPS can increase the turnover of serotonin in the synapse and CNS reducing the concentration in those regions
Anorexia	The reduction of serotonin in the synapse and CNS is proposed as a possible mechanism for anorexia.
Anxiety	LPS disrupts key communication between the hypothalamic-adrenal-pituitary axis thereby increasing the expression of corticosteroid releasing hormone
Chronic Pain	Elevated LPS in sensory neurons in the dorsal root stimulate nociceptors.
Parkinson's	Intra-cranially LPS causes microglial activation and neuronal loss
Hypogonadism (low testosterone)	Increased circulating LPS and the subsequent chronic immune activation has feedback inhibition of testosterone production. GELDING theory.
Autoimmunity	Chronic activation of the innate immune system in various tissues leads to the by-stander effect where self-tissues inadvertently become targeted by the immune system.

METABOLIC ENDOTOXEMIA AND ELEVATED LPS IN DISEASE

Metabolic Endotoxemia Initiates Obesity and Insulin Resistance
Patrice D. Cani, Jacques Amar, et al.
Diabetes 2007 Jul; 56(7): 1761-1772. https://doi.org/10.2337/db06-1491

Metabolic endotoxemia directly increases the proliferation of adipocyte precursors at the onset of metabolic diseases through a CD14-dependent mechanism
Elodie Luche, Béatrice Cousin, et al.
Mol Metab. 2013 Aug; 2(3): 281–291.

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

Elevated endotoxin levels in non-alcoholic fatty liver disease
Alison L Harte et al.
Journal of Inflammation 20107:15
Received: 3 September 2009Accepted: 30 March 2010Published: 30 March 2010

Basic Clin Androl. 2016; 26: 7.
Published online 2016 Jun 22. doi: 10.1186/s12610-016-0034-7
PMCID: PMC4918028

Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING) - a novel theory for the development of late onset hypogonadism in obese men.

Kelton Tremellen

- **Male obesity is associated with late onset hypogonadism, a condition characterized by decreased serum testosterone, sperm quality plus diminished fertility and quality of life.**

- **The GELDING theory (Gut Endotoxin Leading to a Decline IN Gonadal function) – describes the development of obesity related hypogonadism.**

"Several observational studies have previously reported an association between obesity related hypogonadism (low testosterone) and systemic inflammation. However, for the first time we postulate that the trans-mucosal passage of bacterial lipopolysaccharide (LPS) from the gut lumen into the circulation is a key inflammatory trigger underlying male hypogonadism."

"Endotoxin is known to reduce testosterone production by the testis, thereby also leading to a decline in sperm production."

"Testosterone is known to be a powerful immune-suppressive, decreasing a man's ability to fight infection. Therefore we postulate that the male reproductive axis has evolved the capacity to lower testosterone production during times of infection and resulting endotoxin exposure, decreasing the immunosuppressive influence of testosterone, in turn enhancing the ability to fight infection. While this response is adaptive in times of sepsis, it becomes maladaptive in the setting of "non-infectious" obesity related metabolic endotoxaemia."

GUT PERMEABILITY – CHRONIC INFLAMMATION

Stress induces endotoxemia and increasing barrier permeability

Karin de Punder* and Leo Pruimboom
Frontiers in Immunology published: 15 May 2015

“Chronic non-communicable diseases (NCDs) are the leading causes of work absence, disability, and mortality worldwide. Most of these diseases are associated with low-grade inflammation.”

“In combination with modern life-style factors, the increase in **bacteria/bacterial toxin translocation** arising from a more **permeable intestinal** wall causes a low-grade inflammatory state. We support this hypothesis with numerous studies finding **associations with NCDs and markers of endotoxemia**, suggesting that this process plays a pivotal and perhaps even **a causal role** in the development of low-grade inflammation and its related diseases.”

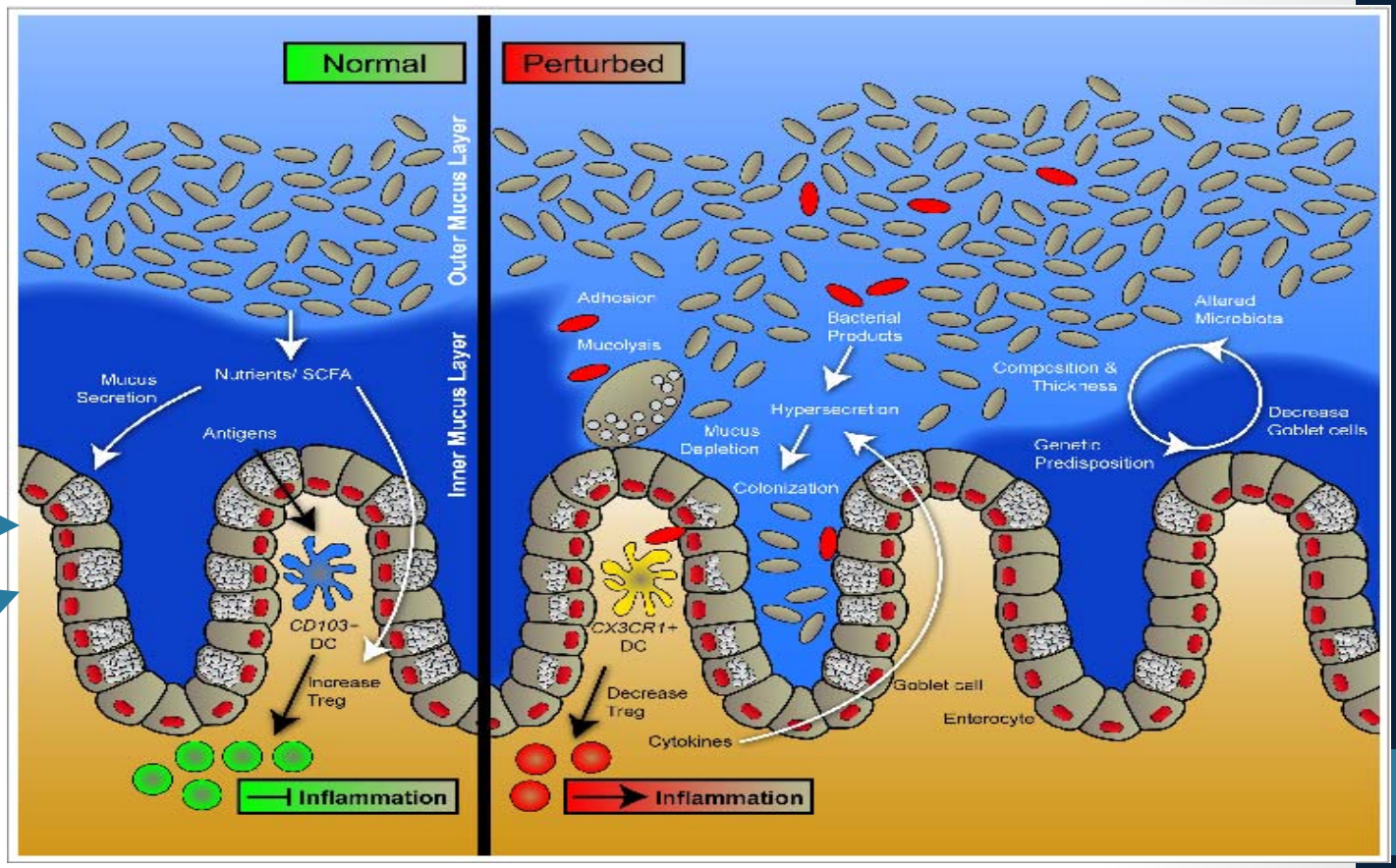
HOW DOES A HEALTHY MICROBIOME PROTECT AGINST METABOLIC ENDOTOXEMIA?

Neutralize LPS
-increase sIgA
-increase PAMP

Increase Mucin2 production

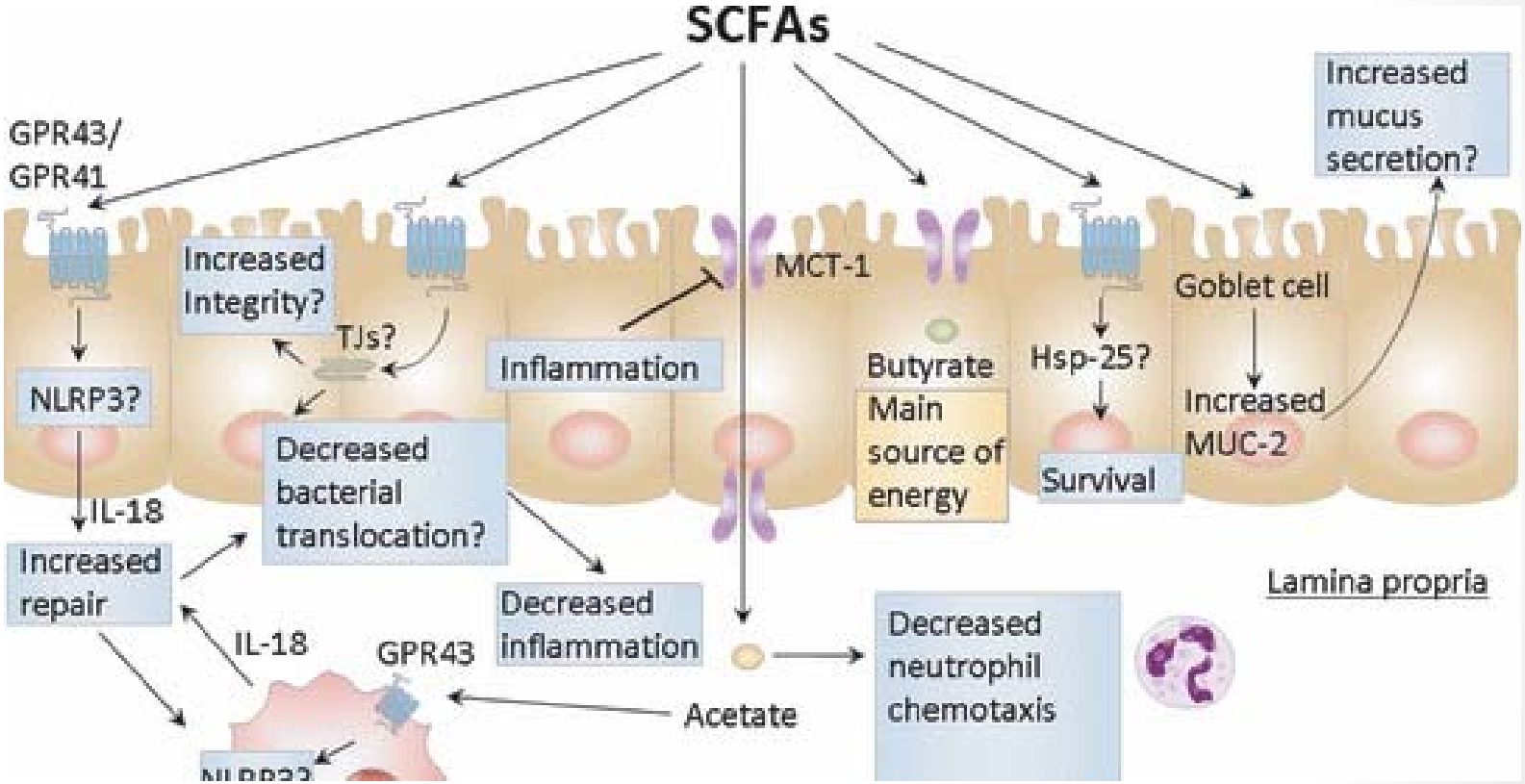
Increase tight junction protein expression

Increase regeneration of expelled IEC



Tissue Barriers. 2015; 3(1-2): e982426. Published online 2015 Jan 15. doi: 10.4161/21688370.2014.982426

SHORT CHAIN FATTY ACIDS



WJGP World Journal of Gastrointestinal Pathophysiology

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World J Gastrointest Pathophysiol 2017 August 15; 8(3): 117-126

DOI: 10.4291/wjgp.v8.i3.117

ISSN 2150-5330 (online)

ORIGINAL ARTICLE

Prospective Study

Oral spore-based probiotic supplementation was associated with reduced incidence of post-prandial dietary endotoxin, triglycerides, and disease risk biomarkers

Brian K McFarlin, Andrea L Henning, Erin M Bowman, Melody M Gary, Kimberly M Carbajal

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Brian K McFarlin, Andrea L Henning, Kimberly M Carbajal, Department of Biological Sciences, University of North Texas, Denton, TX 76203, United States

Author contributions: McFarlin BK designed the study, collected data, interrupted findings, and prepared manuscript; Henning AL, Bowman EM, Gary MM and Carbajal KM collected data, interrupted findings, and prepared manuscript.

Institutional review board statement: The study was reviewed

Manuscript source: Invited manuscript

Correspondence to: Brian K McFarlin, PhD, FACSM, FTOS, Associate Professor, Applied Physiology Laboratory, University of North Texas, 1921 West Chestnut Street, PEB Room 209, Denton, TX 76203, United States. brian.mcfarlin@unt.edu
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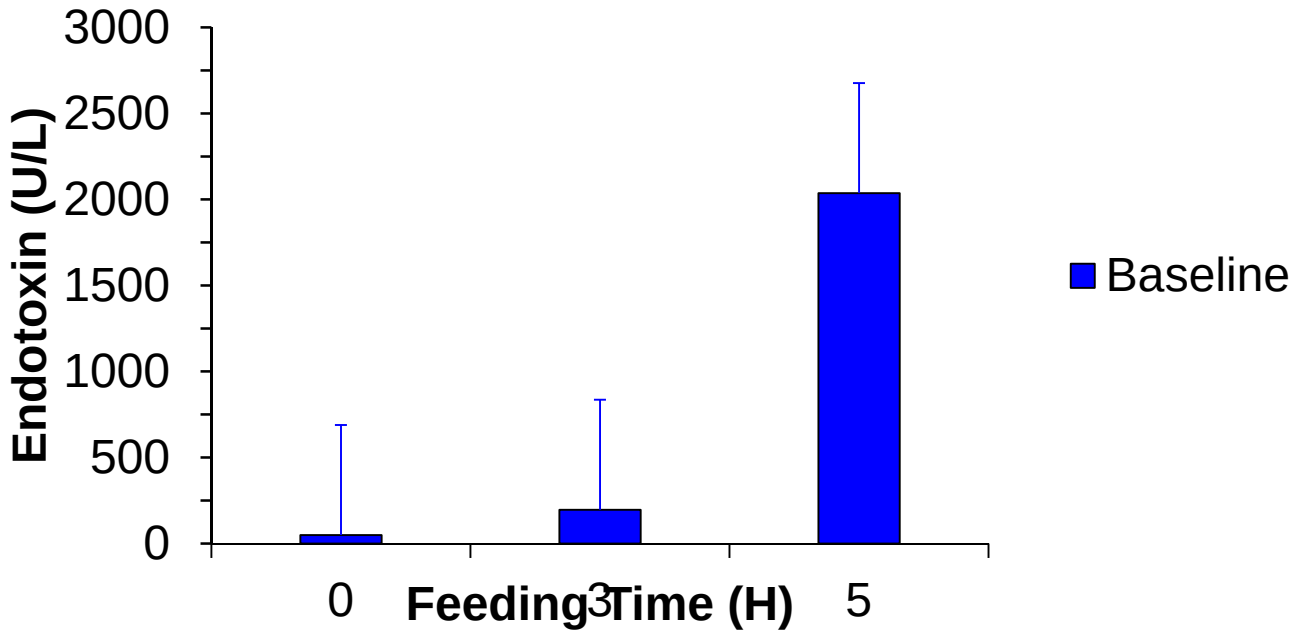
First decision: April 17, 2017

The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: Pilot Study

Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS
University of North Texas



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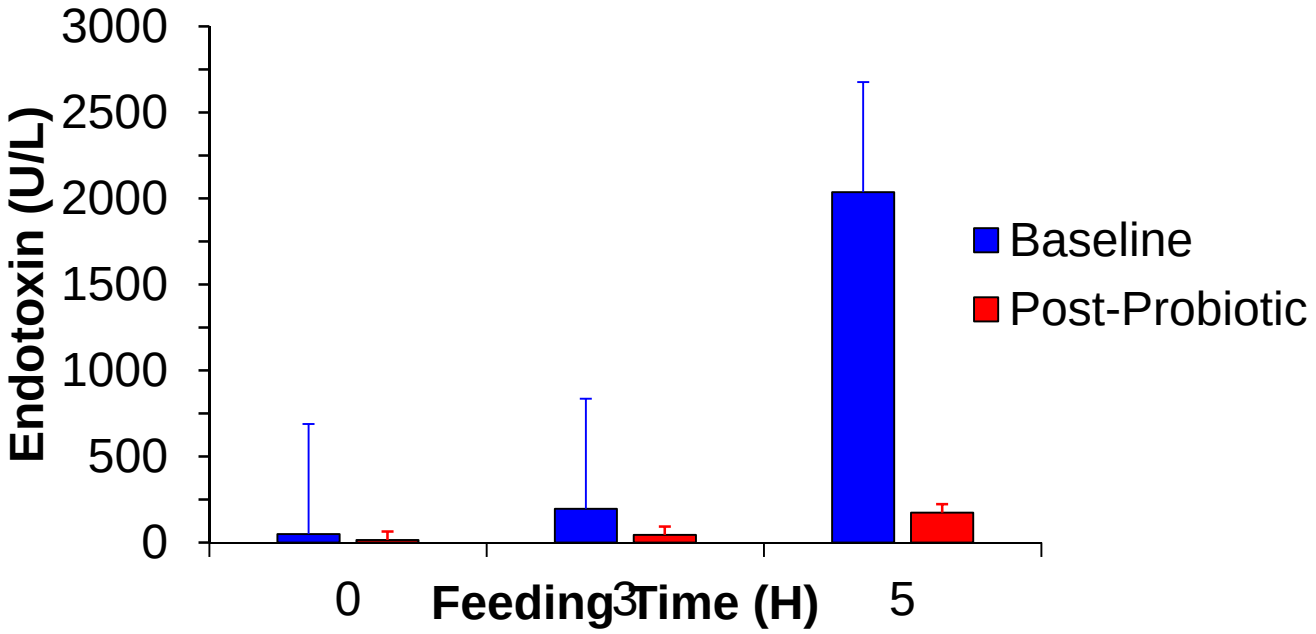
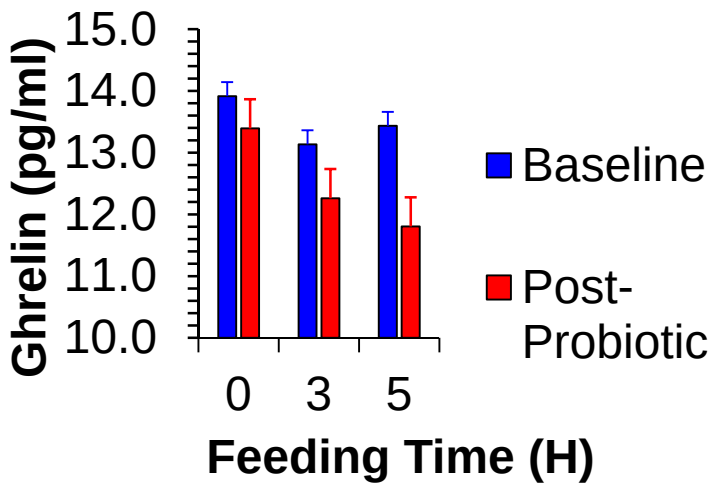
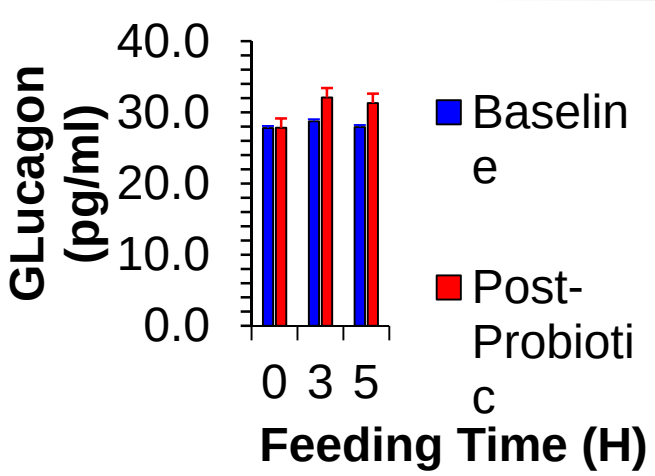
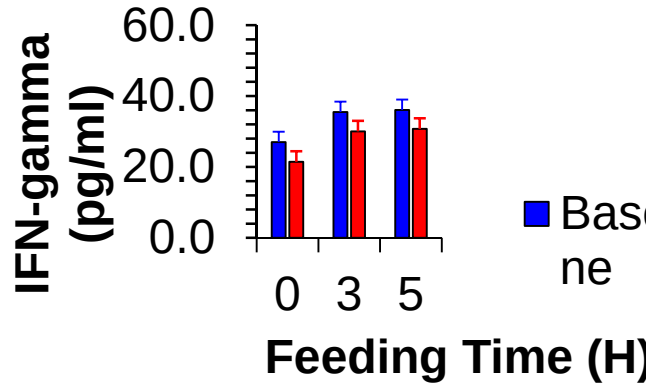
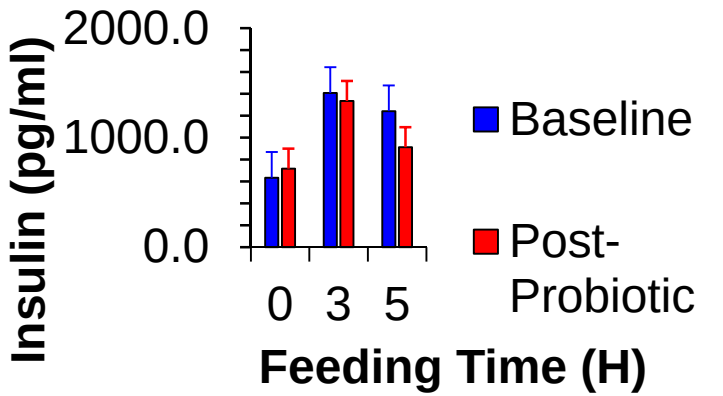



Ghrelin (pg/ml)
15.0
14.0
13.0
12.0
11.0
10.0
0 3 5
Feeding Time (H)
Baseline
Post-Probiotic

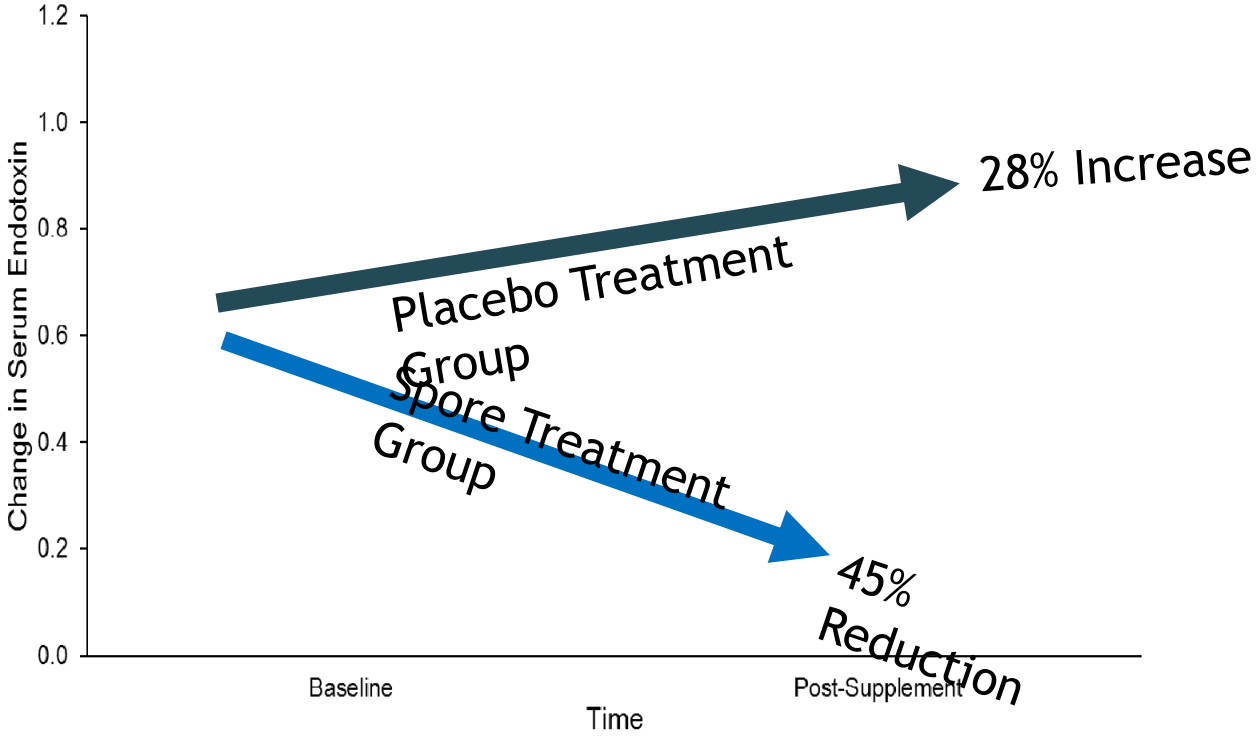

GLucagon (pg/ml)
40.0
30.0
20.0
10.0
0.0
0 3 5
Feeding Time (H)
Baseline
Post-Probiotic


IFN-gamma (pg/ml)
60.0
40.0
20.0
0.0
0 3 5
Feeding Time (H)
Baseline


Insulin (pg/ml)
2000.0
1000.0
0.0
0 3 5
Feeding Time (H)
Baseline
Post-Probiotic

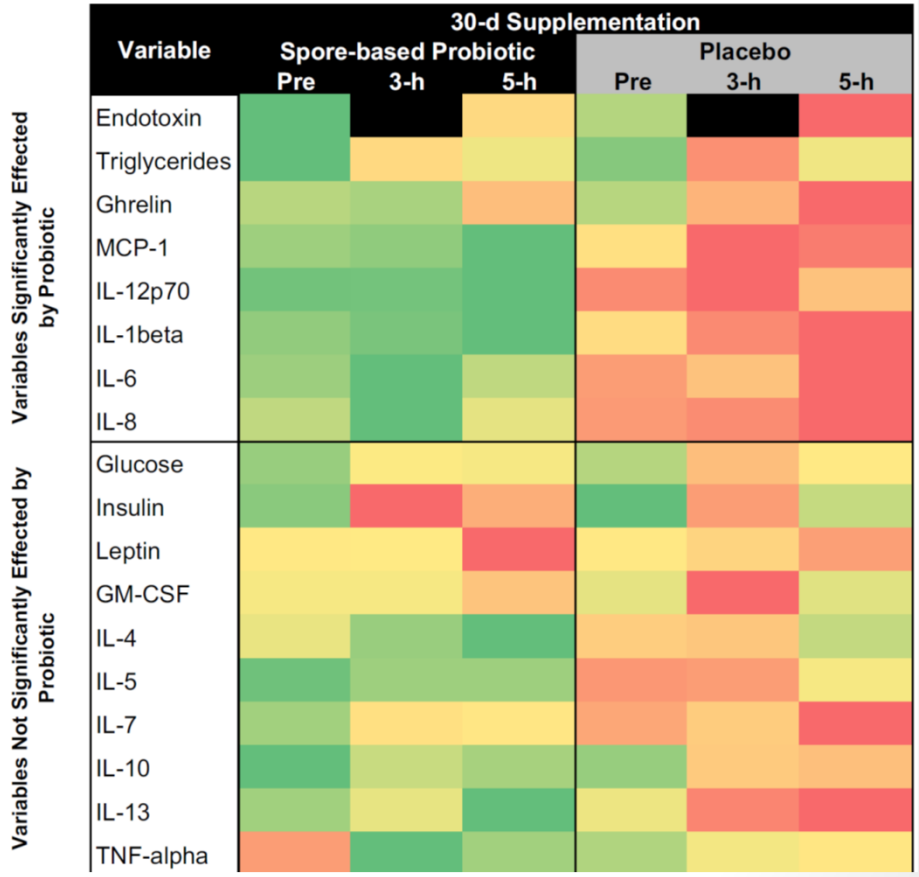
The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: An Expanded Pilot Study

Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS
University of North Texas



The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: An Expanded Pilot Study

Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS
University of North Texas



Periodontal disease may contribute as well…

Mitochondrial dysfunction promoted by Porphyromonas gingivalis lipopolysaccharide as a possible link between cardiovascular disease and periodontitis.

Bullon P[1], Cordero MD, Quiles JL, Morillo JM, del Carmen Ramirez-Tortosa M, Battino M.

Author information

Abstract

Oxidative stress is one of the factors that could explain the pathophysiological mechanism of inflammatory conditions that occur in cardiovascular disease (CVD) and periodontitis. Such inflammatory response is often evoked by specific bacteria, as the lipopolysaccharide (LPS) of Porphyromonas gingivalis is a key factor in this process. The aim of this research was to study the role of mito… …te the influence of … …MCs from patient… …treated fibroblasts … …ression mitochondri… …ondrial dysfunction … oxidative st… …o understandi…

LPS-mediated mitochondrial dysfunction could be at the origin of oxidative stress in periodontal patients. It may promote oxidative stress and alter cytokine homeostasis. Mitochondrial dysfunction could represent a possible link to between periodontitis and Cardiovascular disease.

http://www.ncbi.nlm.nih.gov/pubmed/21354301

Identify which organism are associated with cardiovascular disease and metabolic syndrome

MICROBIAL SPECIES AND CV HEALTH RISKS

Low bacterial richness associated with…

- Obesity
- Diabetes
- Fatty Liver
- Low Grade inflammation (elevated CRP)
- Insulin resistance
  - Elevated leptin
  - Decreased adiponectin
- Dyslipidemia

Low bacterial richness consistent with:

1. Reduction of butyrate-producing bacteria
2. Increase in mucus degradation thereby potentially impairing gut barrier funcrion
    1. decrease in *A muciniphila* and increase in *R gnavus*
3. Increase in oxidative stress.

Energy-restricted diet improved microbial richness and clinical phenotype in LGC subjects but less efficient at improving inflammatory markers

High vs. low bacterial richness

- High bacterial richness species
  - *Faecalibacterium prausnitzii*
  - *Bifidobacterium*
  - *Lactobacillus*
  - *Alistipes*
  - *Akkermansia*
  - *Phylum*
    - *Verrucomicrobia* (eg, *A muciniphila*)
    - *Actinobacter*
- Low bacterial richness
  - *Species level*
    - *Bacteroides sp*
    - *Ruminococcus* sp
  - Phylum level
    - *Bacteroidetes*
    - *Proteobacteria*

http://www.medscape.com/viewarticle/829967_2

Gut microbiota

Original article

A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis

Kathleen Machiels[1], Marie Joossens[2,3], João Sabino[1], Vicky De Preter[4], Ingrid Arijs[1], Venessa Eeckhaut[5], Vera Ballet[1], Karolien Claes[1], Filip Van Immerseel[5], Kristin Verbeke[4], Marc Ferran

+ Author A

Correspond

Professor Se ı,

Herestraat 49, Leuven 3000, Belgium; Severine.Vermeire@uzleuven.be

Reduction in *R hominis* and *F prausnitzii,* both well-known butyrate-producing bacteria increase risk of inflammation

http://gut.bmj.com/content/early/2013/09/10/gutjnl-2013-304833

Summary of findings in patients with Type 2 DM

- LOWER:
  - *Roseburia intestinalis* (produces butyrate)
  - *Faecalibacterium prausnitzii*
- HIGHER
  - *Lactobacillus gasseri* and *Streptococcus mutans*
  - Certain *Clostridial species*
  - *Proteobacteria*
- Increased expression of microbiotal genes involved in oxidative stress leading to proinflammatory signature
- LOWER genes involved in vitamin synthesis like riboflavin

Diet Influences Microbiome

- *Bacteroides* enterotype
  - Animal protein and saturated fats
- *Prevotella* enterotype.
  - Vegetarians
- Positive association with fiber:
  - *Bacteroidetes* and *Actinobacteria*
- Negative association with fiber:
  - *Firmicutes* and *Proteobacteria*
- Animal-based diets resulted in lower levels of SCFAs compared with a plant-based diet.

Drug influence on microbiome

- Metformin involves disruption of the bacterial folate cycle, resulting in decreased levels of s-adenosylmethionine synthase
  - Common side effects include diarrhea and bloating, reduced folate levels and increased homocysteine
  - In mice increases concentrations of *A muciniphila*
  - increased the number of mucin-producing goblet cells

Hypertension and Gut Microbiota

Hypertension. 2015 Jun;65(6):1331-40. doi: 10.1161/HYPERTENSIONAHA.115.05315. Epub 2015 Apr 13.

Gut dysbiosis is linked to hypertension.

Yang T[1], Santisteban MM[1], Rodriguez V[1], Li E[1], Ahmari N[1], Carvajal JM[1], Zadeh M[1], Gong M[1], Qi Y[1], Zubcevic J[1], Sahay B[1], Pepine CJ[1], Raizada MK[2], Mohamadzadeh M[2].

Author information

Abstract

Emerging evidence suggests that gut microbiota is critical in the maintenance of physiological homeostasis. This study was designed to test the hypothesis that dysbiosis in gut microbiota is associated with hypertension because genetic, environmental, and dietary factors profoundly influence both gut microbiota and blood pressure. Bacterial DNA from fecal samples of 2 rat models of hypertension and a small cohort of patients was used for bacterial genomic analysis. We observed a significant decrease in microbial richness, diversity, and evenness in the spontaneously hypertensive rat, in additi bacteria and dive notably restoring by reduc both in a strategy

Emerging evidence suggests that gut microbiota is critical in the maintenance of physiological homeostasis. [There was] decrease in microbial richness, diversity in the spontaneously hypertensive rat and increased Firmicutes/Bacteroidetes ratio. These changes were accompanied by decreases in acetate- and butyrate-producing bacteria. …high blood pressure is associated with gut microbiota dysbiosis

Hypertension and Gut Microbiota

Curr Opin Nephrol Hypertens. 2015 Sep;24(5):403-9. doi: 10.1097/MNH.0000000000000149.

Gut microbiota in hypertension.

Jose PA[1], Raj D.

Author information

Abstract

PURPOSE OF REVIEW: Hypertension, which is present in about one quarter of the world's population, is responsible for about 41% of the number one cause of death - cardiovascular disease. Not included in these statistics is the effect of sodium intake on blood pressure, even though an increase or a marked decrease in sodium intake can increase blood pressure. This review deals with the interaction of gut microbiota and the kidney with genetics and epigenetics in the regulation of blood pressure and salt sensitivity.

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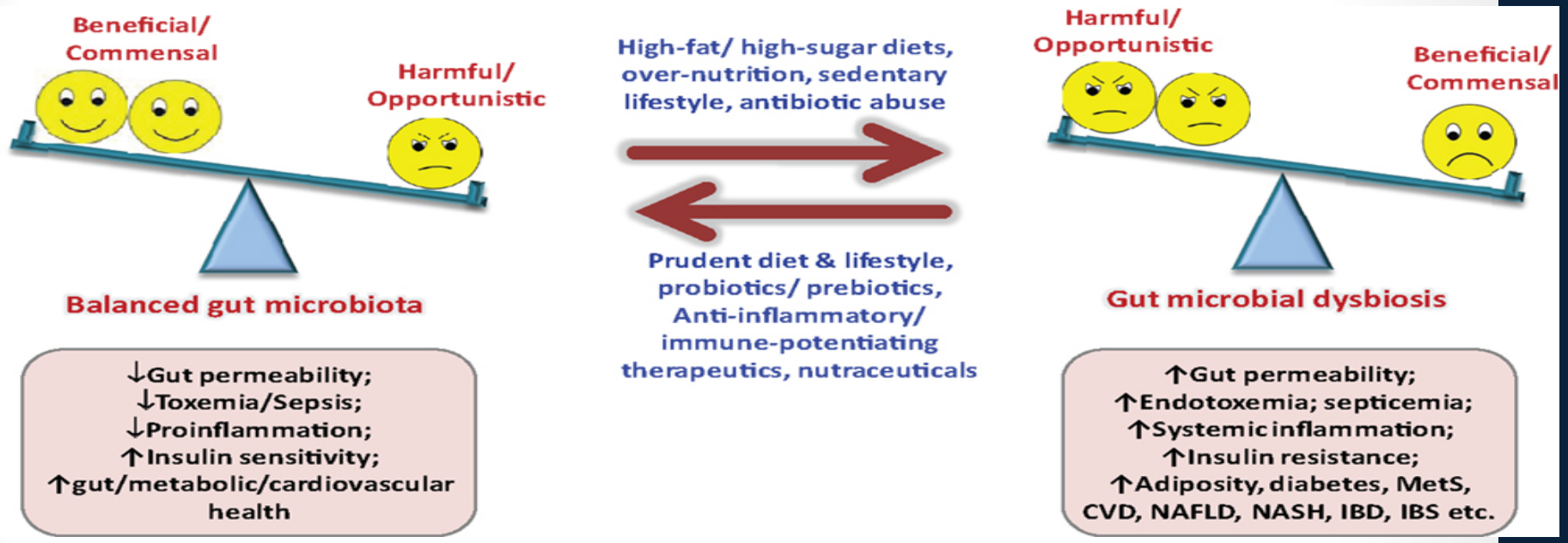
The abundance of the gut microbes, Firmicutes and Bacteroidetes, is associated with increased blood pressure in several models.

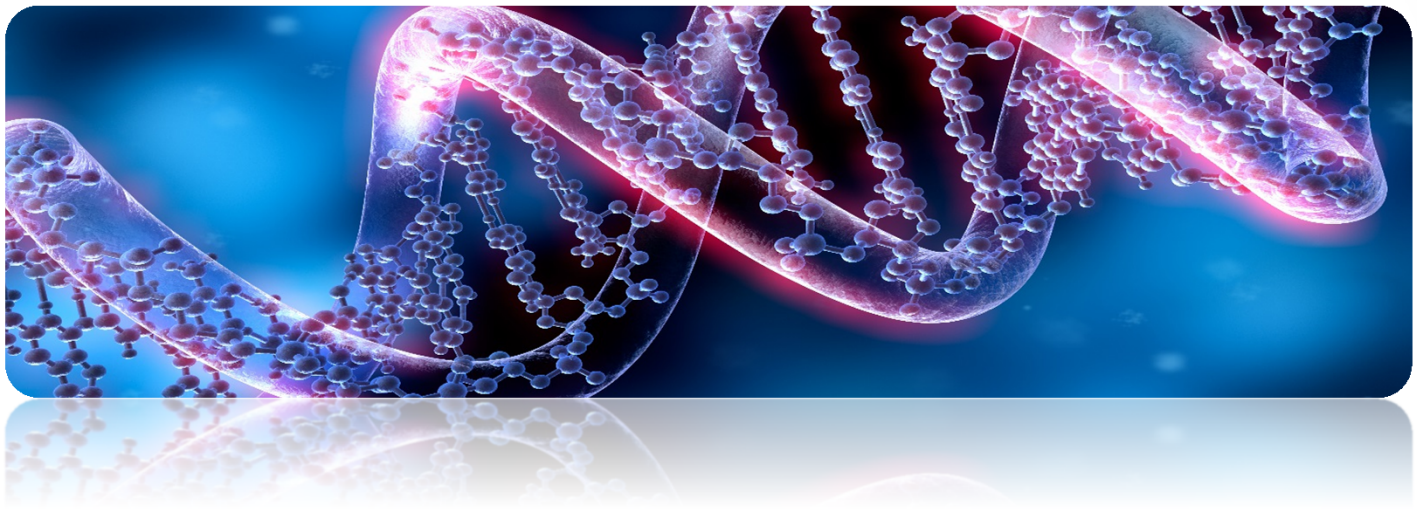
Products of the fermentation of nutrients by gut microbiota can influence blood pressure by regulating expenditure of energy, intestinal metabolism of catecholamines, and gastrointestinal and renal ion transport, and thus, salt sensitivity.

http://www.ncbi.nlm.nih.gov/pubmed/26125644

Summary



http://journal.frontiersin.org/article/10.3389/fmed.2014.00015/full



A new era in understanding Autoimmunity

GENETICS, ENVIRONMENTAL TRIGGERS AND THE MICROBIOME

Triad of Autoimmunity

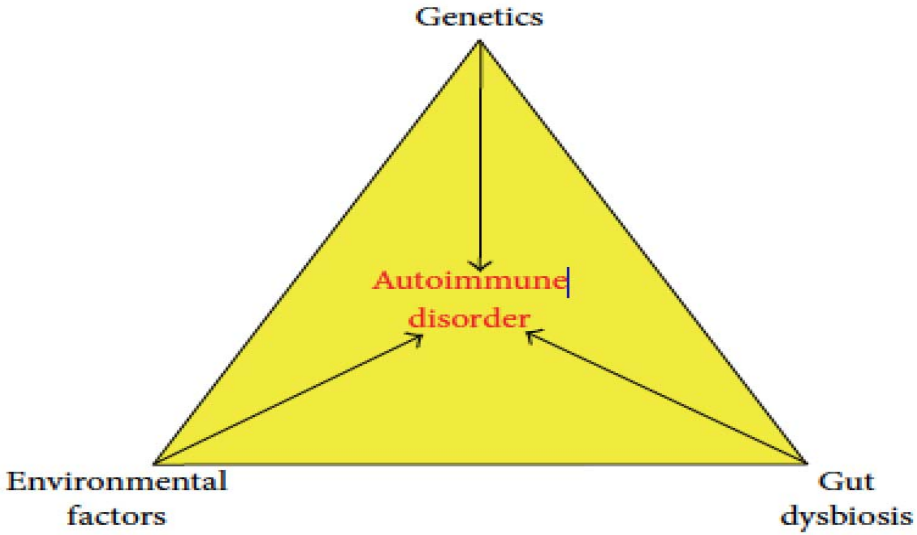


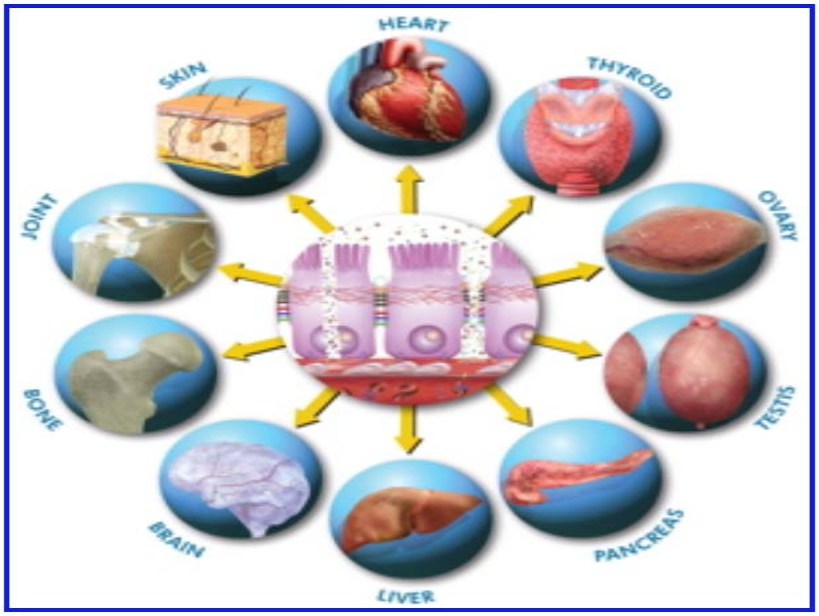
FIGURE 1: The triangle of autoimmune triggers. Gut dysbiosis and genetic and environmental factors play major roles in the development of autoimmune diseases.

Autoimmunity and the Gut - *http://www.hindawi.com/journals/ad/2014/152428/*

Predictive Antibody Testing Facilitates Early Detection of Autoimmune Disorders

Friday, 07 December 2012 01:16

By Erik Goldman - Vol. 13, No. 4. Winter, 2012



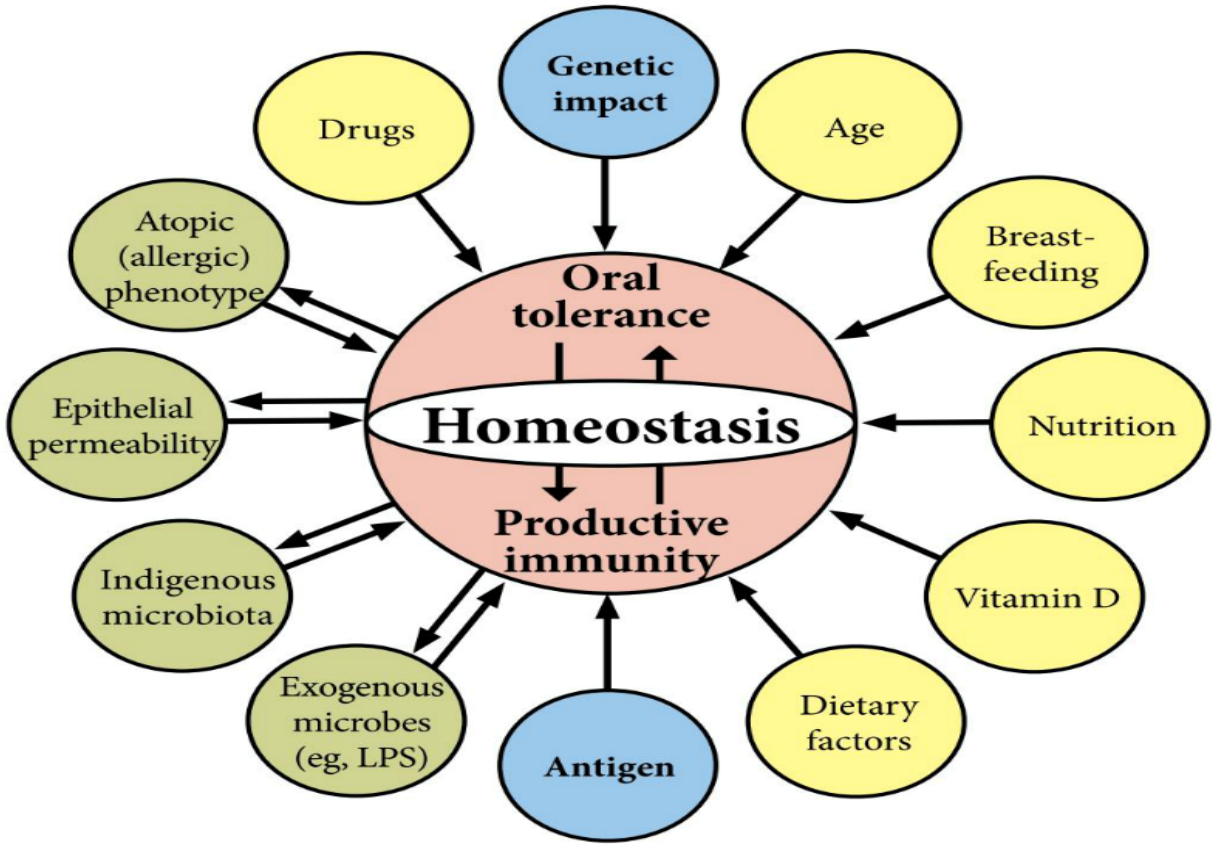
LONG BEACH, CA--Approximately 53 million Americans have autoimmune diseases. That's one in every seven men, and one in every five women. In most cases, they seek care long after the disorders have become debilitating, and often bounce from clinician to clinician before getting an accurate diagnosis.

Advances in molecular immunology have the potential to change that, by providing primary care practitioners with an array of new tests enabling detection of predispositions and triggers for diseases like rheumatoid arthritis, lupus, celiac, Crohn's, and autoimmune thyroid disorders at early stages when they are most manageable.

Triggers for Autoimmunity

- Genetics
- Gut-related
  - Food sensitivities
  - Microbial infections
  - Intestinal permeability
- Environmental Toxins
- Infectious triggers
- Stress

Figure 8. Immunological homeostasis. Homeostasis depends on the balance between mucosally induced oral tolerance and productive immunity, both SIgA-mediated and systemic. Several of the components acting on this balance are reciprocally modulated, as indicated by bidirectional arrows. The impact of genes and antigens are most important as indicated by their blue color.



Abbreviations: IgA, immunoglobulin A; SIgA, secretory IgA; LPS, lipopolysaccharide.

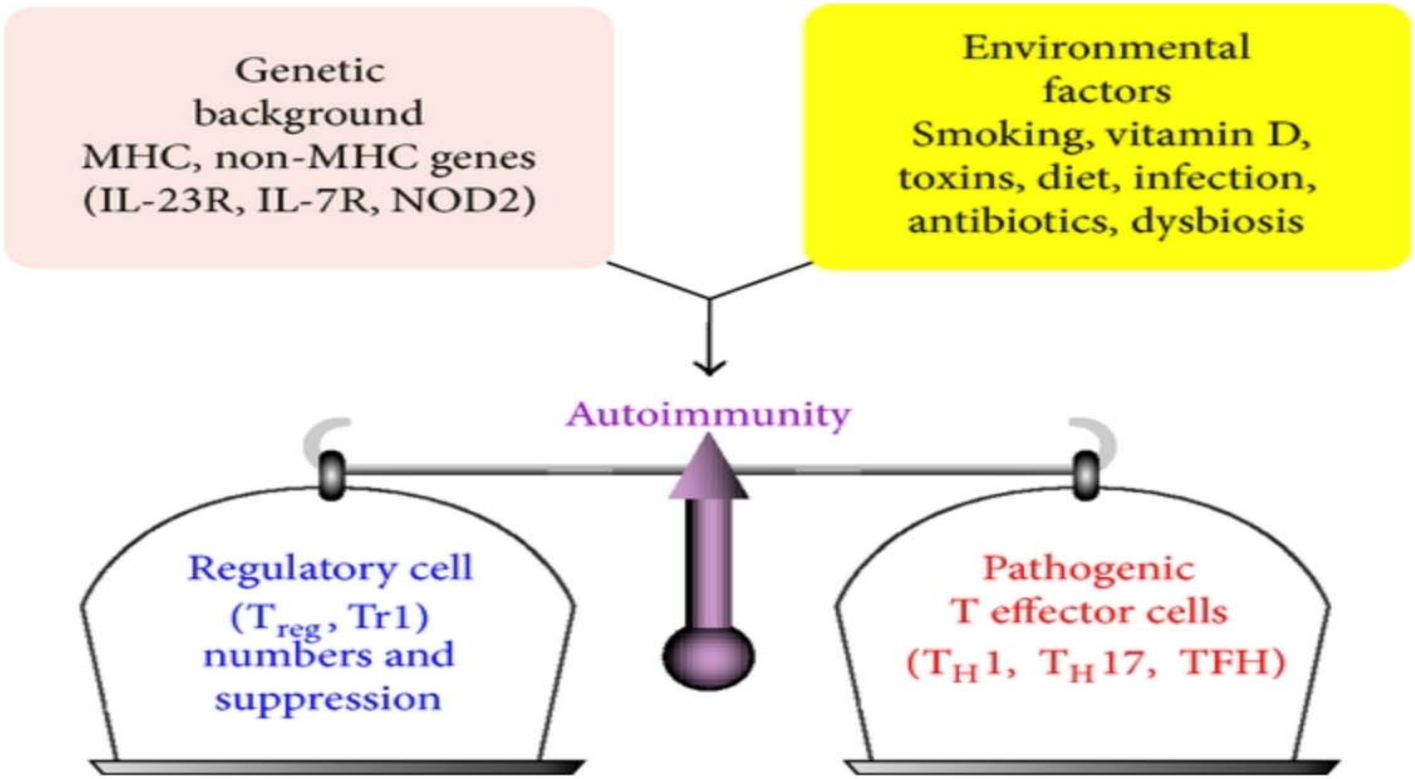


Figure 1: The balance of immunity. A combination of host genetic factors and exposure to environmental triggers promote the development of autoimmune disease. A balance must be maintained between the regulatory T cells and the pathogenic T effector cells.

Environmental Triggers for Autoimmunity

- Chemical toxicants
  - Aluminum hydroxide as adjuvant in vaccine (autoimmune hepatitis)
  - Silicone in breast implants (SLE, RA, vasculitis, systemic sclerosis)
  - Tobacco – known risk for RA
  - Glyphosate (Roundup) and celiac/gluten-related disease
  - Bisphenol A induces autoimmunity
- Heavy metals
- Infectious agents through molecular mimicry, epitope spreading, viral persistance, polyclonal activation, dysregulation, and autoimmune activation
- Emotional stress
- Drugs

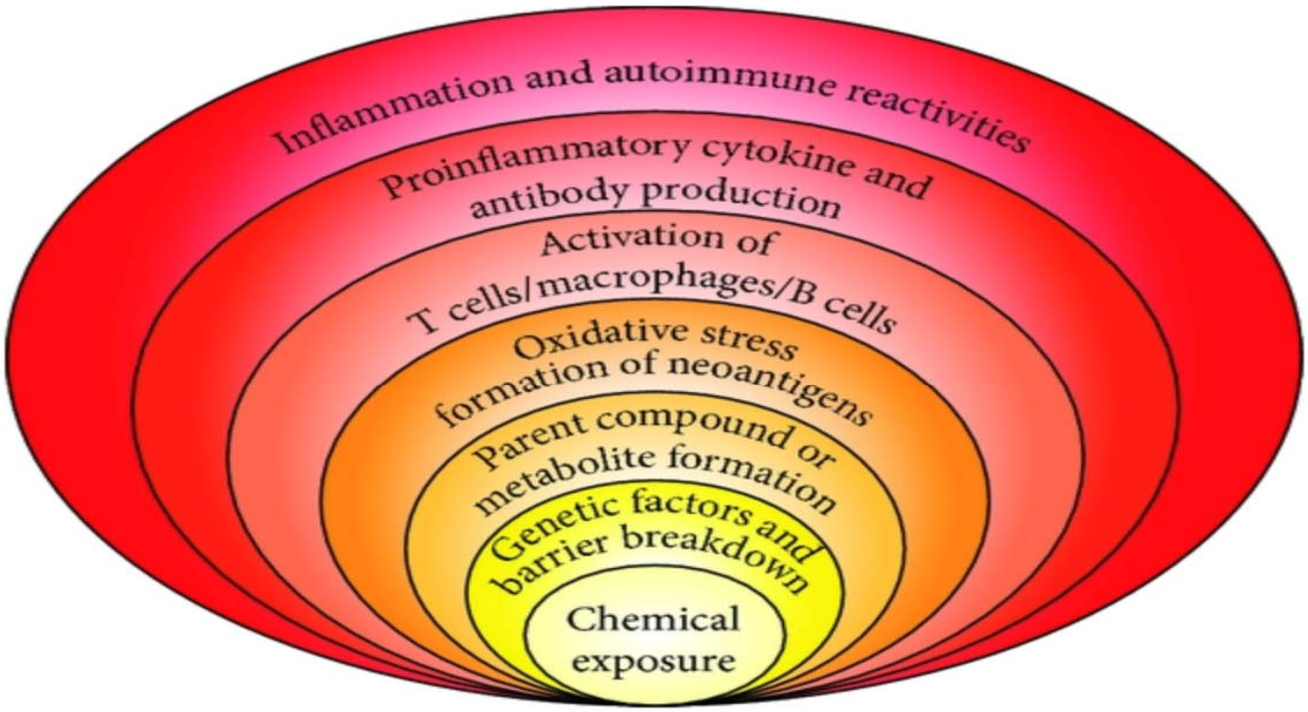


Figure 4: Potential molecular mechanisms implicated in chemical-induced autoimmune reactivities.

Infections and Autoimmunity

Table 3: Examples of bacterial and viral antigens that can cross-react with self-antigens with potentially resultant diseases.

Pathogen antigen	Cross-reactive self-antigen	Autoimmune disease
Herpes simplex virus	Corneal antigen	Stromal keratitis
Campylobacter jejuni	Ganglioside in peripheral nerve	Guillain-Barré syndrome
Coxsackievirus	Glutamic acid decarboxylase	Type 1 diabetes
Theiler's murine encephalomyelitis virus	Proteolipid protein	Multiple sclerosis
Yersinia enterocolitica	Thyrotropin receptor	Thyroid autoimmunity
Borrelia burgdorferi	Leukocyte function associated antigen	Lyme arthritis
Salmonella typhi and *Yersinia enterocolitica*	HLA-B27	Reactive arthritis
HHV-6, EBV, Rubeolla, influenza virus, and HPV	Myelin basic protein	Multiple sclerosis
Streptococcal M protein	Myosin and other heart valve proteins	Rheumatic fever
Trypanosoma cruzi	Cardiac myosis	Chagas heart disease

Nutrients **2012**, *4*, 1095-1119; doi:10.3390/nu4081095

OPEN ACCESS

nutrients

ISSN 2072-6643

www.mdpi.com/journal/nutrients

Review

Diet-Induced Dysbiosis of the Intestinal Microbiota and the Effects on Immunity and Disease

Kirsty Brown †, Daniella DeCoffe †, Erin Molcan and Deanna L. Gibson *

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It is conceivable that some diets promote the growth of microbes that could have detrimental effects on their host while other dietary factors could promote beneficial microbes.

Recent evidence suggests that diet can cause dysbiosis which could lead to aberrant immune responses.

Table 1. Summary of diet-induced dysbiosis.

Diet	Bacteria Altered	Effect on Bacteria	References
High-fat	*Bifidobacteria* spp.	Decreased (absent)	[45]
High-fat and high-sugar	*Clostridium innocuum*, *Catenibacterium mitsuokai and Enterococcus* spp.	Increased	[18]
	Bacteroides spp.	Decreased	[18]
Carbohydrate-reduced	Bacteroidetes	Increased	[49]
Calorie-restricted	*Clostridium coccoides*, *Lactobacillus* spp. and *Bifidobacteria* spp.	Decreased (growth prevented)	[48]
Complex carbohydrates	*Mycobacterium avium* subspecies *paratuberculosis and* Enterobacteriaceae	Decreased	[49]
	B. longum subspecies *longum*, *B.breve* and *B. thetaiotaomicron*	Increased	[53]
Refined sugars	*C. difficile* and *C. perfringens*	Increased	[54,55]
Vegetarian	*E. coli*	Decreased	[56]
High *n*-6 PUFA from safflower oil	Bacteroidetes	Decreased	[59,60]
	Firmicutes, Actinobacteria and Proteobacteria	Increased	[59,60]
	δ-*Proteobacteria*	Increased	[61]
Animal milk fat	δ-*Proteobacteria*	Increased	[62]

Diet Induced Autoimmunity

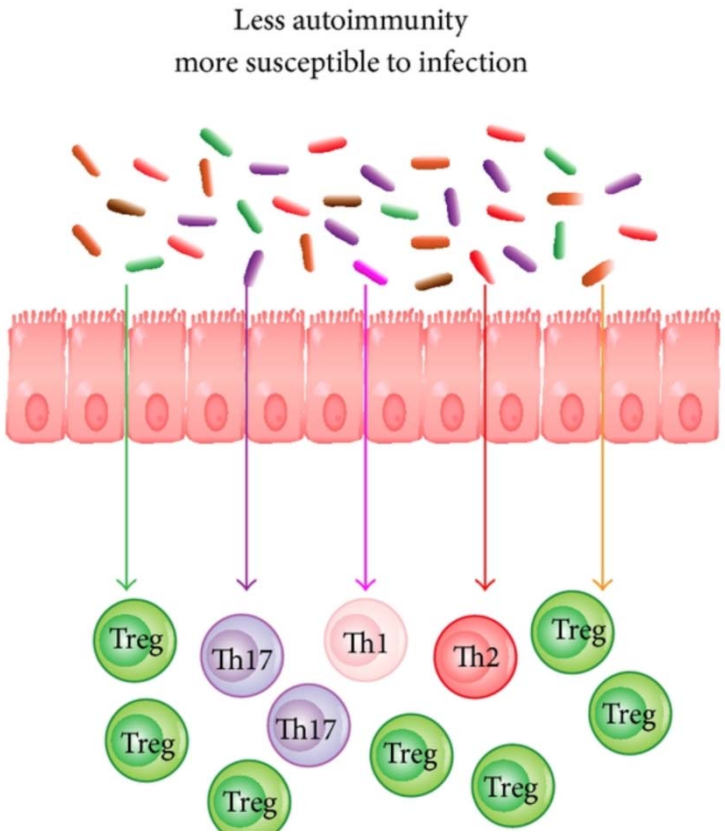
- Foods have undergone considerable transformation
  - New strains of grain: wheat, rice, soy, corn and more GM crops than the rest of the world combined
- Chemical use: pesticides, fungicides, insecticides
- Dairy cows injected with hormones – into milk products
- Chemicals: artificial preservatives, colorings, flavorings
- Heavy metals, such as arsenic in CAFO's
- Pesticides bind to protein in foods altering immune response
- Artificial sweeteners - especially in soft drinks
- High processed salt consumption

Microbiota regulates immune homeostasis

- Changes in the composition of commensal bacteria cause a change in immune homeostasis (Increase in Th17)
- **Increase Th17 causes increase cytokines** and increase in antimicrobial peptide production from epithelial cells to help fight off intestinal infections.
- However, this increase in proinflammatory cytokines renders host more susceptible to chronic ***autoimmune inflammatory response…***

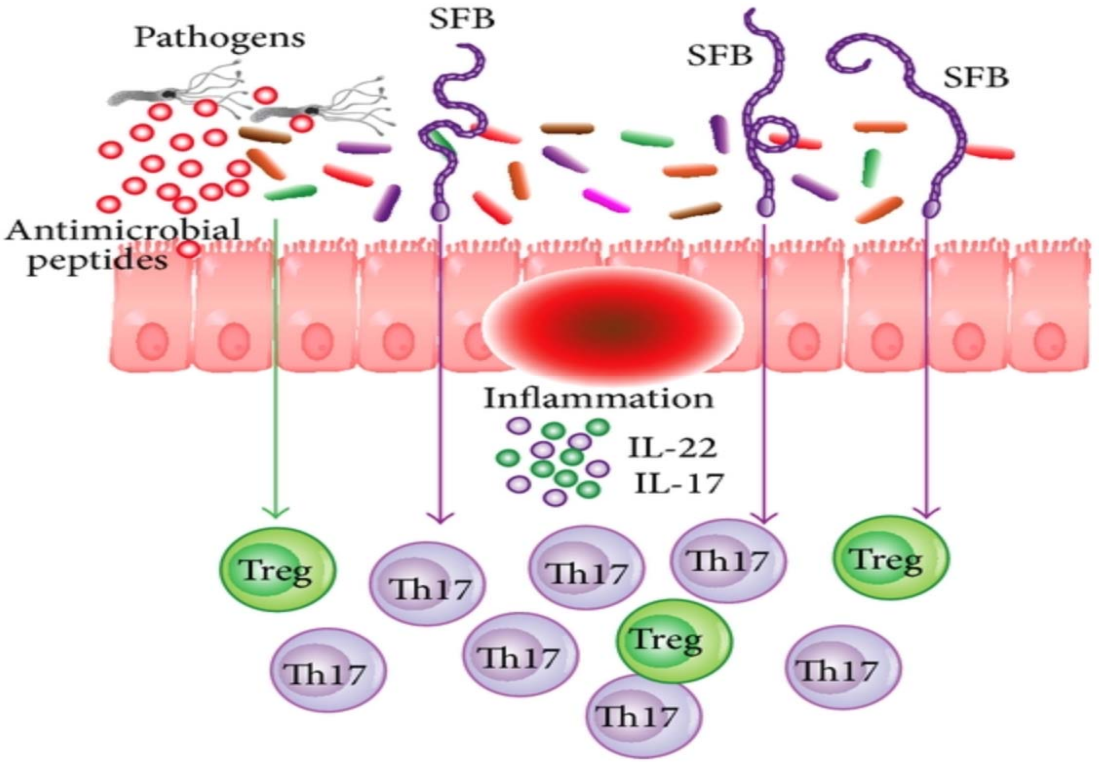
LESS AUTOIMMUNITY

More Susceptible to Infection



MORE AUTOIMMUNITY

Less susceptible to Infection



Microbiota regulates immune homeostasis

- **Differences in composition of commensal bacteria** account for differences in individual response in the face of similar environmental challenges
- A mucosal immune response, ***either one of tolerance or stimulation***, depends on the populations of dendritic cells responsible for the activation of T-Reg cells
- Activation of T-regs that inhibit the immune response and induce mucosal tolerance is **dependent on the production of IL-10**
- There appears to be little disagreement that Th17 cells can be generated from naïve CD4+ T cells in the presence of ***TGF-β and IL-6***

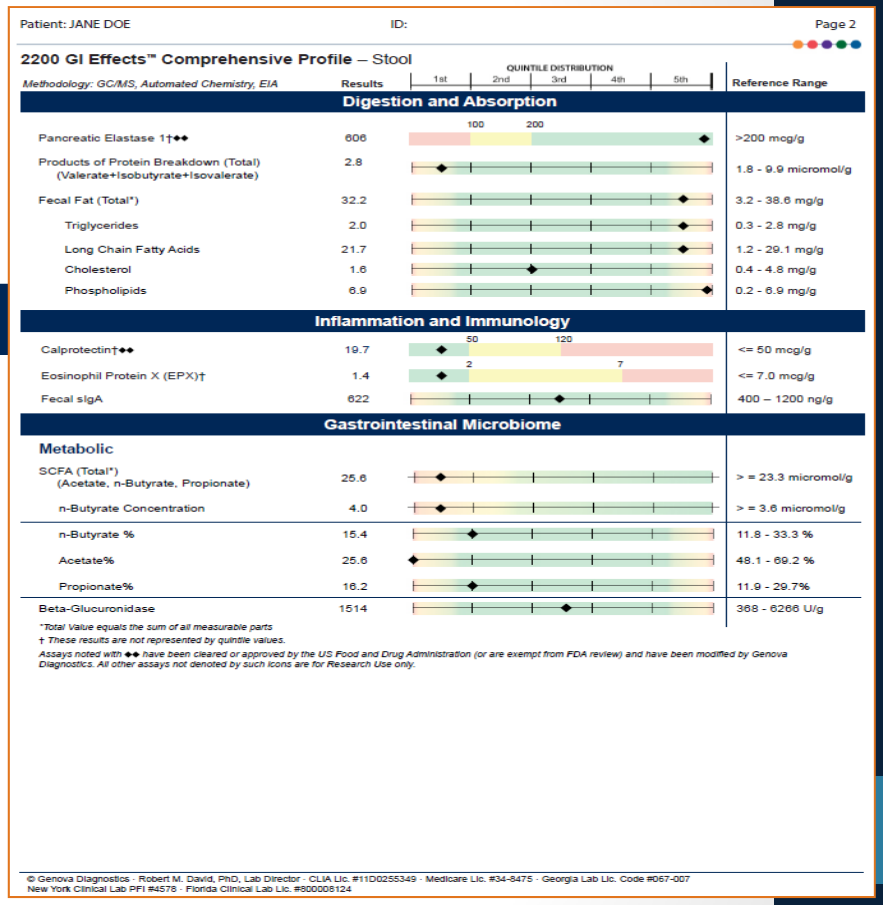
Everything you need to know to assess your patients Gut Microbiome

MICROBIOME TESTING


Wait a second-- this is chocolate! ...what happened to Mr. Feldson's stool sample?!
Specimen Lab
Happy Valentine's Day...

- Digestion and Absorption
- Inflammation and Immunology
- Gastrointestinal Microbiome

D.I.G.



Patient: JANE DOE ID: Page 2

2200 GI Effects™ Comprehensive Profile – Stool

Methodology: GC/MS, Automated Chemistry, EIA

	Results	QUINTILE DISTRIBUTION (1st 2nd 3rd 4th 5th)	Reference Range
Digestion and Absorption			
Pancreatic Elastase 1†◆◆	606	100 / 200	>200 mcg/g
Products of Protein Breakdown (Total) (Valerate+Isobutyrate+Isovalerate)	2.8		1.8 - 9.9 micromol/g
Fecal Fat (Total*)	32.2		3.2 - 38.6 mg/g
Triglycerides	2.0		0.3 - 2.8 mg/g
Long Chain Fatty Acids	21.7		1.2 - 29.1 mg/g
Cholesterol	1.6		0.4 - 4.8 mg/g
Phospholipids	6.9		0.2 - 6.9 mg/g
Inflammation and Immunology			
Calprotectin†◆◆	19.7	50 / 120	<= 50 mcg/g
Eosinophil Protein X (EPX)†	1.4	2 / 7	<= 7.0 mcg/g
Fecal sIgA	622		400 – 1200 ng/g
Gastrointestinal Microbiome			
Metabolic			
SCFA (Total*) (Acetate, n-Butyrate, Propionate)	25.6		> = 23.3 micromol/g
n-Butyrate Concentration	4.0		> = 3.6 micromol/g
n-Butyrate %	15.4		11.8 - 33.3 %
Acetate%	25.6		48.1 - 69.2 %
Propionate%	16.2		11.9 - 29.7%
Beta-Glucuronidase	1514		368 - 6266 U/g

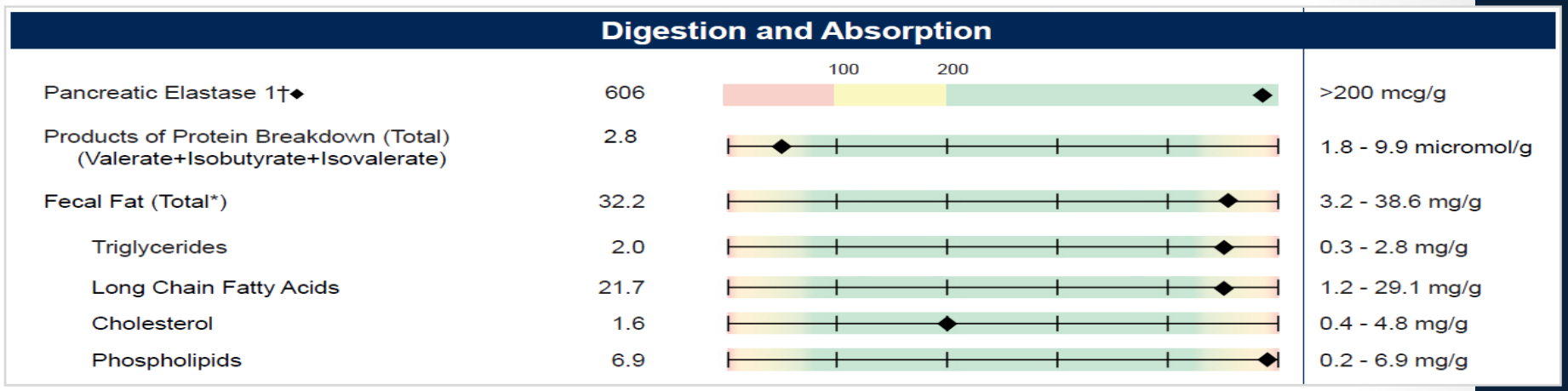
**Total Value equals the sum of all measurable parts*

† These results are not represented by quintile values.

Assays noted with ◆◆ have been cleared or approved by the US Food and Drug Administration (or are exempt from FDA review) and have been modified by Genova Diagnostics. All other assays not denoted by such icons are for Research Use only.

DIGESTION AND ABSORPTION

D = Digestion and Absorption



- Pancreatic Elastase 1
- Products of Protein Breakdown (Putrifactive SCFAs)
- Fecal Fat

Pancreatic Elastase

> 350 µg/g	Normal pancreatic function
200-350 µg/g	Declining pancreatic function Consider supplementation
100-200 µg/g	Moderate pancreatic insufficiency Supplement with broad array of pancreatic enzymes
<100 µg/g	Severe pancreatic insufficiency Supplement with broad array of pancreatic enzymes

Pancreatic Elastase

- Used for initial determination of pancreatic exocrine insufficiency and monitoring of pancreatic exocrine function in patients under treatment.
- Patients in whom testing may be useful include
  - Unexplained diarrhea
  - Weight loss
  - Other signs of malabsorpton
  - Abdominal pain
- Pancreatic Exocrine dysfunction may occur secondary to
  - Chronic Pancreatitis, diabetes, celiac disease, inflammatory bowel disease, Cystic fibrosis, alcohol consumption, gallstone disease

Pancreatic Elastase Treatment

- Smoking cessation
- Reduced alcohol consumption
- Small frequent meals
- Replace fat soluble vitamins
- Supplemental lipase or pancreatic enzymes (plant-based are not strong enough for severe EPI)
- Prescription strength enzymes
  - Creon, zenpep and others

RULE OUT EPI IN CELIAC DISEASE AND SIBO

Exocrine pancreatic insufficiency, MRI of the pancreas and serum nutritional markers in patients with coe

Miroslav Vujas

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Dr Miroslav Vuja

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Received 21 January 2015

Revised 29 June 2015

EPI should be excluded in all patients with CD in the presence of overt malnutrition or in cases of persistent gastrointestinal symptoms despite a gluten-free diet.

Products of Protein Breakdown

- Inadequate protein digestion & fermentation by anaerobic bacteria
  - Causes
    - Low hydrochloric acid (HCL)
    - Protease insufficiency
- Small Intestinal Bacterial Overgrowth (SIBO)
  - Bloating immediately after meals, especially carbohydrate-rich meal
  - Intolerance to fructose (low FODMAPS diet)

Causes of low stomach acid

- Advanced age (30% of elderly)
- Use of proton pump inhibitors
- Autoimmunity, fasting chronic medical conditions

Symptoms

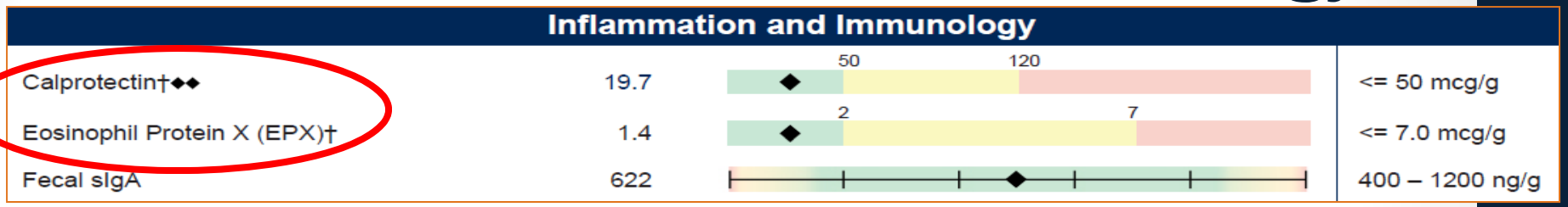
- Bloating/belching after meals
- Intolerance for protein
- Rectal itching
- Weak peeling or cracked fingernails/vertical ridges
- Adult acne
- Undigested food in stool

Consequences of low HCl

- Small Intestinal Bacterial Overgrowth
- Dysbiosis – altered gut bacteria
- Chronic candida Infections
- Mineral Deficiencies
  - Ca, Mg, Zn, Fe, Cr, Mo, Mn, Cu
- B_{12} deficiency
- Unexplained low ferritin or anemia

INFLAMMATION AND IMMUNOLOGY

I = Inflammation and Immunology



- Calprotectin and EPX primary markers of inflammation
- Fecal sIgA
- Lactoferrin available as Add-On

Calprotectin

- Elevated in:
  - Inflammatory Bowel Disease
  - Post-Infectious Irritable Bowel Syndrome
  - Gastrointestinal cancers
  - Certain gastrointestinal infections
  - NSAID enteropathy
  - Food allergy
  - Chronic Pancreatitis

Poullis A et al. *J Gastroenterol Hepatol 2003;18:756-762*

Calprotectin: Know when it's SERIOUS

< 50 µg/g	No significant inflammation
50-120 µg/g	Indicates some GI inflammation: IBD, infection, polyps, neoplasia, NSAIDS
> 120 µg/g	Significant inflammation; referral may be indicated to determine pathology
> 250 µg/g	Active disease present; predicts imminent relapse in treated patients

Tibble J, Teahon K, Thjodleifsson B, et al. Gut 2000;47:506-513.

Eosinophilic Protein X

- Released in eosinophil degranulation
- Sensitive marker of GI inflammation
- May predict relapse in IBD
- Stable in transport up to 7 days
- Sensitive marker for low-level inflammation

,4

Eosinophilic Protein X

- May be elevated with:
  - Inflammatory Bowel Disease
  - Celiac Disease
  - Parasites
  - Allergic reaction
  - Less common
    - GERD
    - Chronic diarrhea
    - Chronic alcoholism
    - Protein-Losing Enteropathy

Fecal IgA

LOW SIGA

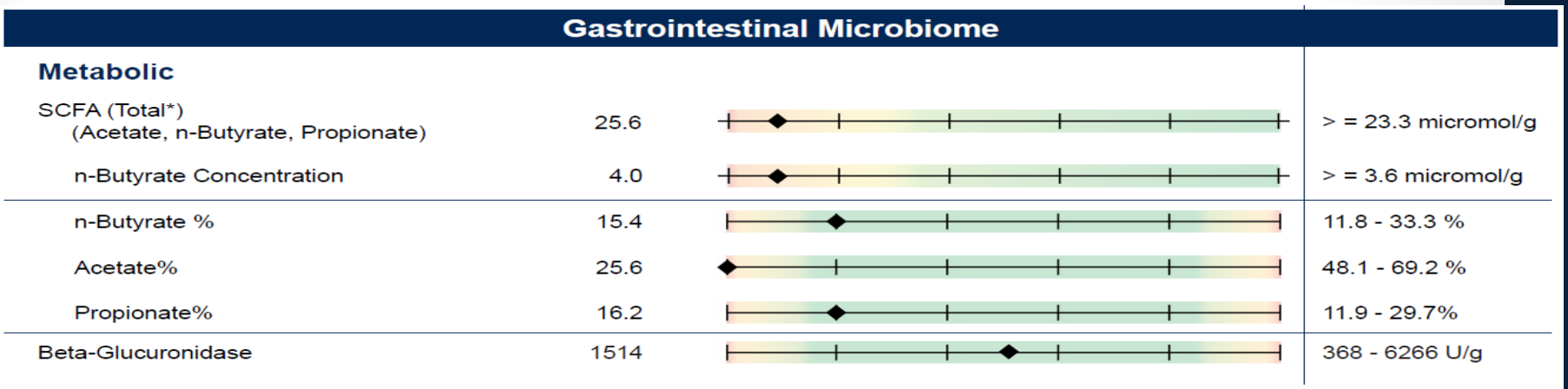
- CAUSES
  - Chronic stress
  - Dysbiosis
  - Immunocompromised
- **TREATMENT: Support mucosa…**
  - L-glutamine,
  - Probiotics – bifido sp.
  - S.boulardii
  - Colostrum or IgG (Enterogam)
  - Fatty Acids
  - Zinc

HIGH SIGA

- CAUSES
  - Response to eliminate pathogens in GI tract
  - Sensitivities to foods
- **TREATMENT**
  - Immune support
  - Remove pathogens, parasites, bacteria, yeast
  - Rule out food sensitivities
  - Elimination diet

GASTROINTESTINAL MICROBIOME & METABOLIC MARKERS

G = Gastrointestinal Microbiome and Metabolic Markers



Gastrointestinal Microbiome			
Metabolic			
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n-Butyrate Concentration	4.0		> = 3.6 micromol/g
n-Butyrate %	15.4		11.8 - 33.3 %
Acetate%	25.6		48.1 - 69.2 %
Propionate%	16.2		11.9 - 29.7%
Beta-Glucuronidase	1514		368 - 6266 U/g

- **Short chain fatty acids** (SCFAs)
  - Acetate, n-Butyrate and Propionate produced by anaerobic bacterial fermentation of indigestible carbohydrate (fiber)
- **Beta-glucuronidase**
  - Enzyme inducible by activity of anaerobes in the gut (E Coli, Bacteroides, Clostridia)

RESEARCH ARTICLE

Butyrate and Propionate Protect against Diet-Induced Obesity and Regulate Gut Hormones via Free Fatty Acid Receptor 3-Independent Mechanisms

Hua V. Lin, Andrea Frassetto, Edward J. Kowalik Jr, Andrea R. Nawrocki, Mofei M. Lu, Jennifer R. Kosinski, James A. Hubert, Daphne Szeto, Xiaorui Yao, Gail Forrest, Donald J. Marsh

Published: April 10, 2012 • DOI: 10.1371/journal.pone.0035240

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are metabolites formed by gut microbiota from complex dietary carbohydrates. Butyrate and acetate were reported to protect against diet-induced obesity without causing hypophagia, while propionate was shown to reduce food intake

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0035240

Short chain fatty acids and colonic health

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Abstract

Recently, colonic health has been linked to the maintaining overall health status and reducing the risk of diseases by changes in lifestyle. Functional foods, such as "prebiotics" and "probiotics", dietary fibers, and other dietary components that target the colon and affect its environment enhancing short fatty acid (SCFA) production have been at the forefront. The topic of this review is the key end products of colonic ferment
Butyrate is the maj
enters the peripher
risk of developing
Text (Free, PDF)
Key words: colon

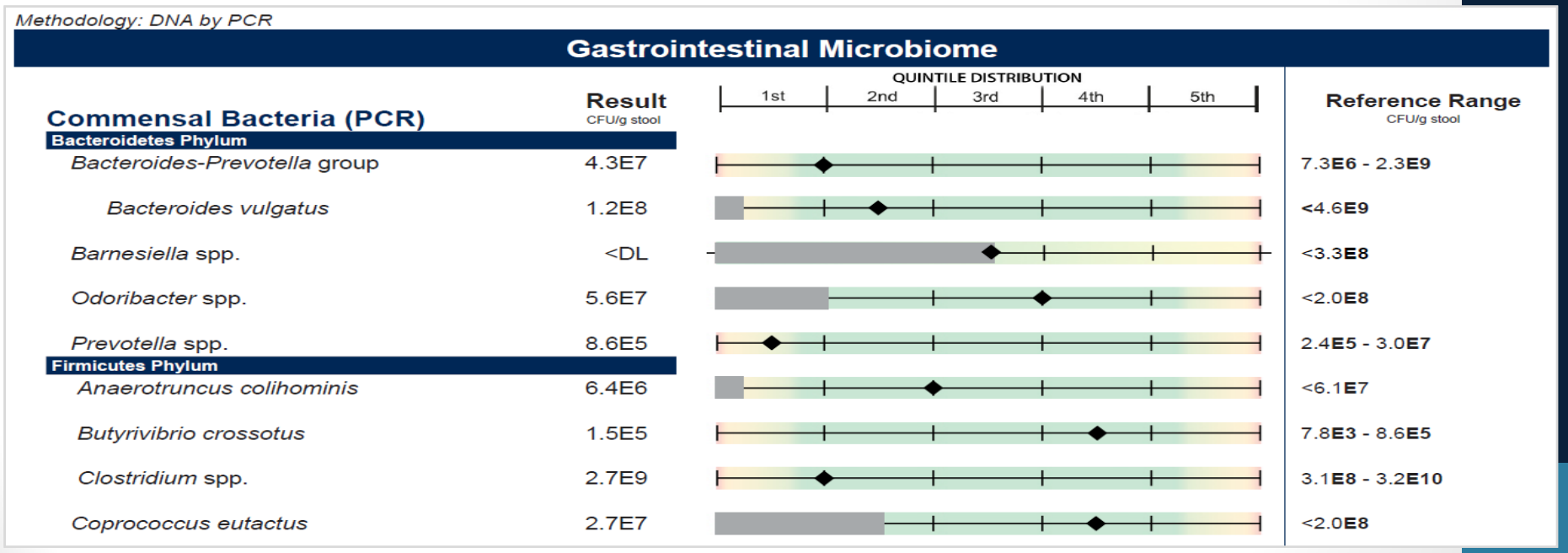
The role of SCFAs has expanded to include their role as nutrients for the colonic epithelium, as modulators of colonic and intracellular pH, cell volume, and other functions associated with ion transport, and as regulators of proliferation, differentiation, and gene expression

http://www.bmj.sk/2007/10808-06.pdf

SCFAs control weight and insulin sensitivity

- **For LOW Beneficial SCFAs**
  - Increase dietary fiber
  - Prebiotics & probiotics
  - Saccharomyces boulardii
- **For HIGH Beta glucoronidase**
  - Decrease meat intake & increase insoluble fiber
  - Probiotics
  - Liver support : Silybum marianum
  - Calcium-D-glucarate

Testing Commmensials



Methodology: DNA by PCR

Gastrointestinal Microbiome

Commensal Bacteria (PCR)	Result (CFU/g stool)	Reference Range (CFU/g stool)
Bacteroidetes Phylum		
Bacteroides-Prevotella group	4.3E7	7.3**E6** - 2.3**E9**
Bacteroides vulgatus	1.2E8	<4.6**E9**
Barnesiella spp.	<DL	<3.3**E8**
Odoribacter spp.	5.6E7	<2.0**E8**
Prevotella spp.	8.6E5	2.4**E5** - 3.0**E7**
Firmicutes Phylum		
Anaerotruncus colihominis	6.4E6	<6.1**E7**
Butyrivibrio crossotus	1.5E5	7.8**E3** - 8.6**E5**
Clostridium spp.	2.7E9	3.1**E8** - 3.2**E10**
Coprococcus eutactus	2.7E7	<2.0**E8**

QUINTILE DISTRIBUTION: 1st | 2nd | 3rd | 4th | 5th

Testing Commmensials

Gut Microbiome and Cardiovascular disorders

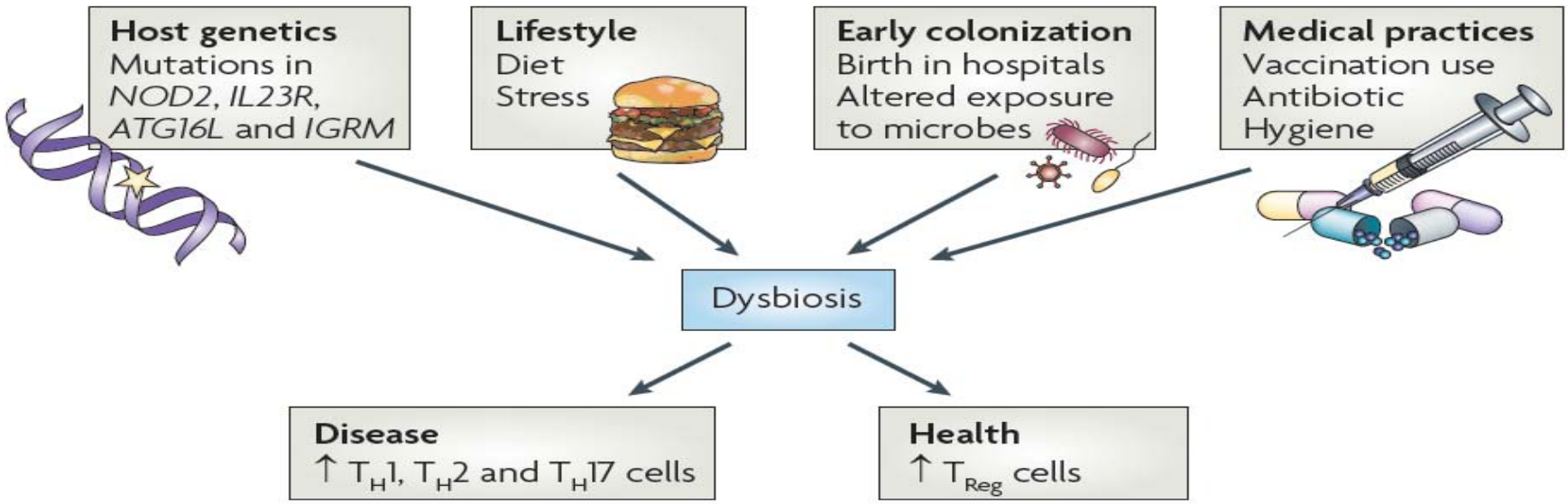
Genus/ Species	PAC Score	Low Risk Range	Moderate Risk Range	High Risk Range	Previous Result
Collinsella	4.78	4 - 6	6 – 8	>8	
Eubacterium	6.68	4 - 6	2 - 4	<2	
Roseburia	1.99	4 – 6	2 – 4	<2	
Clostridium	5.66	4 - 6	2 - 4	<2	
Ruminococcus	7.52	4 - 6	6 - 8	>8	
Peptostreptococcus	5.77	4 - 6	2 - 4	<2	
Prevotella	5.33	4 - 6	6 - 8	>8	
Lactobacillus reuteri	0.85	4 – 6	2 – 4	<2	
Enterococcus faecium	4.68	4 – 6	2 – 4	<2	
Lactobacillus acidophilus	0.11	4 – 6	2 – 4	<2	
Bifidobacterium lactis	4.56	4 – 6	2 – 4	<2	
Lactobacillus plantarum	1.15	4 – 6	2 – 4	<2	
Lactobacillus fermentum	3.65	4 – 6	2 – 4	<2	
Lactobacillus curvatus	5.11	4 – 6	2 – 4	<2	

Causes of dysbiosis

- SAD – low fiber, high in fat & simple carbs
- Broad-spectrum antibiotics
- Chronic maldigestion (including PPIs)
- Chronic constipation
- Stress suppresses Lactobacillus, Bifidobacteria, and sIgA
- Catecholamines stimulate growth of gram-negative organisms (Yersinia, Pseudomonas)
  - 45-50% of total body production of norepinephrine occurs in mesenteric organs
- Anger or fear increases Bacteroides fragilis

Proposed causes of dysbiosis of the microbiota

The composition of microbiota can shape a healthy immune response or predispose to disease



USE CUTTING EDGE MICROBIOTA/STOOL TESTING TO MOVE BEYOND TREATING SYMPTOMS TO ARRIVE AT PERSONALIZED TREATMENTS FOR A HEALTHY GUT!

KEY TAKE-AWAYS

Key Take-aways

- Endotoxemia = LPS
  - Treat leaky gut!
- TMAO: from choline, phostphatidyl choline and carnitine.
  - Depends on the microbiome metabolism of these compounds
- SCFAs: Butyrate, propionate, acetate
  - Key to colonic health, IR, DM, lipid metabolism, gluconeogenesis, lipogenesis, enterocyte health, energy, glucose homeostasis signaling molecules for GPR 41 and 43 and PYY

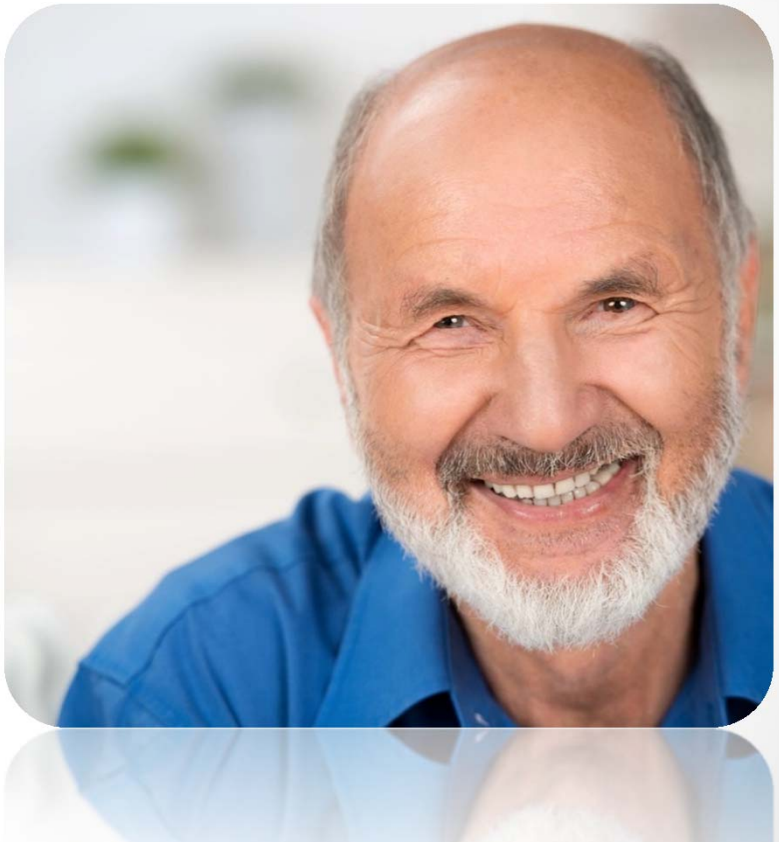
Key Takeaways

- Bile Acid Metabolism
  - Primary to secondary bile acids
  - Metabolic switches for FXR, PRP, TGR5, glucose metabolism, lipoid metabolism, thermogenesis in BAT
  - Role in obesity and alteration with antibiotics
- Products of microbiome affect health and CV disease
- Microbiome affects obesity, IR, DM, HTN, dyslipidemia, CHD, MI and CHF
- TREATMENT:
  - Mediterranean Diet, added fiber, FMT, Prebiotics, probiotics EVOO, DMB (dimethylbutanol)

CASE STUDY

Case Study

- 70 y/o male
- 6’1” 315 pounds
- BP 150/85
- “I want to lose weight”



Case Study

- PMHx – HTN, hyperlipidemia, alcholism, OSA, gout, obesity, arthritis, fatigue, IBS-C
- PSHx – non-contributory
- Social -Alcohol – 3 weeks ago stopped drinking (previously drinking 6 shots per night)
- FHx - two uncles died in 40s. Nearly all male relatives died of acute MI. Many alcoholics in family

Case Study

- Assessment
  - Obesity
  - Back pain/hip pain
  - Hypertension
  - Obstructive sleep apnea
  - Carpel Tunnel syndrome
  - Arthritis
  - History of kidney stones
  - IBS-C

Case Study

- Medications
  - Allupurinol 300mg daily
  - Losartan 100mg daily
  - Atenolol 25mg daily
  - Atorvastatin 40mg daily
  - Celebrex 200mg
  - Lubrisyn HA Take 1 daily
  - Aspirin 81 mg daily
  - Stool softener
  - Metamucil 1 tsp daily
  - Miralax 1 TBSP daily

Case Study

- Supplements
  - Protein shake
  - Multivitamin
  - Fish Oil
  - Digestive Enzyme
  - Probiotic

Case Study

- Testing Ordered
  - Serum Labs
  - NutrEval
  - GI profile
  - SIBO breath test

Abnormal Serum Labs

- Positive DQ8 homozygous
- Low serum IgA
- Homocysteine = 17
- hsCRP = 3.9
- Fasting glucose 95
- Total cholesterol 170
- HDL 37 L
- LDL 105
- LDL particle # 1816 H
- LDL small 478 H
- LDL pattern B H
- Lipoprotein (a) 80 H

Results

INFLAMMATION

Calprotectin ▲

Fecal secretory IgA ▲

INSUFFICIENCY

Fecal Fats (Total) ▲

IMBALANCE

n-Butyrate ▼

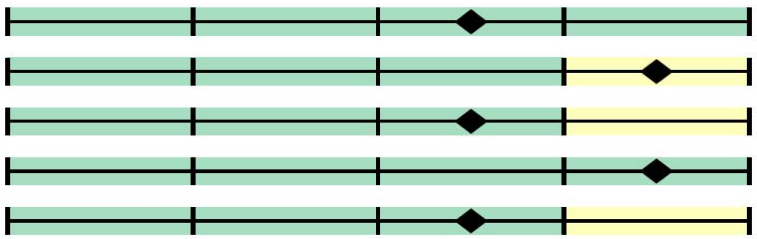
Total SCFA ▼

PP Bacteria ▲

Beneficial Bacteria ▼

Additional Bacteria

alpha haemolytic Streptococcus	3+	NP
Citrobacter freundii	4+	PP
Klebsiella pneumoniae	3+	NP
Streptococcus agalactiae gp B	4+	NP
Pseudomonas aeruginosa	3+	NP



Results

- Calprotectin elevated
- High fecal IgA
- Elevated fecal fat
- Low butyrate
- Low SCFAs
- Bacterial Dysbiosis

New Plan

- **Gluten-free Diet**
  - **Less important but also recommended no egg, dairy, corn or sugar due to IgG testing**
- **Increase fiber in diet**
- **Avoid alcohol**
- **Exercise 30-45min daily – start slowly**

New Plan

- **Curcumin 3 grams daily**
- **Methylation support formula**
- **Gut Support for dysbiosis**
  - **Berberine 3-5 grams daily**
  - **Undecylenic acid 2500mg daily**
- **Brain support**
  - **Acetyl-L Carnitine'**
  - **Ginkgo**
  - **Bacopa**
  - **Vinpocetine**
  - **PS**
- **High dose fish oil 4 grams daily**
- **Once SIBO treatment complete, high dose probiotic**

Follow-up 6 months later

- Sixty pound weight loss!
- Blood pressure normalized
- Remained off all alcohol
- Homocysteine now 12
- hsCRP < 1.0
- Calprotectin normal off gluten

Dr. Jill

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