INFLAMED BY THE WORLD: UNDERSTANDING THE ROLE OF BIOMARKERS ON SYSTEMIC INFLAMMATION

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Educational Director, Progressive Medical Centers



Organ of Immune tolerance

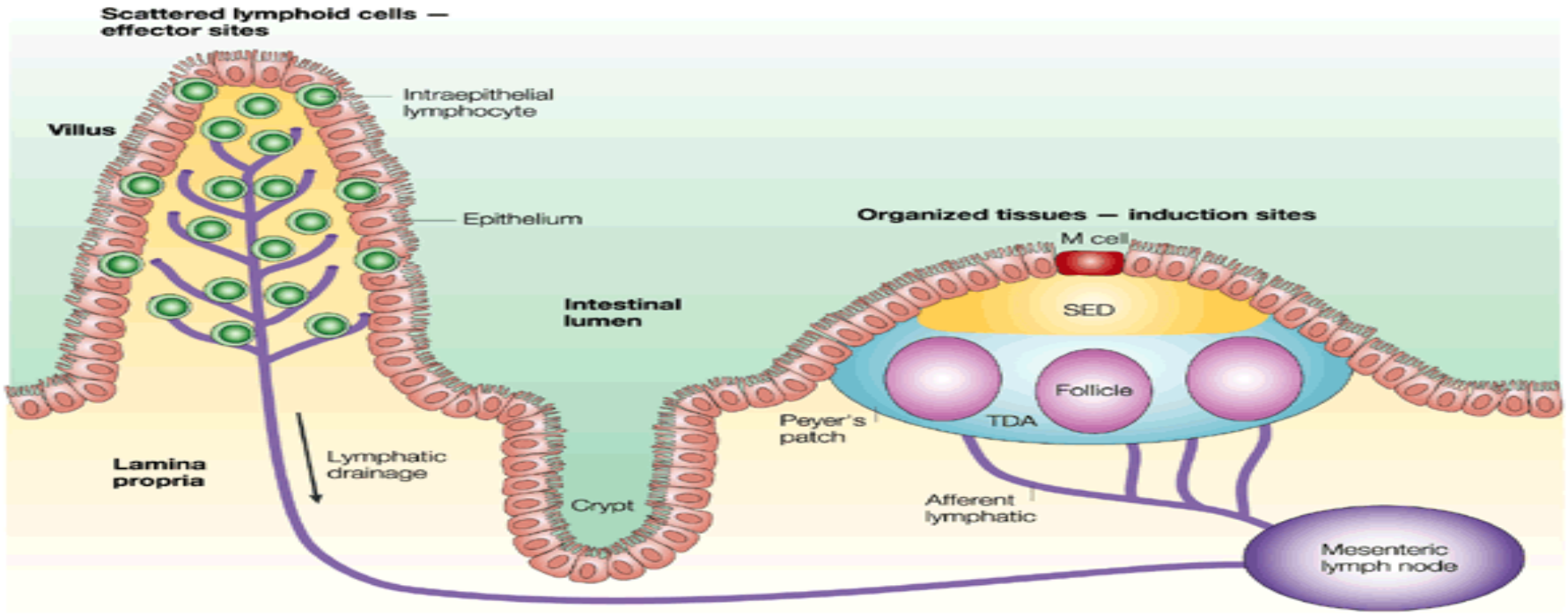
The intestinal mucosa forms the largest area of the body in direct contact with the exterior environment. If expanded, the surface of the small intestine alone can reach roughly the

size of a tennis court, or 100 times the area of the skin.



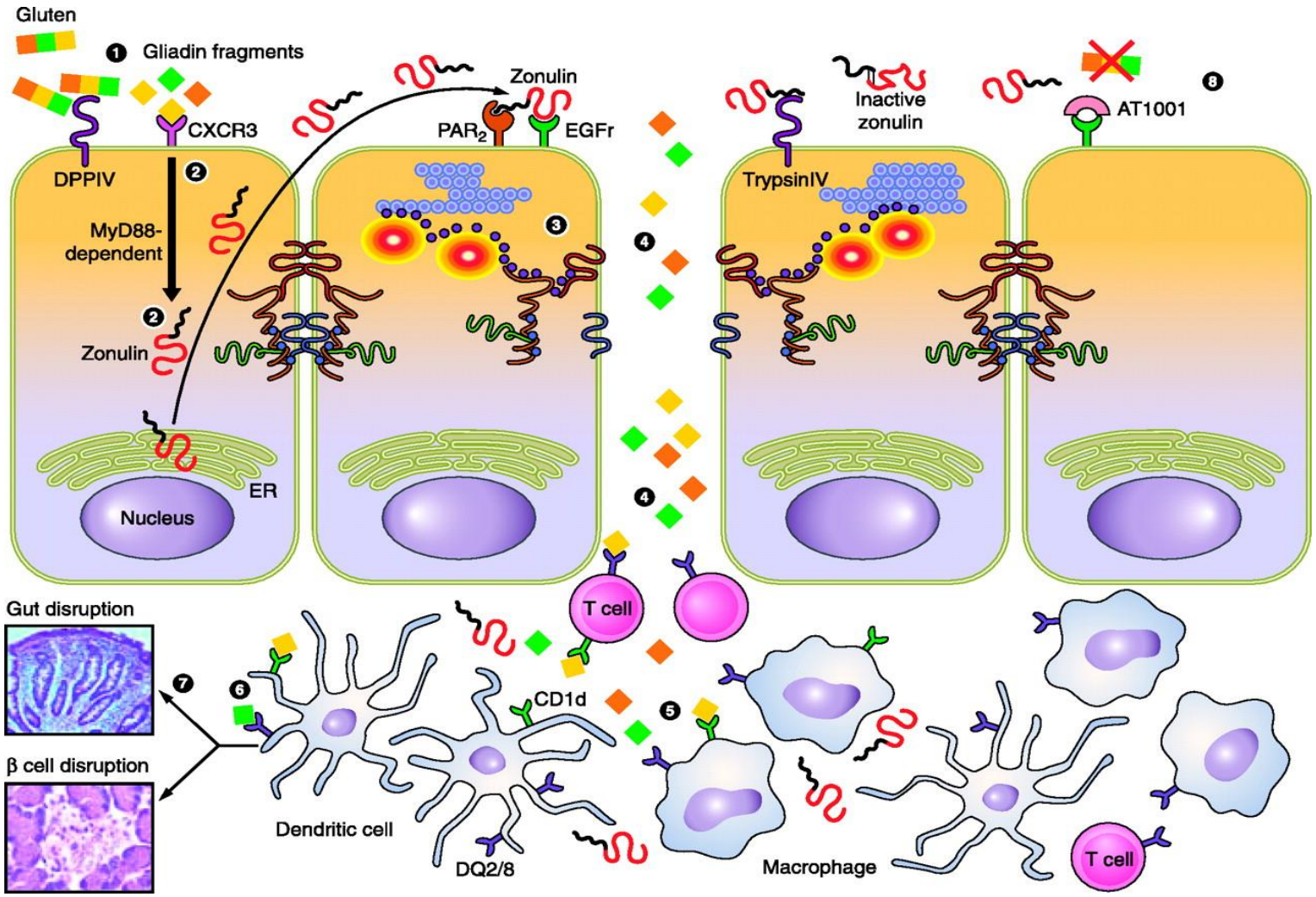
Immune regulation by the gut

As expected, the intestinal mucosa is filled with a diverse and large number of immune cells. The gut-associatedlymphoid-tissue (GALT) includes the Peyer's patches (PP) and isolated lymphoid follicles (ILFs). However, most of the immune cells in the intestine are associated with the intestinal villi, either in the intraepithelial or lamina propria



Complaint	Number Of Patients Reporting For Initial Test	Number Of Patients Reporting For Second Test
Memory/Concentration	22	3
Anxiety/Mood/Depression	20	3
Bloating/Stomach Pain	18	2
Fatigue	18	4
Joint Pain / Stiffness / Swelling	13	1
Muscle Aches	13	1
Craving Sugar	12	2
Sleeplessness/Insomnia	12	0
Lightheaded/Dizzy	11	2
Allergies/Sinus	9	2
Cold Intolerance	9	3
Inability to lose weight	9	2

Mechanisms of gliadin-induced zonulin release, increased intestinal permeability, and onset of autoimmunity.



Fasano A Physiol Rev 2011;91:151-175

Physiological Reviews

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Zonulin

SAMPLE DATE:	
RECEIVE DATE:	
REPORT DATE:	

Nine Dunwoody Park, Suite 121
Dunwoody, GA 30338
Phone: 678-736-6374 | Fax: 770-674-1701
Email: info@dunwoodylabs.com

ADVANCED INTESTINAL BARRIER ASSESSMENT: PROFILE 5150 (PLASMA)

Zonulin

PATIENT RESULT
0.2
ng/ml
REPORTABLE RANGE: <4.0 ng/ml

OPTIMAL

0 1 2 3 4

Diamine Oxidase (DAO)

PATIENT RESULT
1.0
ng/ml
REPORTABLE RANGE: 0-88 ng/ml

ABNORMALLY LOW

0 22 44 66 88

Histamine

PATIENT RESULT
0.84
ng/ml
REPORTABLE RANGE: 0.0–2.4 ng/ml

BORDERLINE

0.0 0.6 1.2 1.8 2.4

DAO: Histamine Ratio

1

0 30 45 60 75

A high DAO-to-Histamine ratio suggests that there is sufficient DAO present to degrade any free histamine.

A low ratio, on the other hand, may be indicative of histamine intolerance. The lower the ratio, and particularly the closer it gets to 1, the stronger that indication.

Inflammation, the fire behind The pathology

- Allergy and related diseases affect at least 100 million people worldwide. (hidden allergy symptoms)
- In the USA alone about 50 million people suffer from allergies at a cost of 18 billion dollars per year.
- In general, the prevalence of food allergies has increased to more than 50% in adults and more than 70% in children in the past few years.
- Food-related allergies cause a wide variety of illnesses ranging from skin rashes and headaches to chronic intestinal diseases.
- Although the symptoms of allergy may differ, allergens (antigens) from food, food additives or environmental sources cause the production of antibodies (IgM, IgA, IgG, IgE and IgD) or interact with the mucosa or epidermis and stimulate T-cells.

The Gut's Role in Inflammation

The cells in the intestinal mucosa consist of mainly activated or antigen experienced T cells (CD45RBlo, CD44hi, CD69hi, CD62Llo) that are capable of producing several proinflammatory cytokines such as IL-4, IFN-*γ*, *IL-17A/F, IL-22, and TNF-α [6–15].*

Living Life on the Edge of the Wall

- Physiological, Pathological, and Therapeutic Implications of Zonulin-Mediated Intestinal Barrier Modulation
  - Am J Pathol. 2008 November; 173(5): 1243–1252.
- Human zonulin, a potential modulator of intestinal tight junctions
  - J Cell Sci 113, 4435-4440. December 15, 2000

Leaky gut and autoimmune diseases.

Leaky gut and autoimmune diseases. Mucosal Biology Research Center, University of Maryland School of Medicine, Baltimore, MD 21201, USA. afasano@mbrc.umaryland.ed

Autoimmune diseases are characterized by tissue damage and loss of function due to an immune response that is directed against specific organs. This review is focused on the role of impaired intestinal barrier function on autoimmune pathogenesis. Together with the gut-associated

This new paradigm subverts traditional theories underlying the development of these diseases and suggests that these processes can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing the zonulin-dependent intestinal barrier function.

Clin Rev Allergy Immunol. 2012 Feb;42(1):71-8. doi: 10.1007/s12016-011-8291-x.
PMID: 22109896 [PubMed - in process]

Leaky gut and type II diabetes

Leaky gut and diabetes mellitus: what is the link?

de Kort S, Keszthelyi D, Masclee AA.

Department of Internal Medicine, Division of Gastroenterology-Hepatology, Maastricht University Medical Centre+, Maastricht, the Netherlands.

Abstract

Diabetes mellitus is a chronic disease requiring lifelong medical attention. With hundreds of millions suffering worldwide, and a rapidly rising incidence, diabetes mellitus poses a great burden on healthcare systems. Recent studies investigating the underlying mechanisms involved in disease development in diabetes point to the role of the dys-regulation of the intestinal barrier. Via alterations in the intestinal permeability, intestinal barrier function becomes compromised whereby access of infectious agents and dietary antigens to mucosal immune elements is facilitated, which may eventually lead to immune reactions with damage to pancreatic beta cells and can lead to increased cytokine production with consequent insulin resistance. Understanding the factors regulating the intestinal barrier function will provide important insight into the interactions between luminal antigens and immune response elements. This review analyses recent advances in the mechanistic understanding of the role of the intestinal epithelial barrier function in the development of type 1 and type 2 diabetes. Given our current knowledge, we may assume that reinforcing the intestinal barrier can offer and open new therapeutic horizons in the treatment of type 1 and type 2

The Gut is more than a filter

Physiol Rev. 2011 Jan;91(1):151-75.

Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer.

Fasano A.

Sour

Muco

The

Zonulin is the only physiological modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance.

Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiol Rev. 2011 Jan;91(1):151-75.

Zonulin, the lens to immune tolerance

Gut 2009;**58**:1152-1167 doi:10.1136/gut.2008.163667

Recent advances in basic science

Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the

Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease

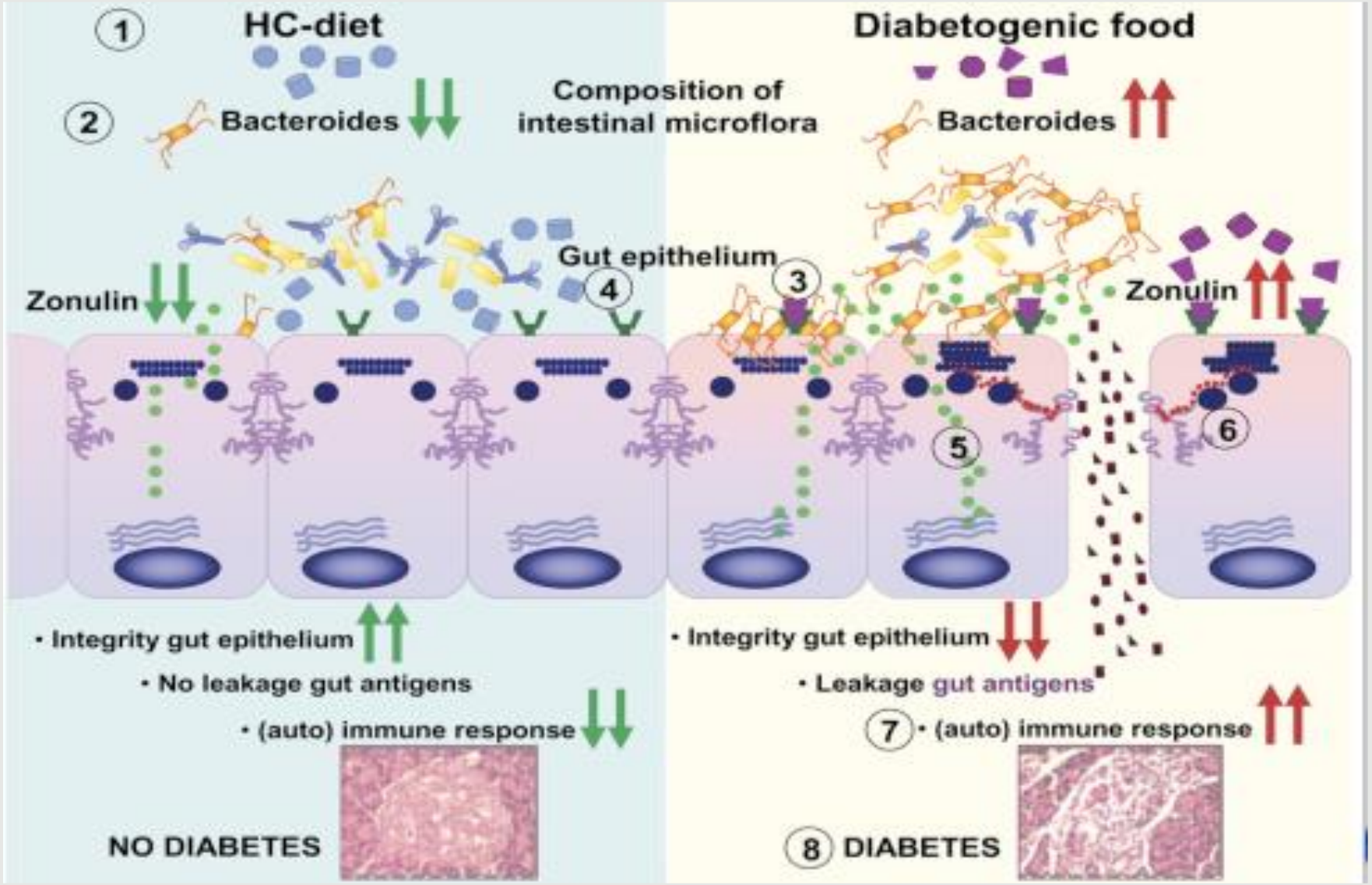
Gut 2009;**58**:1152-1167 doi:10.1136/gut.2008.163667

is

IL1β, IL6, IL21 and IL23. Recent studies indicate that TGFβ is essential not only for the development of murine Th17 cells but also for differentiation of human Th17 cells. TGFβ reciprocally regulates the differentiation of inflammatory Th17 cells and suppressive Treg subsets, with the concomitant presence of proinflammatory cytokines favouring Th17 cell differentiation. Several studies demonstrated an important role of Th17 cells in intestinal inflammation, particularly in Crohn's disease. Genome-wide association studies indicate that *IL23R* and five additional genes involved in Th17 differentiation (*IL12B*, *JAK2*, *STAT3*, *CCR6* and *TNFSF15*) are associated with susceptibility to Crohn's disease and partly also to ulcerative colitis. Taken together, both Th1 and Th17 cells are important mediators of inflammation in Crohn's disease, although activities previously ascribed to IL12 may be mediated by IL23. Anti-IL12/IL23p40 antibody therapy, which targets both Th1 and Th17 cells, is effective in Crohn's disease. However, the complex relationship between Th1 and Th17 cells has not been completely analysed. This will be of great importance to delineate the specific contributions of these cells to Crohn's disease and other autoimmune diseases.

Dysbiotic Diet and LPS

Alter intestinal tight junction function



Degradation of tight junctions determines symptoms/virulence

Biochim Biophys Acta. 2009 Apr;1788(4):832-41. Epub 2008 Nov 14.

Tight junctions as targets of infectious agents.

Guttman JA, Finlay BB.

Source

Simon Fraser University, Department of Biological Sciences, Shrum Science Centre, Burnaby, BC, Canada V5A 1S6. jguttman@sfu.ca

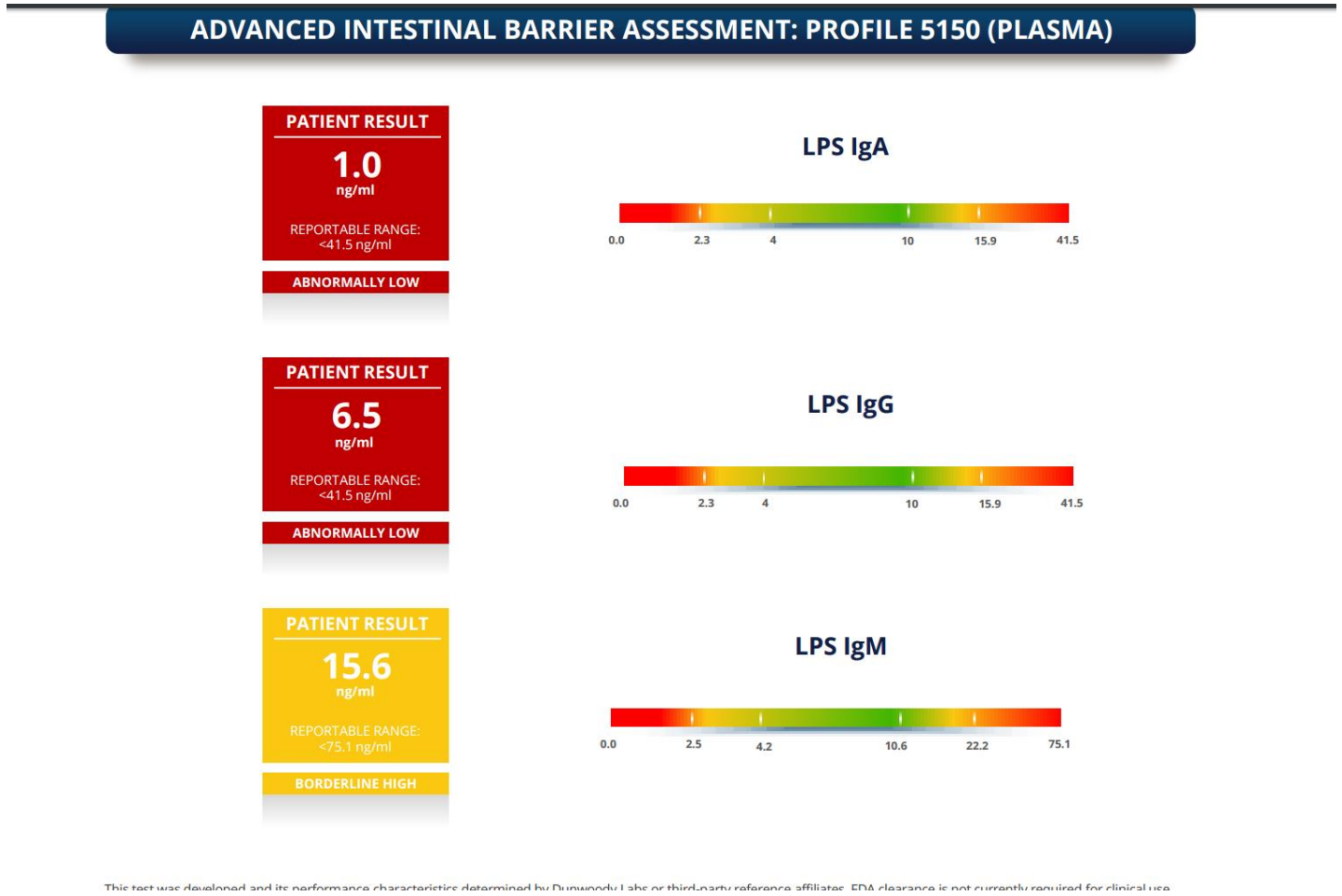
Abstract

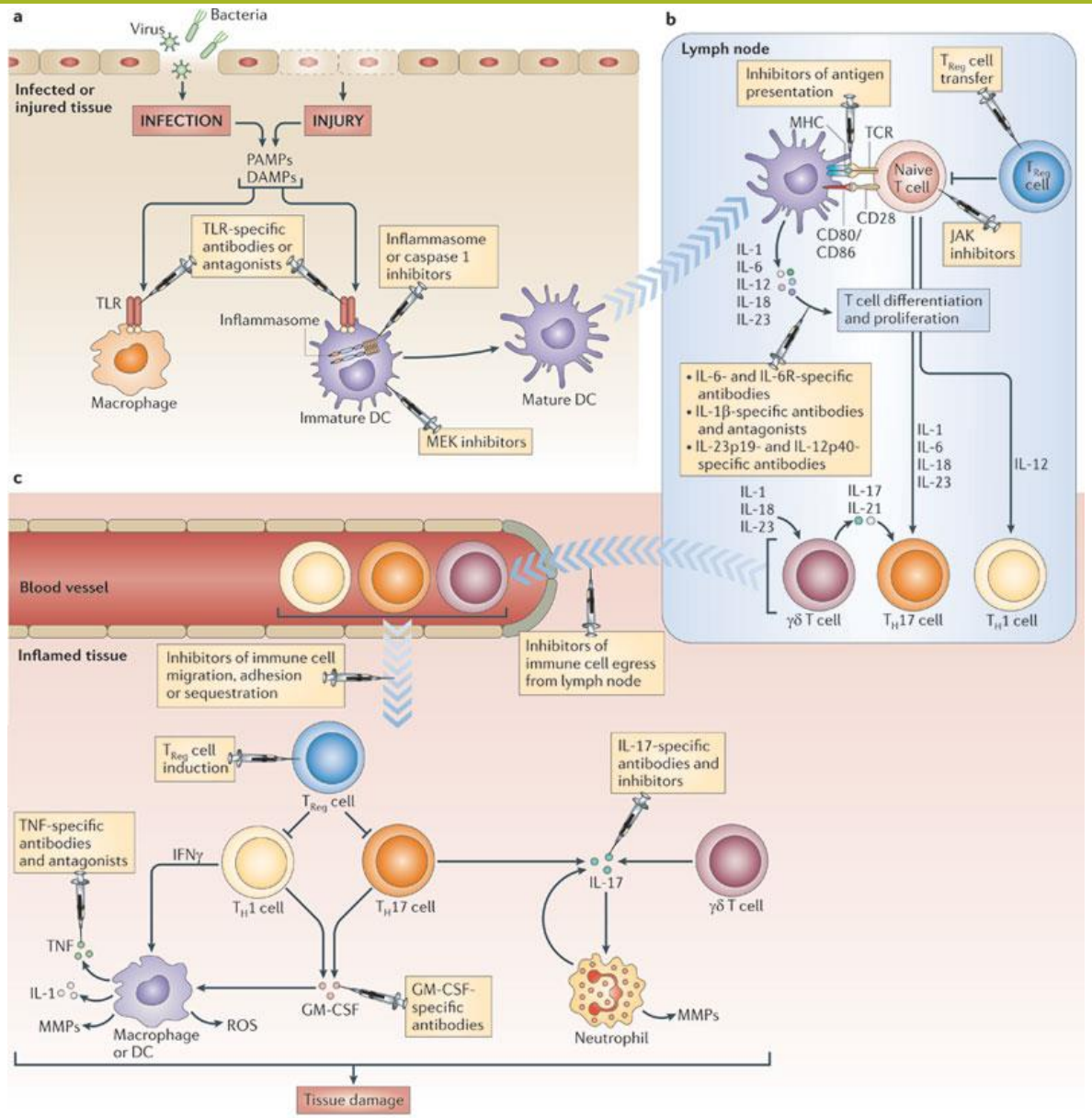
The epithelial barrier is a critical border that segregates luminal material from entering tissues. Essential components of this epithelial fence are physical intercellular structures termed tight junctions. These junctions use a variety of transmembrane proteins coupled with cytoplasmic adaptors, and the actin cytoskeleton, to attach adjacent cells together thereby forming intercellular seals. Breaching of this barrier has profound effects on human health and disease, as barrier deficiencies have been linked with the onset of inflammation, diarrhea generation and pathogenic effects. Although tight junctions efficiently restrict most microbes from penetrating into deeper tissues and contain the microbiota, some pathogens have developed specific strategies to alter or disrupt these structures as part of their pathogenesis, resulting in either pathogen penetration, or other consequences such as diarrhea. Understanding the strategies that microorganisms use to commandeer the functions of tight junctions is an active area of research in microbial pathogenesis. In this review we highlight and overview the tactics bacteria and viruses use to alter tight junctions during disease. Additionally, these studies have identified novel tight junction protein functions by using pathogens and their virulence factors as tools to study the cell biology of junctional structures.

Zonulin Treatment

- Antimicrobials
- Gluten Removal
- Antifungals
- Immunoglobulins

LPS


ADVANCED INTESTINAL BARRIER ASSESSMENT: PROFILE 5150 (PLASMA)
PATIENT RESULT
1.0
ng/ml
REPORTABLE RANGE:
<41.5 ng/ml
ABNORMALLY LOW
LPS IgA
0.0
2.3
4
10
15.9
41.5
PATIENT RESULT
6.5
ng/ml
REPORTABLE RANGE:
<41.5 ng/ml
ABNORMALLY LOW
LPS IgG
0.0
2.3
4
10
15.9
41.5
PATIENT RESULT
15.6
ng/ml
REPORTABLE RANGE:
<75.1 ng/ml
BORDERLINE HIGH
LPS IgM
0.0
2.5
4.2
10.6
22.2
75.1
This test was developed and its performance characteristics determined by Dunwoody Labs or third-party reference affiliates. FDA clearance is not currently required for clinical use.



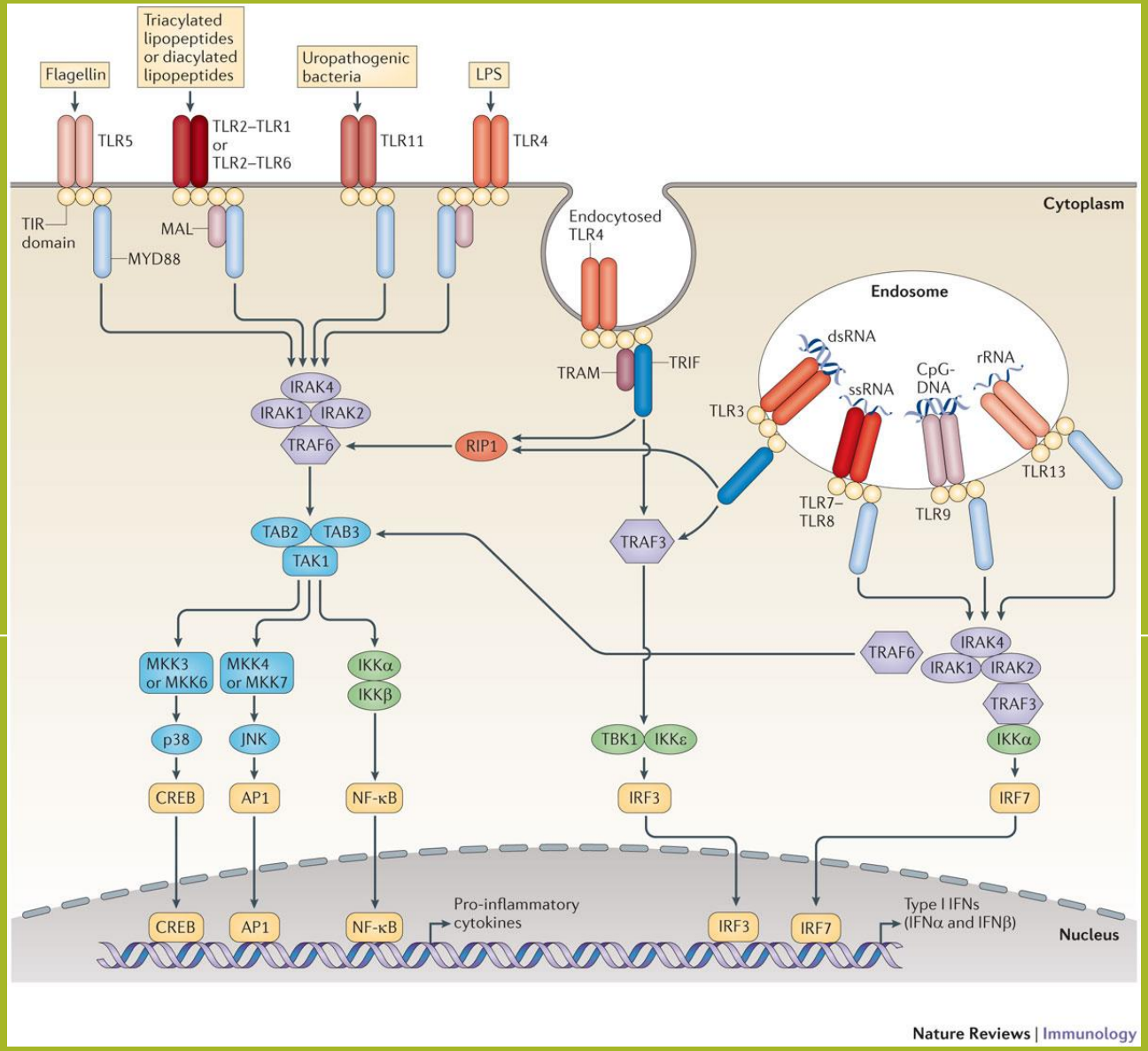
Nature Reviews | Immunology

LPS.

Compared to the classic exotoxins of bacteria, endotoxins are less potent and less specific in their action, since they do not act enzymatically. Endotoxins are heat stable, boiling for 30 minutes does not destabilize endotoxin

- But certain powerful oxidizing agents such as superoxide, peroxide and hypochlorite, have been reported to neutralize them. Endotoxins, although antigenic, cannot be converted to toxoids.




Flagellin
Triacylated lipopeptides or diacylated lipopeptides
Uropathogenic bacteria
LPS
TLR5
TLR2–TLR1 or TLR2–TLR6
TLR11
TLR4
TIR domain
MAL
MYD88
Cytoplasm
Endocytosed TLR4
Endosome
dsRNA
ssRNA
CpG-DNA
rRNA
TLR3
TLR13
TLR7–TLR8
TLR9
TRAM
TRIF
IRAK4
IRAK1
IRAK2
TRAF6
RIP1
TAB2
TAB3
TAK1
TRAF3
MKK3 or MKK6
MKK4 or MKK7
IKKα
IKKβ
p38
JNK
CREB
AP1
NF-κB
TBK1
IKKε
IRF3
IRF7
Pro-inflammatory cytokines
Type I IFNs (IFNα and IFNβ)
Nucleus
Nature Reviews | Immunology

LPS is a factor in inducing Autoimmunity

- Lipopolysaccharide (LPS) is a component of the Gram-negative bacterial cell wall that activates B cells, resulting in marked production of polyclonal antibodies.

LPS is also a potent substance that secretes various kinds of mediators, including interleukin-12 (IL-12) and interferon-γ (IFN-γ)

- Therefore, a number of studies have demonstrated that LPS plays a role in some diseases in which autoantibodies or self antigen-specific T cells are involved.
- LPS enhances nephritis, experimental autoimmune uveitis, experimental autoimmune myocarditis and experimental autoimmune enterocolitis, and autoimmune arthritis.



LPS Treatment

- Berberines
- Probiotics
- Immunoglobulins

Normalizing Treg function

- Eliminate LPS
- Andrographis
- Curcuminoids
- Resveratrol
- Vitamin D
- Vitamin A
- Omega 3 fatty acids

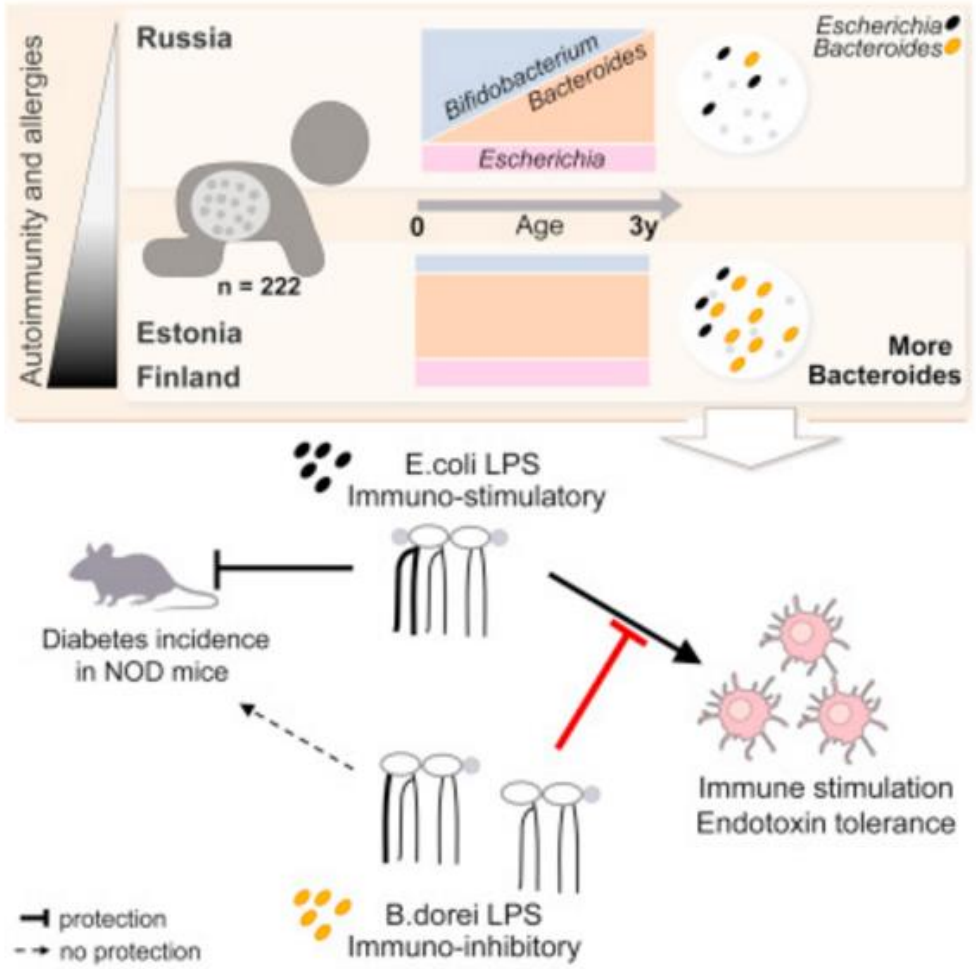


LPS

- **Endotoxins** are part of the outer membrane of the cell wall of Gram-negative bacteria.
- Endotoxin is invariably associated with Gram-negative bacteria whether the organisms are pathogenic or not. Although the term "endotoxin" is occasionally used to refer to any cell-associated bacterial toxin, in bacteriology it is properly reserved to refer to the **lipopolysaccharide** complex associated with the outer membrane of Gram-negative pathogens such as *Escherichiacoli*, *Salmonella*, *Shigella*, *Pseudomonas*, *Neisseria*, *Haemophilus influenzae*, *Bordetella pertussis* and *Vibrio cholerae*.



Graphical Abstract



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of immune education.

LPS, Zinc and Alkaline Phosphatase

- The making of LPS can be modified in order to present a specific sugar structure. Those can be recognized by either other LPS (which enables to inhibit LPS toxins) or glycosyltransferases that use those sugar structure to add more specific sugars.
- It has recently been shown that a specific enzyme in the intestine (alkaline phosphatase) can detoxify LPS by removing the two phosphate groups found on LPS carbohydrates

- Bates JM, Akerlund J, Mittge E, Guillemin K (2007). "Intestinal alkaline phosphatase detoxifies lipopolysaccharide and prevents inflammation in zebrafish in response to the gut microbiota". *Cell Host Microbe*. **2** (6): 371–82.



World Journal of Gastrointestinal Pathophysiology

Reversed with Zinc

PMC full text: World J Gastrointest Pathophysiol. 2014 Nov 15; 5(4): 496–513.
Published online 2014 Nov 15. doi: 10.4291/wjgp.v5.i4.496
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World J Gastrointest Pathophysiol Wo

Table 1

Gastrointestinal morbidities associated with Zinc deficiency

Condition	Model used	Reversibility with Zn supplementation	Ref.
Esophageal cancer	Rodent	Yes	Fong et al[27], 2011
Diarrhea	Human	Yes	Hambidge[72], 1992
Inflammatory bowel diseases	Porcine	Yes	Sturniolo et al[82], 2002
Celiac disease	Human	Not determined	Wierdsma et al[143], 2013
Alcoholic liver disease	Mouse	Yes	Lambert et al[198], 2003
Malnutrition	Guinea pig	Yes	Rodriguez et al[65], 1996

Bacterial Endotoxin

- LPS-A marker of transcellular leaky gut
- Profound research with heart disease
- Connects gut to systemic inflammatory problems
- Higher in auto-immune conditions (worse with Mercury)



LPS antibodies

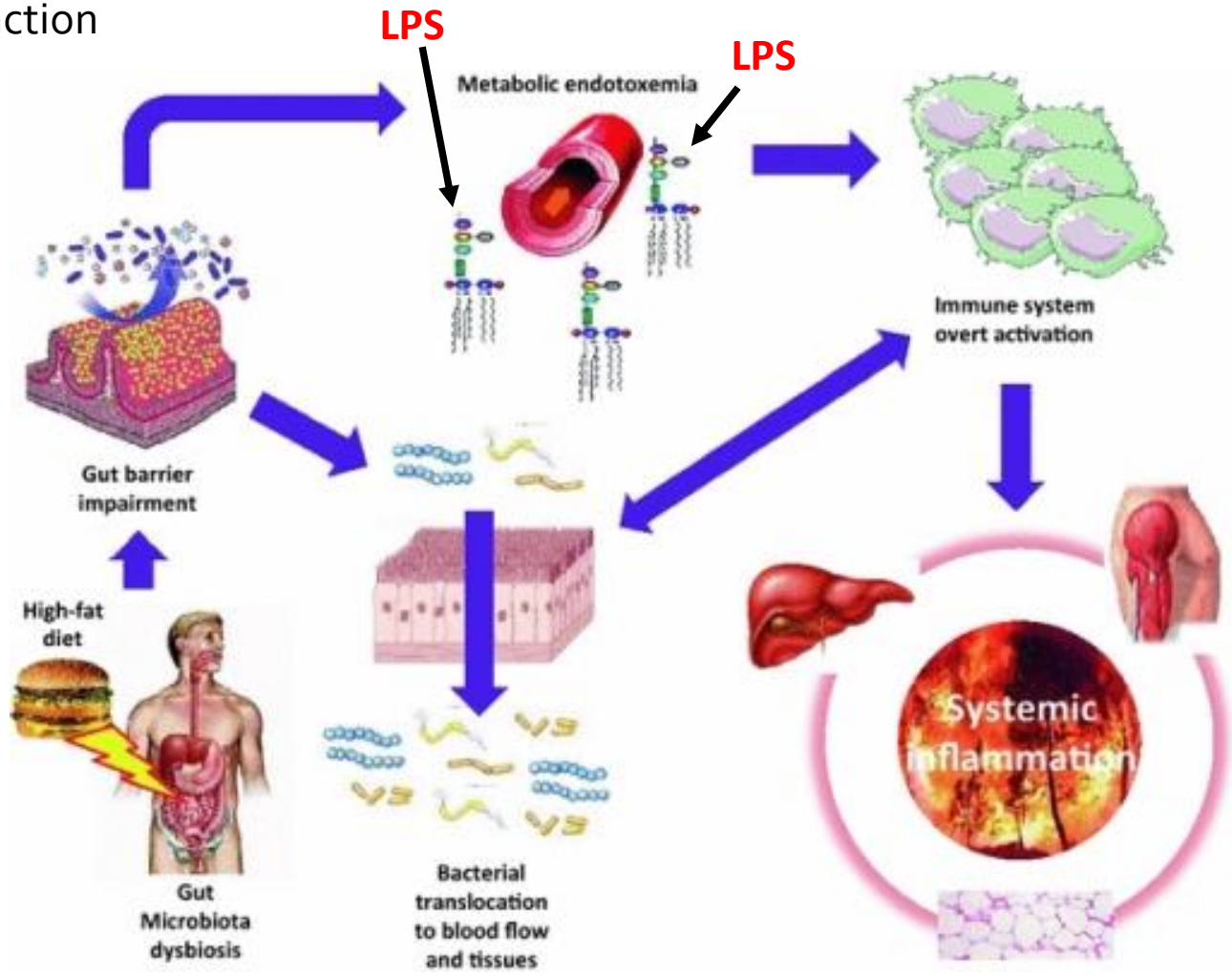
- LPS IgM
- LPS IgA
- LPS IgG

- High: Under high level of attack
- Low Levels: Immune System has no bottomed out



Metabolic Endotoxemia – Increased Systemic LPS

- **Elevated plasma levels of endotoxin associated with:**
  - ❖ Shock
  - ❖ Multiple organ dysfunction
  - ❖ Depression
  - ❖ Anxiety
  - ❖ Sepsis
  - ❖ Atherosclerosis
  - ❖ Obesity
  - ❖ Type 2 diabetes
  - ❖ Alzheimer's
  - ❖ Autoimmunity
  - ❖ Infertility
  - ❖ Hypogonadism



Neviere R. Pathophysiology of sepsis. In: UpToDate, Manaker, S (Ed), UpToDate, Waltham, MA, 2014;
Erridge, et al. Am J Clin Nutr. 2007;86:1286-1292;

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

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

Diamine Oxidase Evaluation

SAMPLE DATE:	
RECEIVE DATE:	
REPORT DATE:	

Nine Dunwoody Park, Suite 121
Dunwoody, GA 30338
Phone: 678-736-6374 | Fax: 770-674-1701
Email: info@dunwoodylabs.com

ADVANCED INTESTINAL BARRIER ASSESSMENT: PROFILE 5150 (PLASMA)

Zonulin

PATIENT RESULT
0.2
ng/ml
REPORTABLE RANGE: <4.0 ng/ml

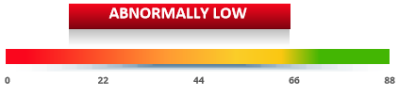
OPTIMAL



Diamine Oxidase (DAO)

PATIENT RESULT
1.0
ng/ml
REPORTABLE RANGE: 0-88 ng/ml

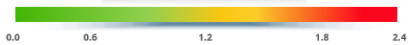
ABNORMALLY LOW



Histamine

PATIENT RESULT
0.84
ng/ml
REPORTABLE RANGE: 0.0–2.4 ng/ml

BORDERLINE

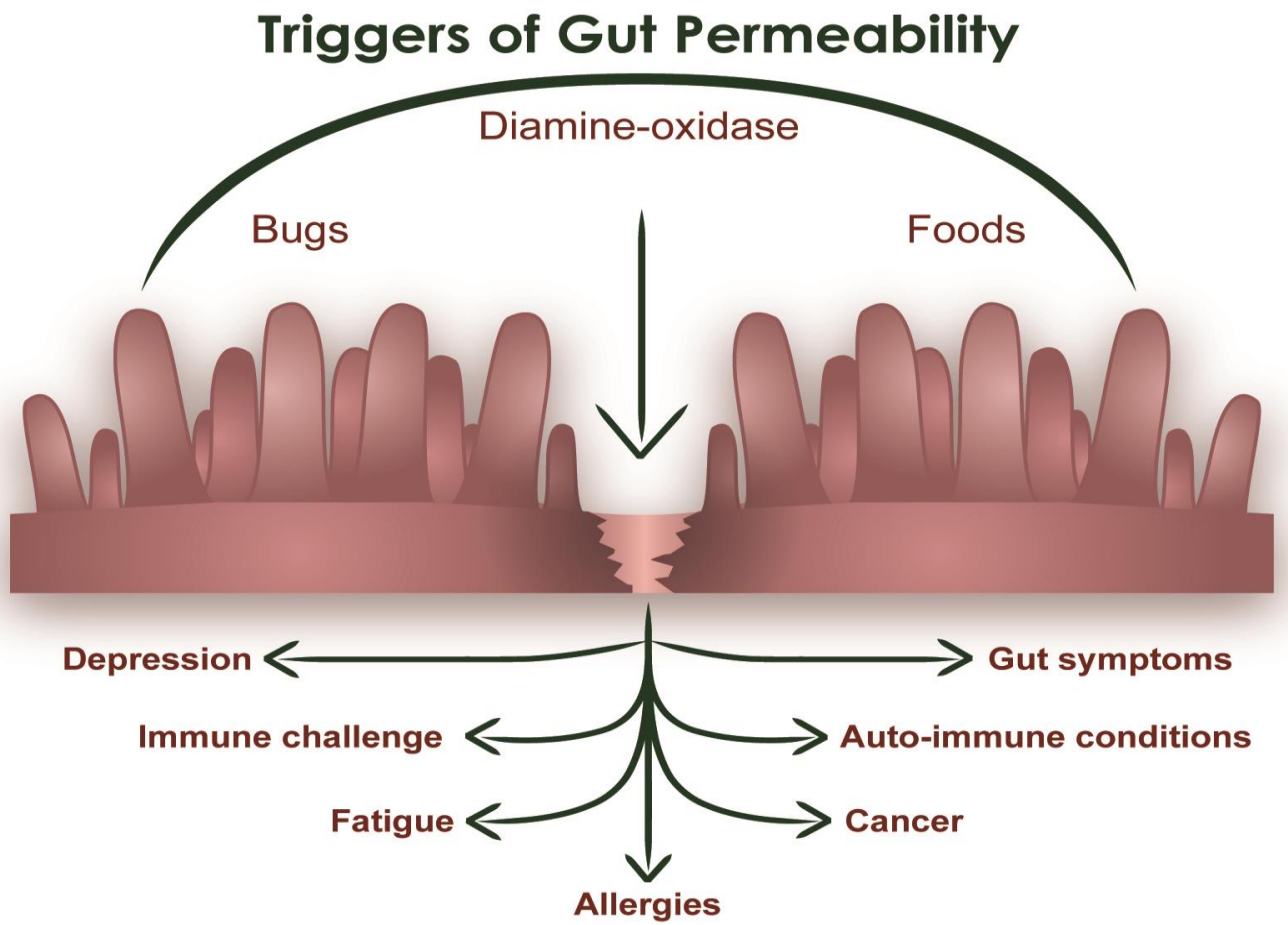


DAO: Histamine Ratio

1

A high DAO-to-Histamine ratio suggests that there is sufficient DAO present to degrade any free histamine.

A low ratio, on the other hand, may be indicative of histamine intolerance. The lower the ratio, and particularly the closer it gets to 1, the stronger that indication.


Triggers of Gut Permeability
Diamine-oxidase
Bugs
Foods
Depression
Gut symptoms
Immune challenge
Auto-immune conditions
Fatigue
Cancer
Allergies

Diamine oxidase is a meaningful marker in newborns

Journal of Applied Clinical Pediatrics》 2008-06

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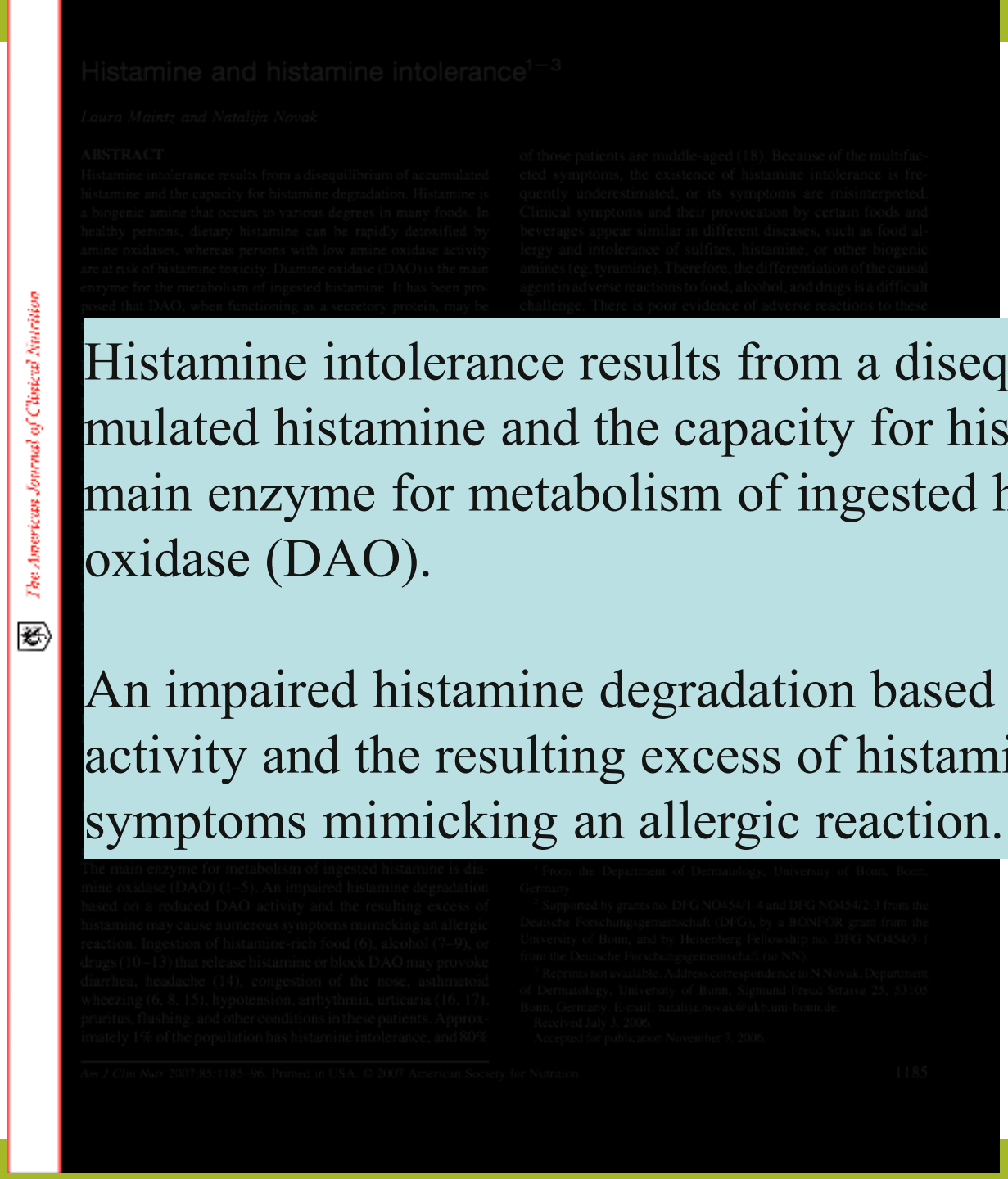
Significance of Determining Serum Diamine Oxidase and D-Lactate in Newborn Infant with Critically Ill

WEI Qiu-wen,WANG Lin-lin,LI Xiao-rong (Department of Pediatrics,the First Affiliated Hospital of Guangxi Medical University,Nanning 530021,China)

Objective To explore the changes of levels of serum diamine oxidase(DAO) and D-lactate in neonates with critically ill and those clinical significances.Methods Fifty-two newborn infants with critical ill were selected as study group,and 15 cases of no-critical and no-gastrointestinal dysfunction were selected as control group.The study group was divided into gastrointestinal dysfunction group(n=18) and no-gastrointestinal dysfunction group(n=34).All cases were required to sample the blood from vein to determine the levels of serum DAO and D-lactate by using spectrophoto metry admission,and the differences in all groups were analyzed.Results The level of serum DAO in study group was significantly higher than that in control group(t=-4.706 P0.01),and the level in gastrointestinal dysfunction group was higher than that in no-gastrointestinal dysfunction group and control group,ANOVA analysis in 3 groups had statistic significance(F=16.694 P0.01).There was no statistic significances of serum DAO in gastrointestinal dysfunction patient whether he was severe or mild(t=0.633 P0.05).The levels of serum D-lactate in study group was significantly higher than that in control group(t=-2.332 P0.05),and that in gastrointestinal dysfunction group was higher than that in control group(t=0.814 P0.05),but there was no statistic difference between no-gastrointestinal dysfunction group and control group(t=0.679 P0.05).There was no statistic significance of serum D-lactate in gastrointestinal dysfunction patient whether he was severe or mild(t=0.561 P0.05).Conclusions Serum DAO can be used as a sensitive marker to early diagnose gastrointestinal dysfunction in critical neonates.Serum D-lactate will be of high specific clinical significance in diagnosis,the change of D-lactate may have relations to the features of intestinal microflora in early neonates.



Histamine and histamine intolerance[1–3]

Laura Maintz and Natalija Novak

ABSTRACT

Histamine intolerance results from a disequilibrium of accumulated histamine and the capacity for histamine degradation. Histamine is a biogenic amine that occurs to various degrees in many foods. In healthy persons, dietary histamine can be rapidly detoxified by amine oxidases, whereas persons with low amine oxidase activity are at risk of histamine toxicity. Diamine oxidase (DAO) is the main enzyme for the metabolism of ingested histamine. It has been proposed that DAO, when functioning as a secretory protein, may be

of those patients are middle-aged (18). Because of the multifaceted symptoms, the existence of histamine intolerance is frequently underestimated, or its symptoms are misinterpreted. Clinical symptoms and their provocation by certain foods and beverages appear similar in different diseases, such as food allergy and intolerance of sulfites, histamine, or other biogenic amines (eg, tyramine). Therefore, the differentiation of the causal agent in adverse reactions to food, alcohol, and drugs is a difficult challenge. There is poor evidence of adverse reactions to these

The main enzyme for metabolism of ingested histamine is diamine oxidase (DAO) (1–3). An impaired histamine degradation based on a reduced DAO activity and the resulting excess of histamine may cause numerous symptoms mimicking an allergic reaction. Ingestion of histamine-rich food (6), alcohol (7–9), or drugs (10–13) that release histamine or block DAO may provoke diarrhea, headache (14), congestion of the nose, asthmatoid wheezing (6, 8, 15), hypotension, arrhythmia, urticaria (16, 17), pruritus, flushing, and other conditions in these patients. Approximately 1% of the population has histamine intolerance, and 80%

[1] From the Department of Dermatology, University of Bonn, Bonn, Germany.

[2] Supported by grants no. DFG NO454/1-4 and DFG NO454/2-3 from the Deutsche Forschungsgemeinschaft (DFG), by a BONFOR grant from the University of Bonn, and by Heisenberg Fellowship no. DFG NO454/3-1 from the Deutsche Forschungsgemeinschaft (to NN).

[3] Reprints not available. Address correspondence to N Novak, Department of Dermatology, University of Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany. E-mail: natalija.novak@ukb.uni-bonn.de.

Received July 3, 2006.

Accepted for publication November 7, 2006.

The American Journal of Clinical Nutrition

Histamine intolerance results from a disequilibrium of accumulated histamine and the capacity for histamine degradation. The main enzyme for metabolism of ingested histamine is dia- mine oxidase (DAO).

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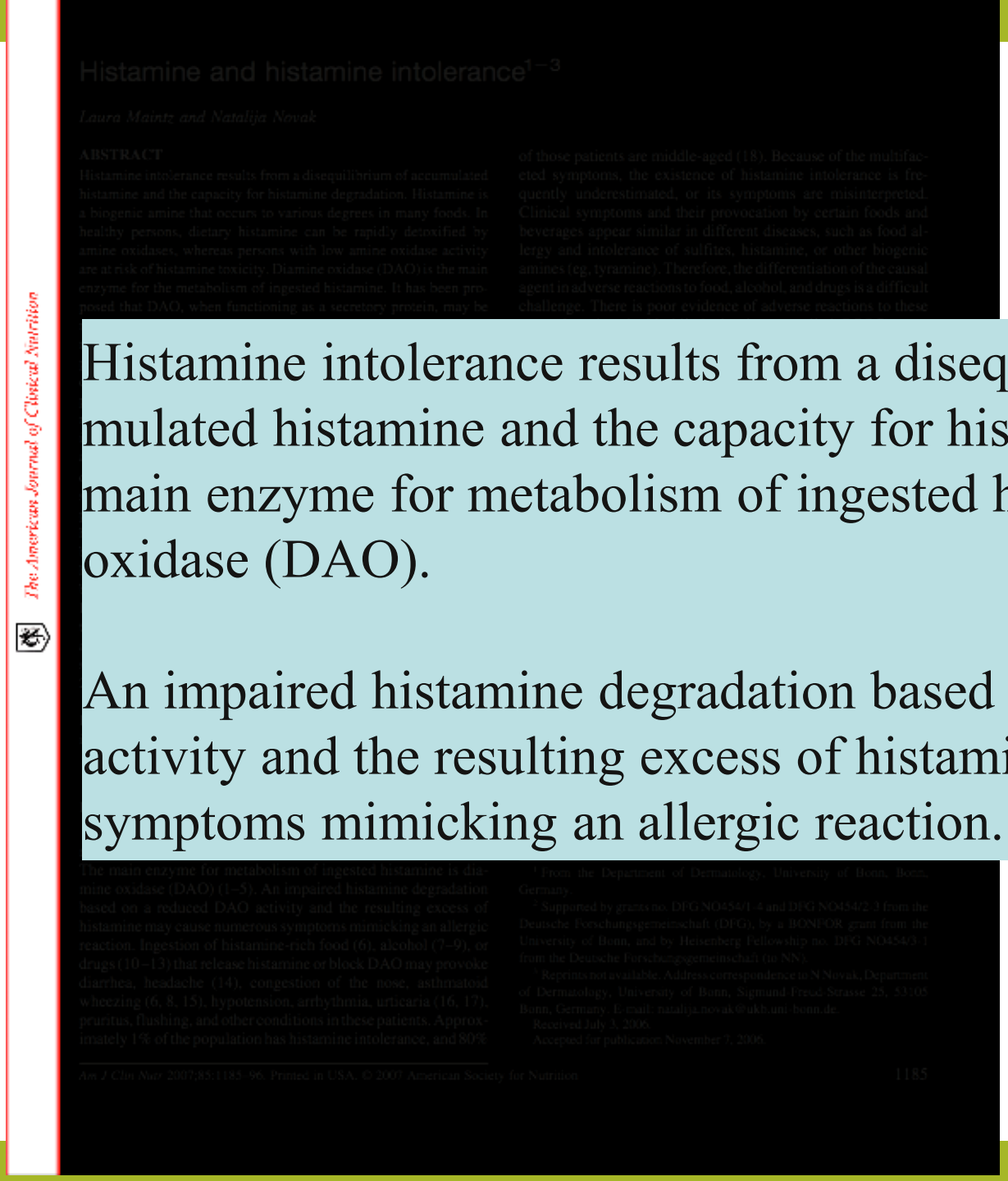

Histamine and histamine intolerance[1–3]

Laura Maintz and Natalija Novak

ABSTRACT

Histamine intolerance results from a disequilibrium of accumulated histamine and the capacity for histamine degradation. Histamine is a biogenic amine that occurs to various degrees in many foods. In healthy persons, dietary histamine can be rapidly detoxified by amine oxidases, whereas persons with low amine oxidase activity are at risk of histamine toxicity. Diamine oxidase (DAO) is the main enzyme for the metabolism of ingested histamine. It has been proposed that DAO, when functioning as a secretory protein, may be

of those patients are middle-aged (18). Because of the multifaceted symptoms, the existence of histamine intolerance is frequently underestimated, or its symptoms are misinterpreted. Clinical symptoms and their provocation by certain foods and beverages appear similar in different diseases, such as food allergy and intolerance of sulfites, histamine, or other biogenic amines (eg, tyramine). Therefore, the differentiation of the causal agent in adverse reactions to food, alcohol, and drugs is a difficult challenge. There is poor evidence of adverse reactions to these

The main enzyme for metabolism of ingested histamine is diamine oxidase (DAO) (1–3). An impaired histamine degradation based on a reduced DAO activity and the resulting excess of histamine may cause numerous symptoms mimicking an allergic reaction. Ingestion of histamine-rich food (6), alcohol (7–9), or drugs (10–13) that release histamine or block DAO may provoke diarrhea, headache (14), congestion of the nose, asthmatoid wheezing (6, 8, 15), hypotension, arrhythmia, urticaria (16, 17), pruritus, flushing, and other conditions in these patients. Approximately 1% of the population has histamine intolerance, and 80%

[1] From the Department of Dermatology, University of Bonn, Bonn, Germany.

[2] Supported by grants no. DFG NO454/1-4 and DFG NO454/2-3 from the Deutsche Forschungsgemeinschaft (DFG), by a BONFOR grant from the University of Bonn, and by Heisenberg Fellowship no. DFG NO454/3-1 from the Deutsche Forschungsgemeinschaft (to NN).

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Besides headache, gastrointestinal ailments including diffuse stomach ache, colic, flatulence, and diarrhea are leading symptoms of histamine intolerance. Elevated histamine concentrations and diminished DAO activities have been shown for various inflammatory and neoplastic diseases such as Crohn disease, ulcerative colitis, allergic enteropathy, food allergy, and colorectal neoplasmas.

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Downl

KEY WORDS Histamine intolerance, histamine, diamine oxidase, food intolerance, allergy

INTRODUCTION

Histamine intolerance results from a disequilibrium of accumulated histamine and the capacity for histamine degradation. The main enzyme for metabolism of ingested histamine is diamine oxidase (DAO) (1–5). An impaired histamine degradation based on a reduced DAO activity and the resulting excess of histamine may cause numerous symptoms mimicking an allergic reaction. Ingestion of histamine-rich food (6), alcohol (7–9), or drugs (10–13) that release histamine or block DAO may provoke diarrhea, headache (14), congestion of the nose, asthmatoid wheezing (6, 8, 15), hypotension, arrhythmia, urticaria (16, 17), pruritus, flushing, and other conditions in these patients. Approximately 1% of the population has histamine intolerance, and 80%

cytokines, hyperosmolarity, lipoproteins, adenosine, superoxidases (22), hypoxia, chemical and physical factors (eg, extreme temperatures, traumas) (23), or alcohol and certain food and drugs, may activate mast cells.

Histamine exerts its effects by binding to its 4 receptors [histamine 1 receptor (H1R), H2R, H3R, and and H4R] on target cells in various tissues (**Figure 1**, **Table 1**). It causes smooth

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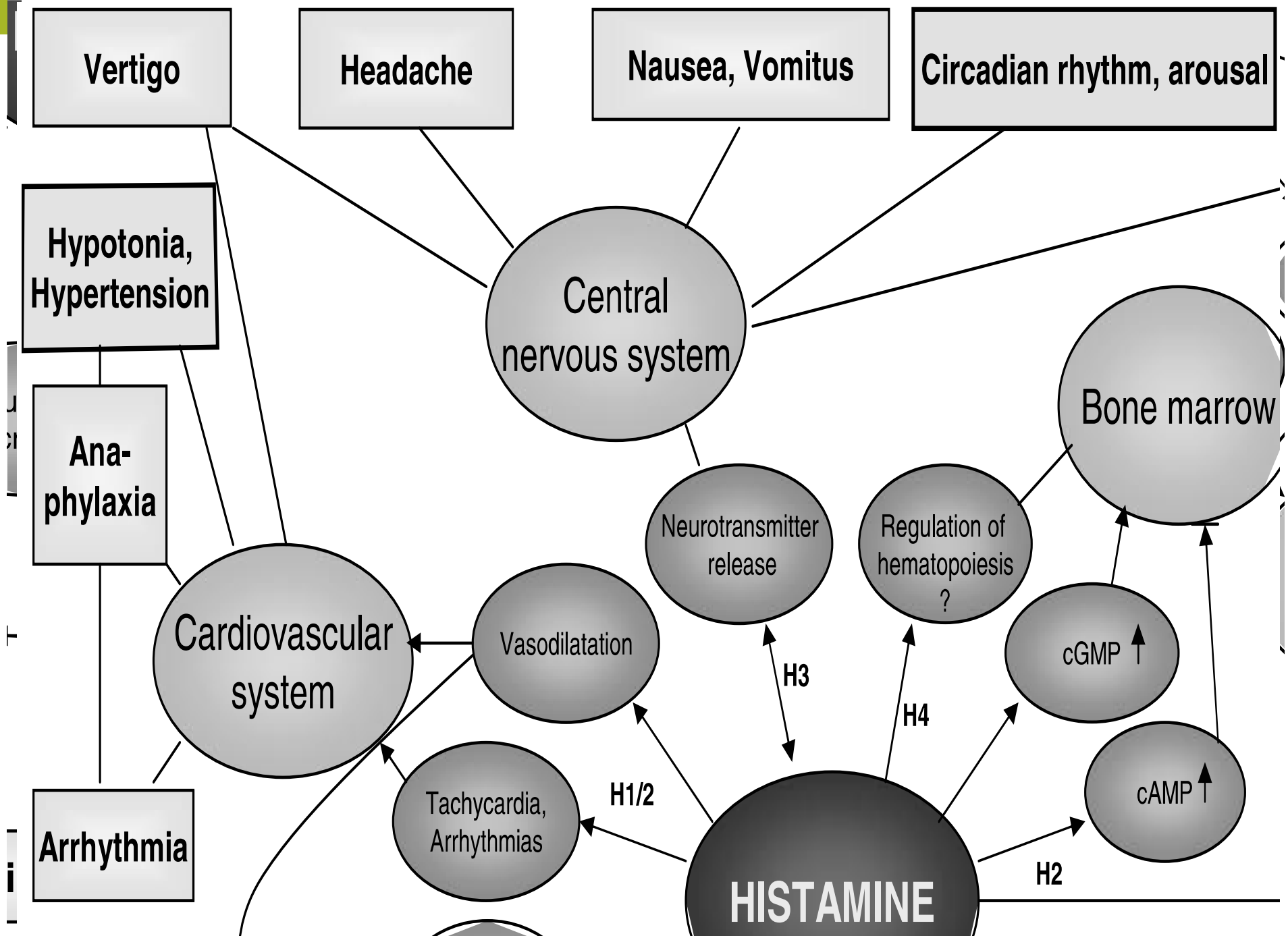

Adapted from Maintz L et al. Dtsch Artzebl 2006;103:A3477-83

DAO varies with menstrual cycle

Clin Biochem. 2012 Oct 22. pii: S0009-9120(12)00568-1. doi: 10.1016/j.clinbiochem.2012.10.013. [Epub ahead of print]

Effect of the menstrual cycle on serum diamine oxidase levels in healthy women.

Hamada Y, Shinohara Y, Yano M, Yamamoto M, Yoshio M, Satake K, Toda A, Hirai M, Usami M.

Serum diamine oxidase (DAO) level is employed as a useful marker of intestinal mucosal integrity.

RESULTS:
Biochemical parameters, except for DAO levels, were comparable between the two phases. However, serum DAO levels during the luteal phase were significantly higher than those during the follicular phase.

Clin Biochem. 2012 Oct 22. pii: S0009-9120(12)00568-1. doi: 10.1016/j.clinbiochem.2012.10.013. [Epub ahead of print]



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J Clin Invest. 1980 July; 66(1): 66–70.
doi: 10.1172/JCI109836

PMCID: PMC371506

Copyright notice

Diamine oxidase (histaminase). A circulating marker for rat intestinal mucosal maturation and integrity.

G D Luk, T M Bayless, and S B Baylin

This article has been cited by other articles in PMC.

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29, P less than 0.04). Diamine oxidase activity is thus unique among intestinal mucosal enzymes studied to date in that circulating levels can serve as a marker of mucosal maturation and integrity.

"With increasing mucosal damage, there was a progressive decrease in the enzyme activities studied; first, lactase levels fell, then maltase and sucrase, and finally mucosal and plasma diamine oxidase activity levels fell.

The decrease in plasma diamine oxidase reflected the degree of mucosal damage (n = 29, P less than 0.04). Diamine oxidase activity is thus unique among intestinal mucosal enzymes studied to date in that circulating levels can serve as a marker of mucosal maturation and integrity."

Factors That Contribute To Histamine Excess

- Allergies
- Mastocytosis
- Bacteria
- GI bleeding
- Ingestion of histidine or histamine by food or alcohol
- DAO deficiency

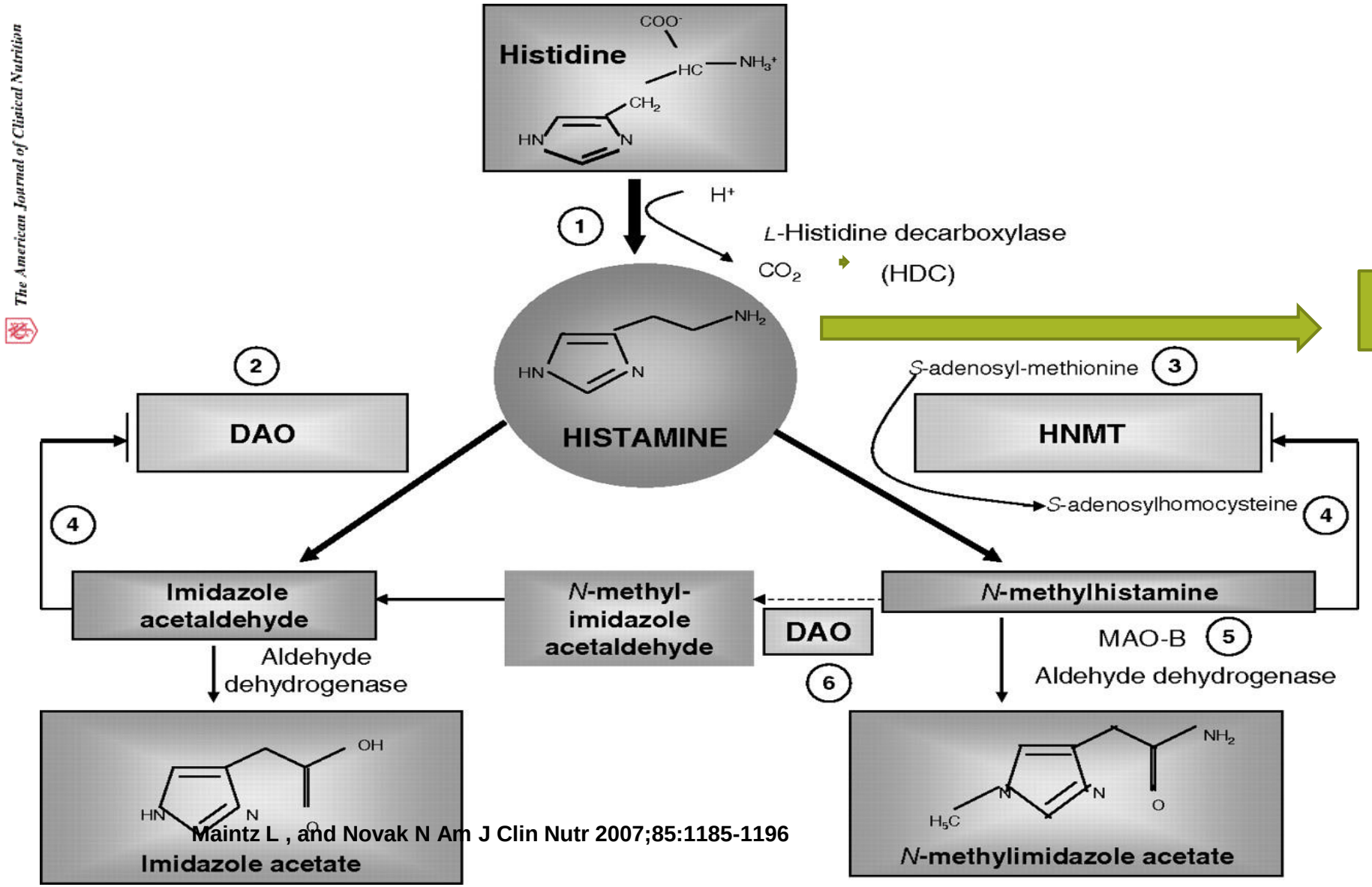


Impact of Histamine

- Smooth muscle cell contraction
- Vasodilatation
- Increased vascular permeability
- Mucus secretion
- Tachycardia
- Alterations of blood pressure
- Arrhythmias
- Nociceptive nerve fibers
- Neurotransmission
- Immunomodulation
- Hematopoiesis
- Wound healing
- Day-night rhythm
- Angiogenesis in tumor models
- Intestinal ischemia



Summary of the histamine metabolism.



Maintz L , and Novak N Am J Clin Nutr 2007;85:1185-1196

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Patient KF

- Chronic hives
- Gut issues
- Only maintained on prednisone

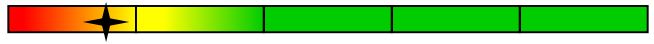
.

4646 N. Shallowford Rd., Suite N
Dunwoody, GA 30338
678-736-6374
678-736-6390 (fax)
contact@nutratestlabs.com

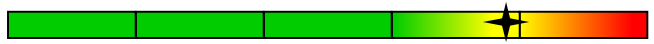
Patient Name: KF Pre
Patient DOB:
Clinic Name:
Ordering Physician:
Sample Date:
Date of Report:

Zonulin:DAO Profile 5100

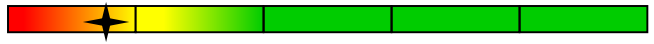
	Patient Results	Reference Range
Diamine Oxidase	21.2	21.2-46.4 ng/mL



	Patient Results	Reference Range
Histamine	2.1	0.9-2.2 ng/mL



	Patient Results	Reference Range
DAO:Histamine Ratio	9.9	11.9-33.2



not expect the same results as those found in case studies alone.

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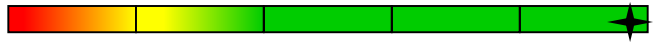
Dunwoody, GA 30338
678-736-6374
678-736-6390 (fax)
contact@nutratestlabs.com

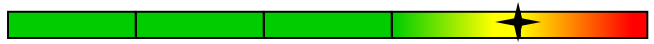
Patient Name: KF post
Patient DOB:
Clinic Name:
Ordering Physician:
Sample Date:
Date of Report:

Zonulin:DAO Profile 5100

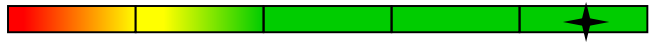
	Patient Results	Reference Range
Diamine Oxidase	66.5	21.2-46.4 ng/mL



	Patient Results	Reference Range
Histamine	2.2	0.9-2.2 ng/mL



	Patient Results	Reference Range
DAO:Histamine Ratio	30.2	11.9-33.2



not expect the same results as those found in case studies alone.

Follow up with KF

- Able to back down prednisone, now off prednisone
- Gut feels better
- Energy is better
- “This is the first time I feel better, not worse, I have hope”



DAO Treatment

- Diamine Oxidase
- Copper, B6
- Omega 3s
- Saccharomyces
- All Gut Permeability Therapies



INFLAMED BY THE WORLD: UNDERSTANDING THE ROLE OF BIOMARKERS ON SYSTEMIC INFLAMMATION

Cheryl Burdette, ND

