Insulin Resistance:

Updates and Clinical Applications

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February 28, 2020
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Objectives

- Early detection of insulin resistance (IR)
  - Look for history, signs and symptoms of insulin resistance
  - Attempt to clinically assess the stage of IR
  - Find the underlying root cause or causes
- Diagnose appropriately IR, IGT, Pre-DM, DM-II
  - Clinical exam
  - Laboratory measures
  - If you cannot diagnose but have a high index of suspicion for IR, treat as insulin resistant
- Individualize Treatment
  - Diet and lifestyle
  - Address gut microbiota
  - Nutraceuticals / pharmaceuticals

Which Came First?

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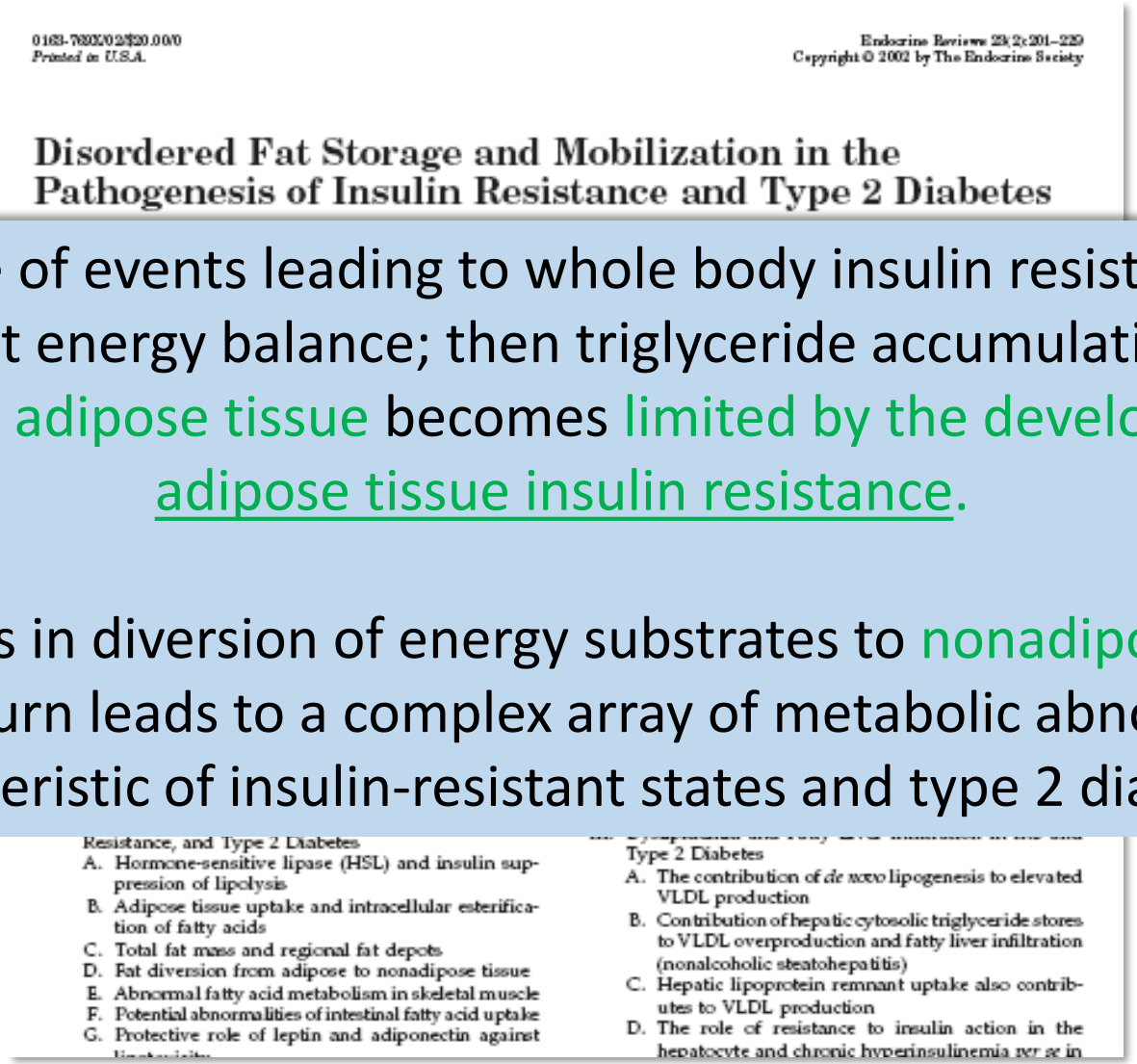
Erion K, Corkey B. *Curr Obes Rep*. 2017; 6(2): 178–186.

Adipocyte Dysregulation



0163-769X/02/$20.00/0
Printed in U.S.A.

Endocrine Reviews 23(2):201–229
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Disordered Fat Storage and Mobilization in the Pathogenesis of Insulin Resistance and Type 2 Diabetes

Resistance, and Type 2 Diabetes
A. Hormone-sensitive lipase (HSL) and insulin suppression of lipolysis
B. Adipose tissue uptake and intracellular esterification of fatty acids
C. Total fat mass and regional fat depots
D. Fat diversion from adipose to nonadipose tissue
E. Abnormal fatty acid metabolism in skeletal muscle
F. Potential abnormalities of intestinal fatty acid uptake
G. Protective role of leptin and adiponectin against

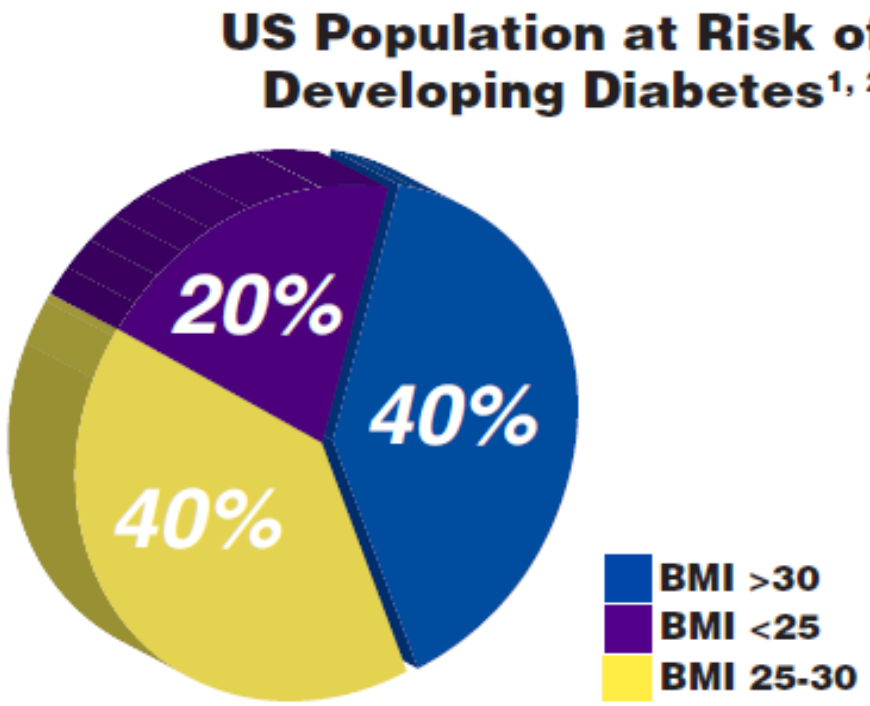
Type 2 Diabetes
A. The contribution of *de novo* lipogenesis to elevated VLDL production
B. Contribution of hepatic cytosolic triglyceride stores to VLDL overproduction and fatty liver infiltration (nonalcoholic steatohepatitis)
C. Hepatic lipoprotein remnant uptake also contributes to VLDL production
D. The role of resistance to insulin action in the hepatocyte and chronic hyperinsulinemia per se in

The sequence of events leading to whole body insulin resistance is first a positive net energy balance; then triglyceride accumulation in "fat-buffering" adipose tissue becomes limited by the development of adipose tissue insulin resistance.

This results in diversion of energy substrates to nonadipose tissue, which in turn leads to a complex array of metabolic abnormalities characteristic of insulin-resistant states and type 2 diabetes.

Lewis GF, et al. *Endocr Rev*. 2002 Apr;23(2):201-29.

According to the CDC, only **40%** of the risk of developing diabetes occurs in people who are **obese**!



How do we find the **other 60%** of the people at risk for developing diabetes who are NOT obese?

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Rates of Cardiometabolic Syndrome

ORIGINAL INVESTIGATION

The Obese Without Cardiometabolic Risk Factor Clustering and the Normal Weight With Cardiometabolic Risk Factor Clustering

Prevalence and Correlates of 2 Phenotypes Among the US Population (NHANES 1999-2004)

Rachel P. Wildman, PhD; Paul Muntner, PhD; Kristi Reynolds, PhD; Aileen P. McGinn, PhD; Swapnil Rajpathak, MD, DrPH; Judith Wylie-Rosett, EdD; MaryFran R. Sowers, PhD

	BMI < 25	BMI 25-30	BMI >30
MEN	**30%**	**51%**	**71%**
WOMEN	**21%**	**43%**	**65%**
TOTAL	**26%**	**46%**	**68%**

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Wildman RP, et al. *Arch Intern Med*. 2008 Aug 11;168(15):1617-24.

Body Mass Index

SCIENTIFIC REPORTS

OPEN

Body mass index trajectory patterns and changes in visceral fat and glucose metabolism before the onset of type 2 diabetes

Received: 26 July 2016

identified in adults developing and not developing diabetes, respectively. Among adults developing diabetes, 47.3% were classified as "medium BMI" (n = 895), and had increased mean BMI within the obesity category before diagnosis. The "low BMI" group (38.4%, n = 726) had an initial mean BMI of 21.9 kg/m^2, and demonstrated small weight gain. The "high BMI" group (n = 271) were severely obese and showed greater increase in BMI until diagnosis. All groups which developed diabetes showed absolute and/or relative increase in visceral fat and impaired β-cell compensation for insulin resistance. All groups not developing diabetes showed measured variables were relatively stable during observation. These data suggest that visceral fat gain may induce β-cell failure in compensation for insulin resistance, resulting in diabetes regardless of obesity level.

Diabetes is of growing concern worldwide. In particular, East Asia is experiencing a rapidly emerging diabetes epidemic and accounts for more than 25% of the global diabetic population[1]. Obesity is a major risk factor for

"These data suggest that visceral fat gain may induce β-cell failure in compensation for insulin resistance, resulting in diabetes regardless of obesity level."

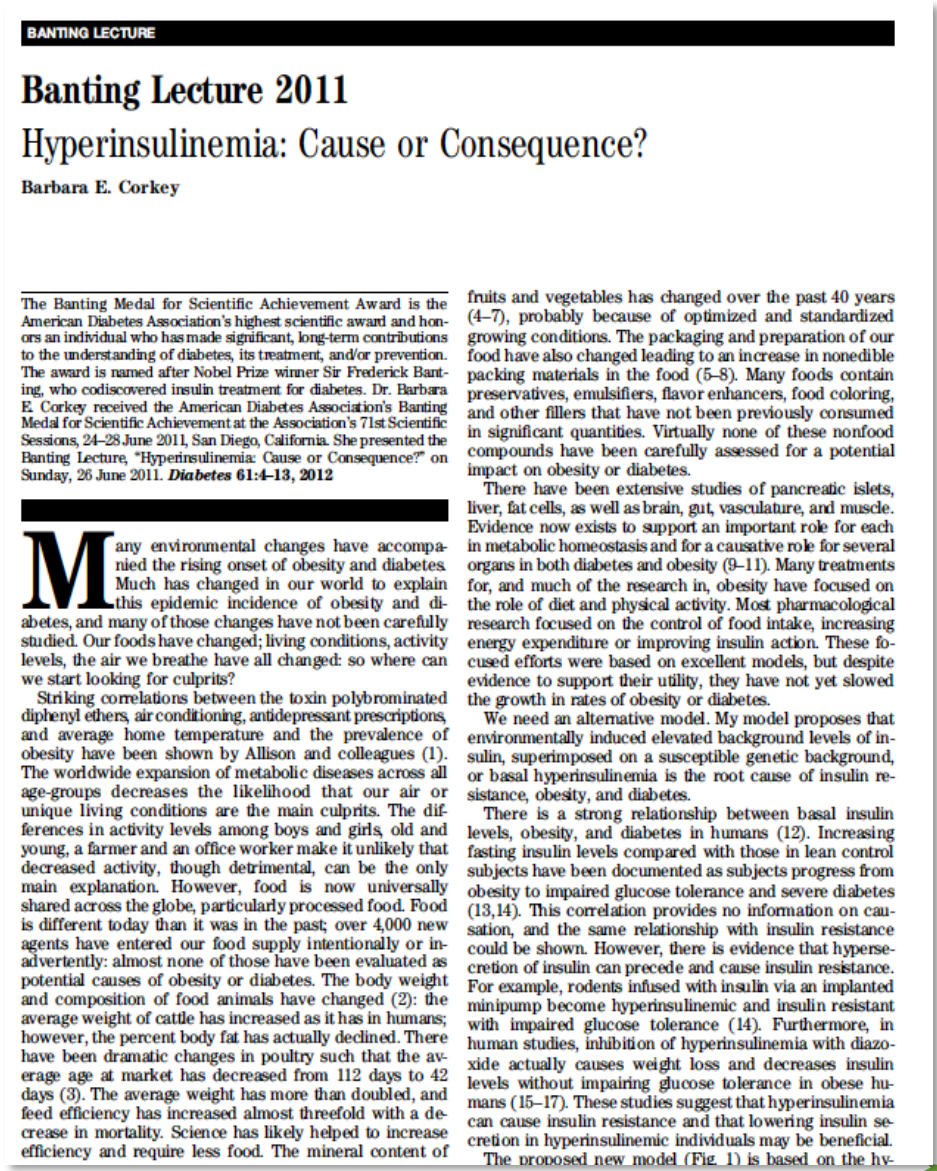
Kuwahara K, et al. *Sci Rep*. 2017 Mar 7;7:43521.

Other Theories

"Insulin resistance starts in the Beta cell with hyperinsulinemia causing insulin resistance. The initial cause is damage to the Beta cell."

– Barbara Corkey

Dr. Corkey initially observed that mono-oleoylglycerol, iron, and saccharin may all be common dietary ingredients that are capable of producing hyperinsulinemia. Then in 2014 she published a much more extensive list of food additives and toxins leading to insulin resistance



BANTING LECTURE

Banting Lecture 2011

Hyperinsulinemia: Cause or Consequence?

Barbara E. Corkey

The Banting Medal for Scientific Achievement Award is the American Diabetes Association's highest scientific award and honors an individual who has made significant, long-term contributions to the understanding of diabetes, its treatment, and/or prevention. The award is named after Nobel Prize winner Sir Frederick Banting, who codiscovered insulin treatment for diabetes. Dr. Barbara E. Corkey received the American Diabetes Association's Banting Medal for Scientific Achievement at the Association's 71st Scientific Sessions, 24–28 June 2011, San Diego, California. She presented the Banting Lecture, "Hyperinsulinemia: Cause or Consequence?" on Sunday, 26 June 2011. *Diabetes* **61:4–13, 2012**

Many environmental changes have accompanied the rising onset of obesity and diabetes. Much has changed in our world to explain this epidemic incidence of obesity and diabetes, and many of those changes have not been carefully studied. Our foods have changed; living conditions, activity levels, the air we breathe have all changed: so where can we start looking for culprits?

Striking correlations between the toxin polybrominated diphenyl ethers, air conditioning, antidepressant prescriptions, and average home temperature and the prevalence of obesity have been shown by Allison and colleagues (1). The worldwide expansion of metabolic diseases across all age-groups decreases the likelihood that our air or unique living conditions are the main culprits. The differences in activity levels among boys and girls, old and young, a farmer and an office worker make it unlikely that decreased activity, though detrimental, can be the only main explanation. However, food is now universally shared across the globe, particularly processed food. Food is different today than it was in the past; over 4,000 new agents have entered our food supply intentionally or inadvertently: almost none of those have been evaluated as potential causes of obesity or diabetes. The body weight and composition of food animals have changed (2): the average weight of cattle has increased as it has in humans; however, the percent body fat has actually declined. There have been dramatic changes in poultry such that the average age at market has decreased from 112 days to 42 days (3). The average weight has more than doubled, and feed efficiency has increased almost threefold with a decrease in mortality. Science has likely helped to increase efficiency and require less food. The mineral content of fruits and vegetables has changed over the past 40 years (4–7), probably because of optimized and standardized growing conditions. The packaging and preparation of our food have also changed leading to an increase in nonedible packing materials in the food (5–8). Many foods contain preservatives, emulsifiers, flavor enhancers, food coloring, and other fillers that have not been previously consumed in significant quantities. Virtually none of these nonfood compounds have been carefully assessed for a potential impact on obesity or diabetes.

There have been extensive studies of pancreatic islets, liver, fat cells, as well as brain, gut, vasculature, and muscle. Evidence now exists to support an important role for each in metabolic homeostasis and for a causative role for several organs in both diabetes and obesity (9–11). Many treatments for, and much of the research in, obesity have focused on the role of diet and physical activity. Most pharmacological research focused on the control of food intake, increasing energy expenditure or improving insulin action. These focused efforts were based on excellent models, but despite evidence to support their utility, they have not yet slowed the growth in rates of obesity or diabetes.

We need an alternative model. My model proposes that environmentally induced elevated background levels of insulin, superimposed on a susceptible genetic background, or basal hyperinsulinemia is the root cause of insulin resistance, obesity, and diabetes.

There is a strong relationship between basal insulin levels, obesity, and diabetes in humans (12). Increasing fasting insulin levels compared with those in lean control subjects have been documented as subjects progress from obesity to impaired glucose tolerance and severe diabetes (13,14). This correlation provides no information on causation, and the same relationship with insulin resistance could be shown. However, there is evidence that hypersecretion of insulin can precede and cause insulin resistance. For example, rodents infused with insulin via an implanted minipump become hyperinsulinemic and insulin resistant with impaired glucose tolerance (14). Furthermore, in human studies, inhibition of hyperinsulinemia with diazoxide actually causes weight loss and decreases insulin levels without impairing glucose tolerance in obese humans (15–17). These studies suggest that hyperinsulinemia can cause insulin resistance and that lowering insulin secretion in hyperinsulinemic individuals may be beneficial.

The proposed new model (Fig. 1) is based on the hy-

Corkey B. *Diabetes*. 2012 Jan; 61(1): 4–13.

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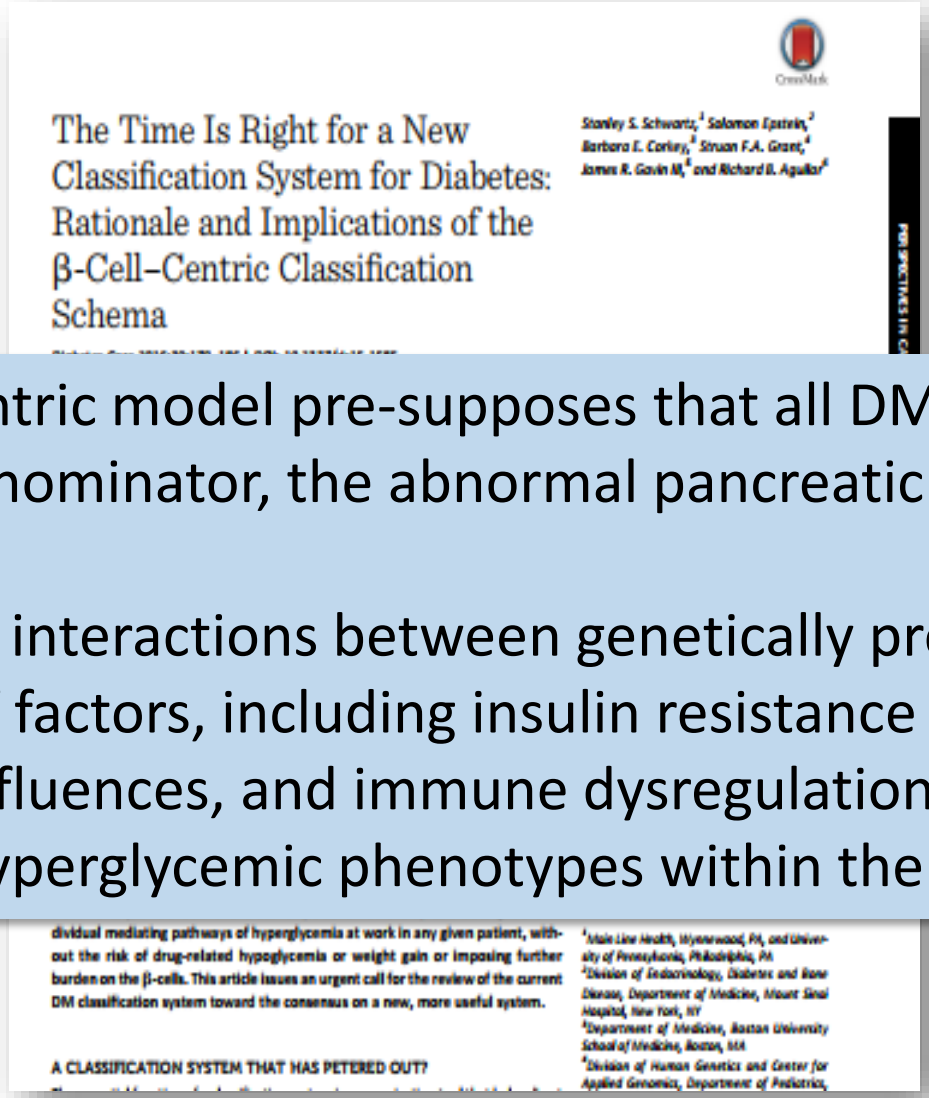
Corkey, et al. What Are We Putting in Our Food That Is Making Us Fat? Food Additives, Contaminants, and Other Putative Contributors to Obesity. Curr Obes Rep. 2014 Jun 1;3(2):273-285.

New Classification System for Diabetes?



The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell–Centric Classification Schema

Stanley S. Schwartz,[1] Salomon Epstein,[2] Barbara E. Corkey,[3] Struan F.A. Grant,[4] James R. Gavin III,[5] and Richard B. Aguilar[6]

dividual mediating pathways of hyperglycemia at work in any given patient, without the risk of drug-related hypoglycemia or weight gain or imposing further burden on the β-cells. This article issues an urgent call for the review of the current DM classification system toward the consensus on a new, more useful system.

A CLASSIFICATION SYSTEM THAT HAS PETERED OUT?

The beta-cell–centric model pre-supposes that all DM originates from a final common denominator, the abnormal pancreatic b-cell.

It recognizes that interactions between genetically predisposed b-cells with a number of factors, including insulin resistance (IR), susceptibility to environmental influences, and immune dysregulation/inflammation, lead to the range of hyperglycemic phenotypes within the spectrum of DM.

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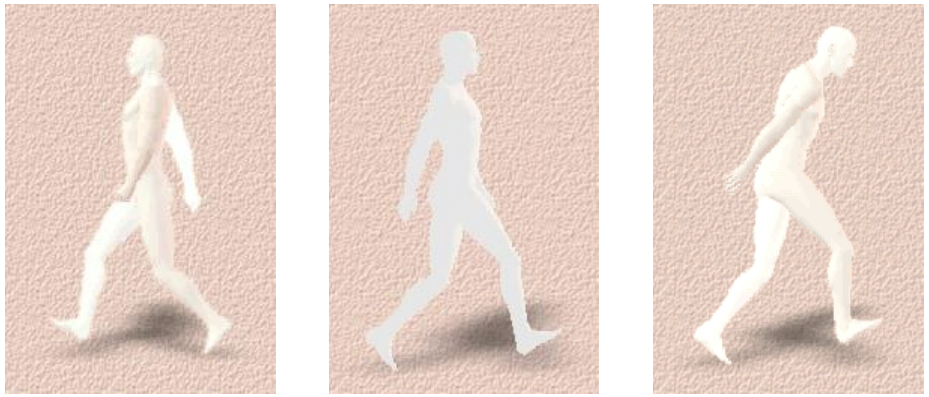
Schwartz SS, et al. *Diabetes Care*. 2016 Feb;39(2):179-86.

Continuum of Insulin Resistance



Insulin Sensitive | Insulin Resistance | IGT | Pre-Diabetes | Diabetes

Health | ***No Symptoms*** | ***Symptoms/Pathology***

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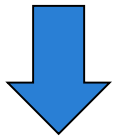
Where Do You See Manifestations of Insulin Resistance or the Metabolic Syndrome?

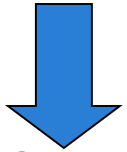
GENOVA DIAGNOSTICS®

Insulin Resistance



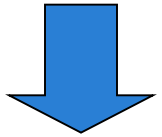
Hyperinsulinemia with maintenance of normal (or near normal) glucose control

(Compensated Hyperinsulinemia)

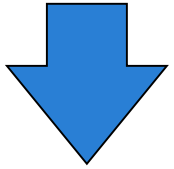


Impaired Glucose Tolerance

(Uncompensated Hyperinsulinemia)



Pre-Diabetes



Diabetes

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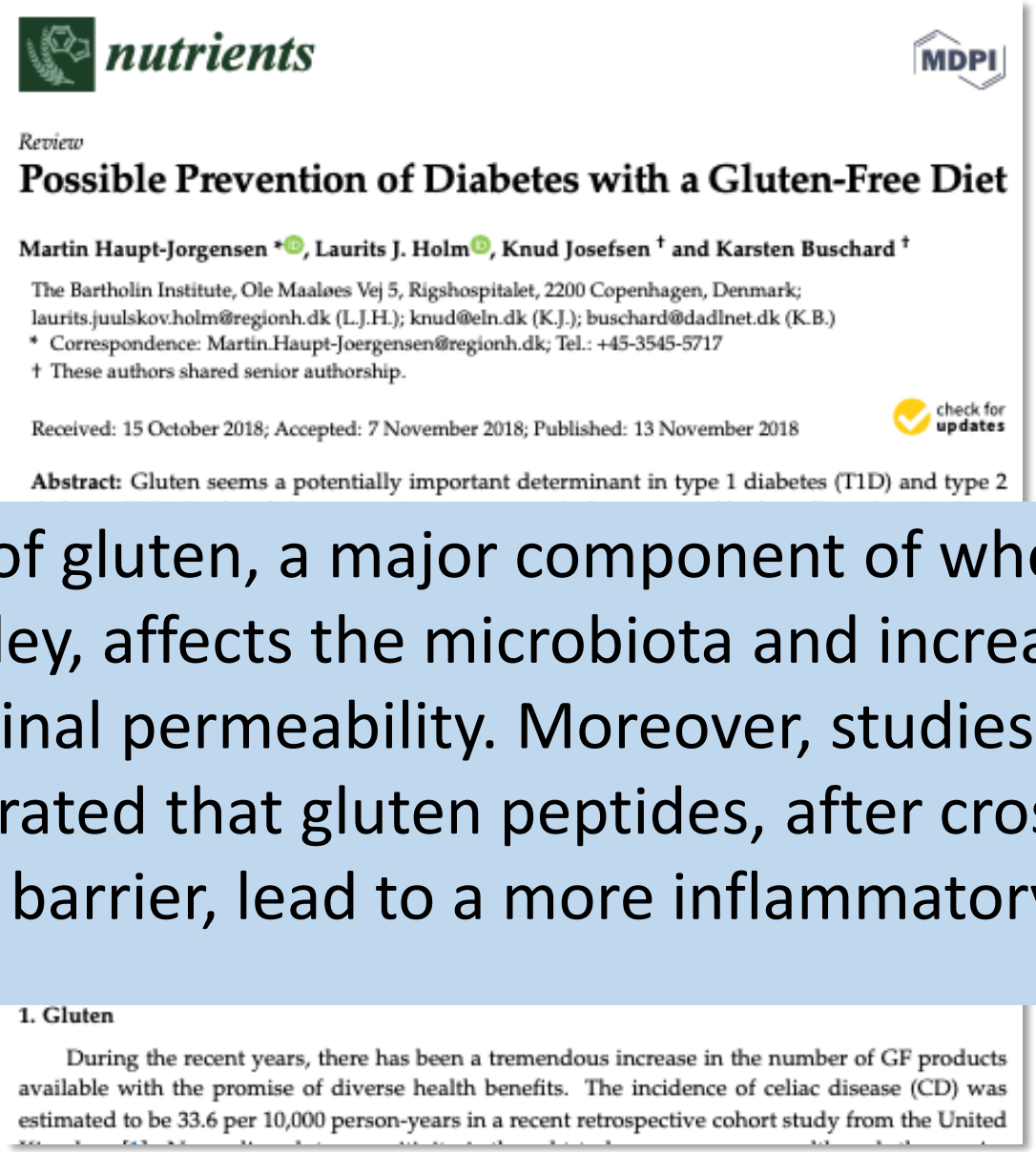
How Does Someone Develop Insulin Resistance / Type II DM?

Consider the Following:

- Food allergies and/or sensitivities
- Food additives or excesses
- Dysbiosis, leaky gut, and gut microbiota factors
- Digestive insufficiencies
- Oxidative Stress
- Mitochondrial dysfunction
- Nutrient deficiencies/excesses
- Obesity
- Stress or adrenal fatigue/dysfunction
- Lack of sleep
- Hormone imbalances
- Infections (especially occult-dental)
- Toxins
- Rx Drugs (statins and DM)
- Genetic predispositions/SNPs
- More than one cause?

Gluten



nutrients

MDPI

Review

Possible Prevention of Diabetes with a Gluten-Free Diet

Martin Haupt-Jorgensen *, Laurits J. Holm, Knud Josefsen † and Karsten Buschard †

The Bartholin Institute, Ole Maaløes Vej 5, Rigshospitalet, 2200 Copenhagen, Denmark; laurits.juulskov.holm@regionh.dk (L.J.H.); knud@eln.dk (K.J.); buschard@dadlnet.dk (K.B.)

* Correspondence: Martin.Haupt-Joergensen@regionh.dk; Tel.: +45-3545-5717

† These authors shared senior authorship.

Received: 15 October 2018; Accepted: 7 November 2018; Published: 13 November 2018

check for updates

Abstract: Gluten seems a potentially important determinant in type 1 diabetes (T1D) and type 2

"Intake of gluten, a major component of wheat, rye, and barley, affects the microbiota and increases the intestinal permeability. Moreover, studies have demonstrated that gluten peptides, after crossing the intestinal barrier, lead to a more inflammatory milieu."

1. Gluten

During the recent years, there has been a tremendous increase in the number of GF products available with the promise of diverse health benefits. The incidence of celiac disease (CD) was estimated to be 33.6 per 10,000 person-years in a recent retrospective cohort study from the United

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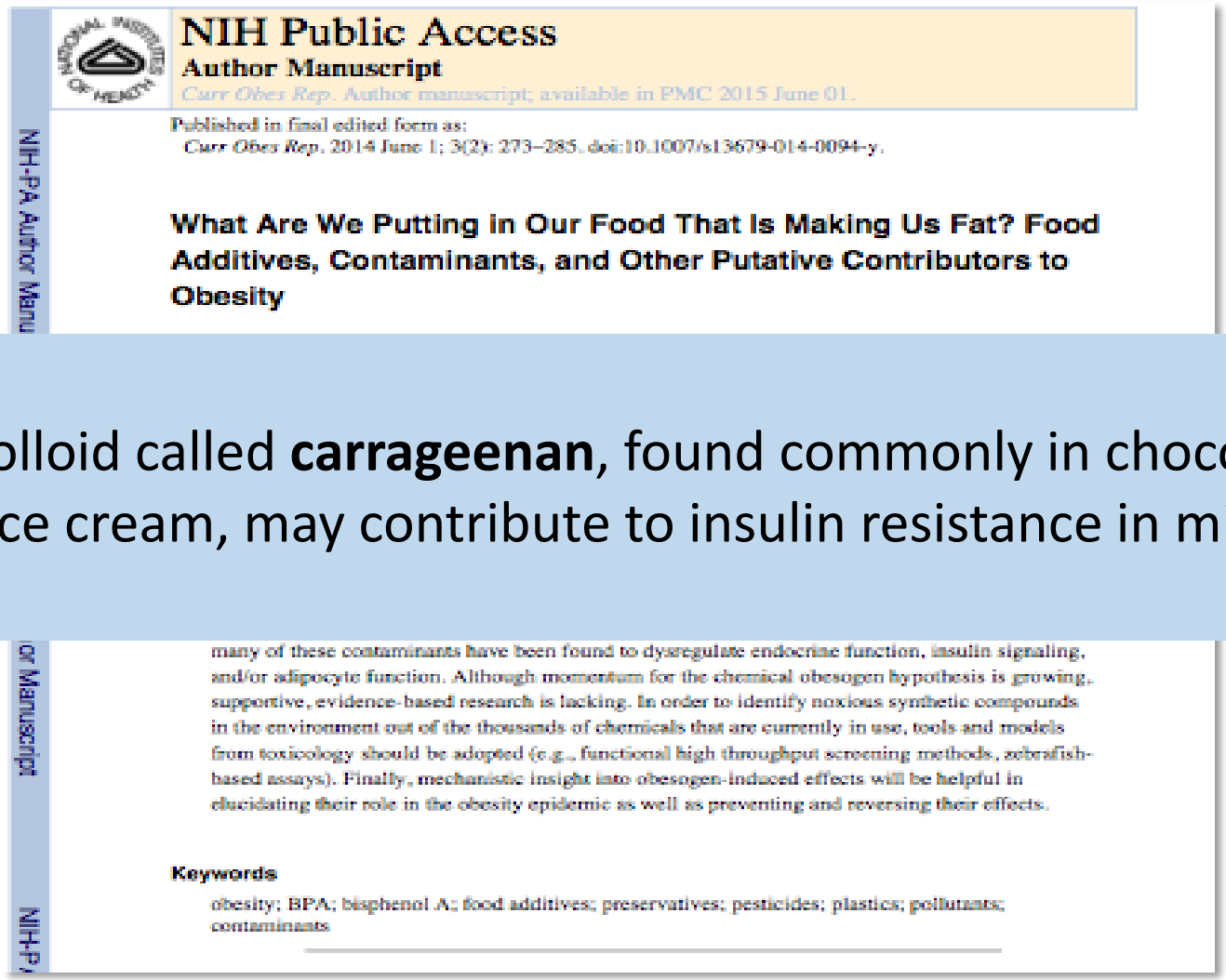
Haupt-Jorgensen M, et al. *Nutrients*. 2018 Nov; 10(11): 1746.

Food Additives



NIH Public Access
Author Manuscript
Curr Obes Rep. Author manuscript; available in PMC 2015 June 01.

Published in final edited form as:
Curr Obes Rep. 2014 June 1; 3(2): 273–285. doi:10.1007/s13679-014-0094-y.

What Are We Putting in Our Food That Is Making Us Fat? Food Additives, Contaminants, and Other Putative Contributors to Obesity

A "hydrocolloid called **carrageenan**, found commonly in chocolate milk and ice cream, may contribute to insulin resistance in mice."

many of these contaminants have been found to dysregulate endocrine function, insulin signaling, and/or adipocyte function. Although momentum for the chemical obesogen hypothesis is growing, supportive, evidence-based research is lacking. In order to identify noxious synthetic compounds in the environment out of the thousands of chemicals that are currently in use, tools and models from toxicology should be adopted (e.g., functional high throughput screening methods, zebrafish-based assays). Finally, mechanistic insight into obesogen-induced effects will be helpful in elucidating their role in the obesity epidemic as well as preventing and reversing their effects.

Keywords

obesity; BPA; bisphenol A; food additives; preservatives; pesticides; plastics; pollutants; contaminants

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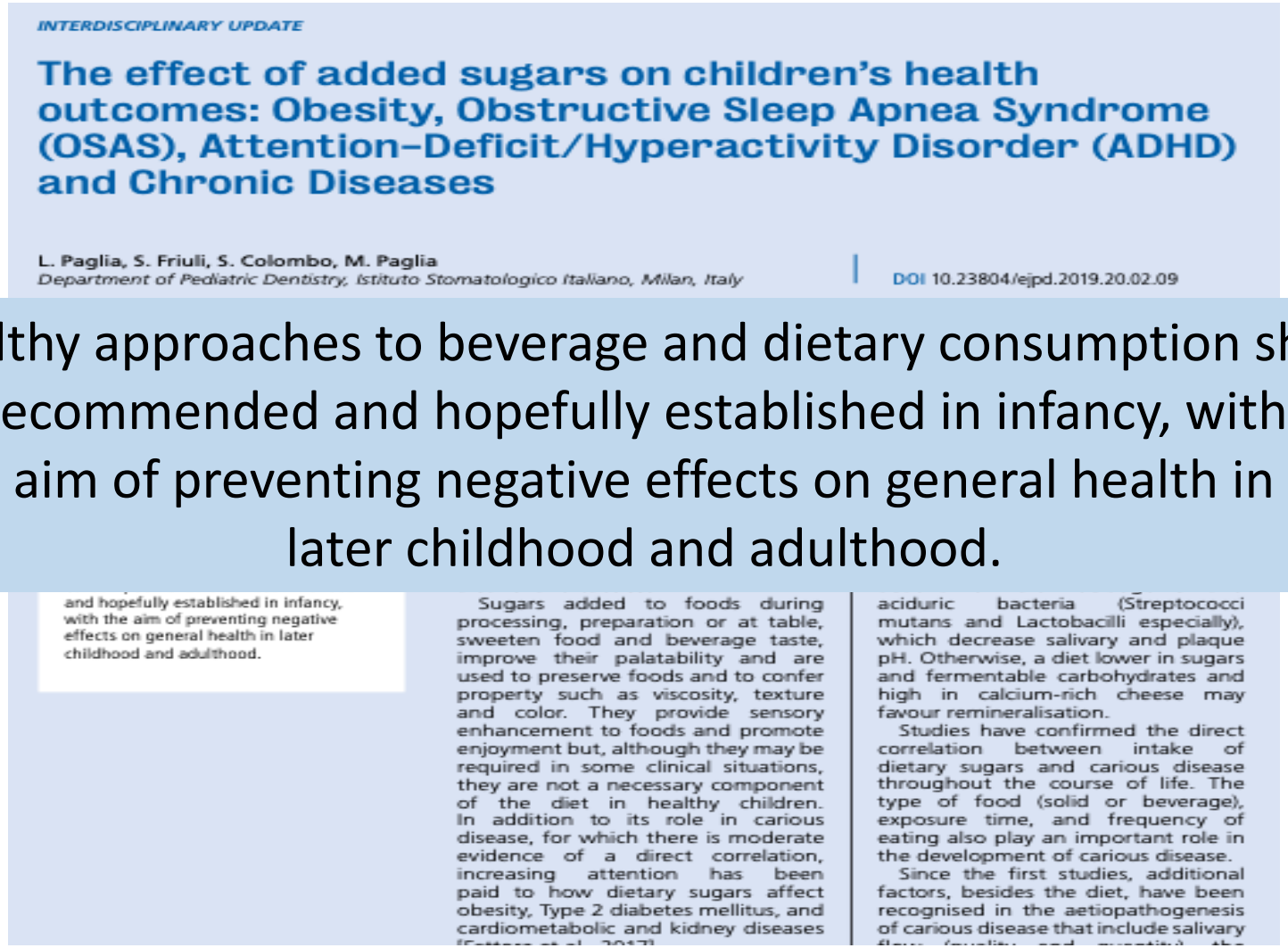
Saha D, et al. *Curr Obes Rep*. 2014 Jun 1; 3(2): 273–285.

Added Sugars



INTERDISCIPLINARY UPDATE

The effect of added sugars on children's health outcomes: Obesity, Obstructive Sleep Apnea Syndrome (OSAS), Attention–Deficit/Hyperactivity Disorder (ADHD) and Chronic Diseases

L. Paglia, S. Friuli, S. Colombo, M. Paglia
Department of Pediatric Dentistry, Istituto Stomatologico Italiano, Milan, Italy

DOI 10.23804/ejpd.2019.20.02.09

"Healthy approaches to beverage and dietary consumption should be recommended and hopefully established in infancy, with the aim of preventing negative effects on general health in later childhood and adulthood.

and hopefully established in infancy, with the aim of preventing negative effects on general health in later childhood and adulthood.

Sugars added to foods during processing, preparation or at table, sweeten food and beverage taste, improve their palatability and are used to preserve foods and to confer property such as viscosity, texture and color. They provide sensory enhancement to foods and promote enjoyment but, although they may be required in some clinical situations, they are not a necessary component of the diet in healthy children. In addition to its role in carious disease, for which there is moderate evidence of a direct correlation, increasing attention has been paid to how dietary sugars affect obesity, Type 2 diabetes mellitus, and cardiometabolic and kidney diseases

aciduric bacteria (Streptococci mutans and Lactobacilli especially), which decrease salivary and plaque pH. Otherwise, a diet lower in sugars and fermentable carbohydrates and high in calcium-rich cheese may favour remineralisation.

Studies have confirmed the direct correlation between intake of dietary sugars and carious disease throughout the course of life. The type of food (solid or beverage), exposure time, and frequency of eating also play an important role in the development of carious disease.

Since the first studies, additional factors, besides the diet, have been recognised in the aetiopathogenesis of carious disease that include salivary

Artificial Sweeteners

Nature. 2014 Oct 9;514(7521):181-6. doi: 10.1038/nature13793. Epub 2014 Sep 17.

Artificial sweeteners induce glucose intolerance by altering the gut microbiota.

Suez J[1], Korem T[2], Zeevi D[2], Zilberman-Schapira G[3], Thaiss CA[1], Maza O[1], Israeli D[4], Zmora N[5], Gilad S[6], Weinberger A[7], Kuperman Y[8], Harmelin A[8], Kolodkin-Gal I[9], Shapiro H[1], Halpern Z[10], Segal E[7], Elinav E[1].

Author information

Abstract

Non-caloric artificial sweeteners (NAS) are among the most widely used food additives worldwide, regularly consumed by lean and obese individuals alike. NAS consumption is considered safe and beneficial owing to their low caloric content, yet supporting scientific data remain sparse and controversial. Here we demonstrate that consumption of commonly used NAS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota. These NAS-mediated deleterious metabolic effects are abrogated by antibiotic treatment, and are fully transferrable to germ-free mice upon faecal transplantation of microbiota configurations from NAS-consuming mice, or of microbiota anaerobically incubated in the presence of NAS. We identify NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrate similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, our results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.

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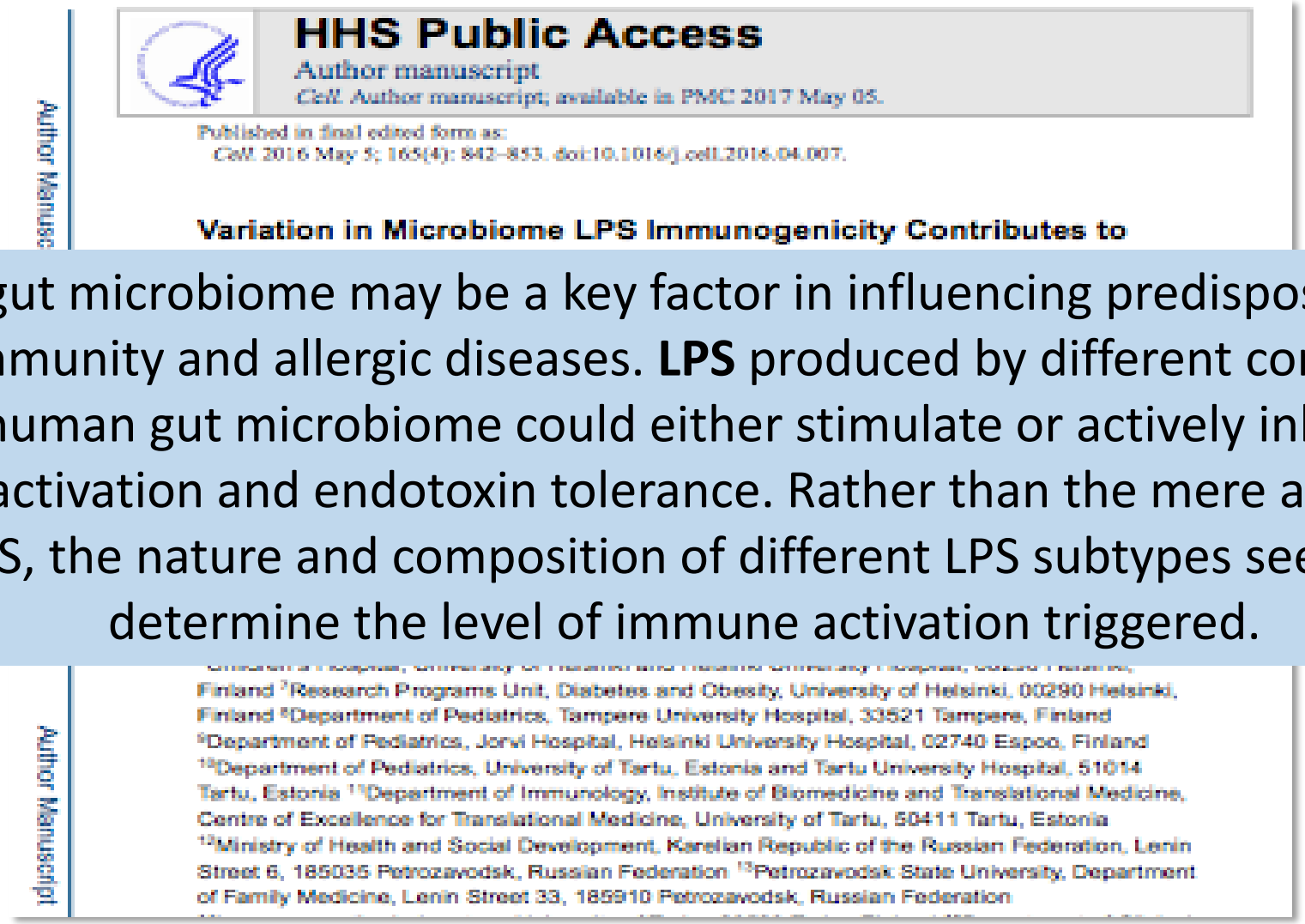
Suez J, et at. Nature. 2014 Oct 9;514(7521):181-6.

Gut Microbiome and Autoimmunity



HHS Public Access

Author manuscript

Cell. Author manuscript; available in PMC 2017 May 05.

Published in final edited form as:

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Variation in Microbiome LPS Immunogenicity Contributes to

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Finland [2]Research Programs Unit, Diabetes and Obesity, University of Helsinki, 00290 Helsinki, Finland [3]Department of Pediatrics, Tampere University Hospital, 33521 Tampere, Finland [4]Department of Pediatrics, Jorvi Hospital, Helsinki University Hospital, 02740 Espoo, Finland [12]Department of Pediatrics, University of Tartu, Estonia and Tartu University Hospital, 51014 Tartu, Estonia [11]Department of Immunology, Institute of Biomedicine and Translational Medicine, Centre of Excellence for Translational Medicine, University of Tartu, 50411 Tartu, Estonia [13]Ministry of Health and Social Development, Karelian Republic of the Russian Federation, Lenin Street 6, 185035 Petrozavodsk, Russian Federation [13]Petrozavodsk State University, Department of Family Medicine, Lenin Street 33, 185910 Petrozavodsk, Russian Federation

The gut microbiome may be a key factor in influencing predisposition to autoimmunity and allergic diseases. **LPS** produced by different constituents of the human gut microbiome could either stimulate or actively inhibit TLR4, NFκB activation and endotoxin tolerance. Rather than the mere amount of LPS, the nature and composition of different LPS subtypes seem to determine the level of immune activation triggered.

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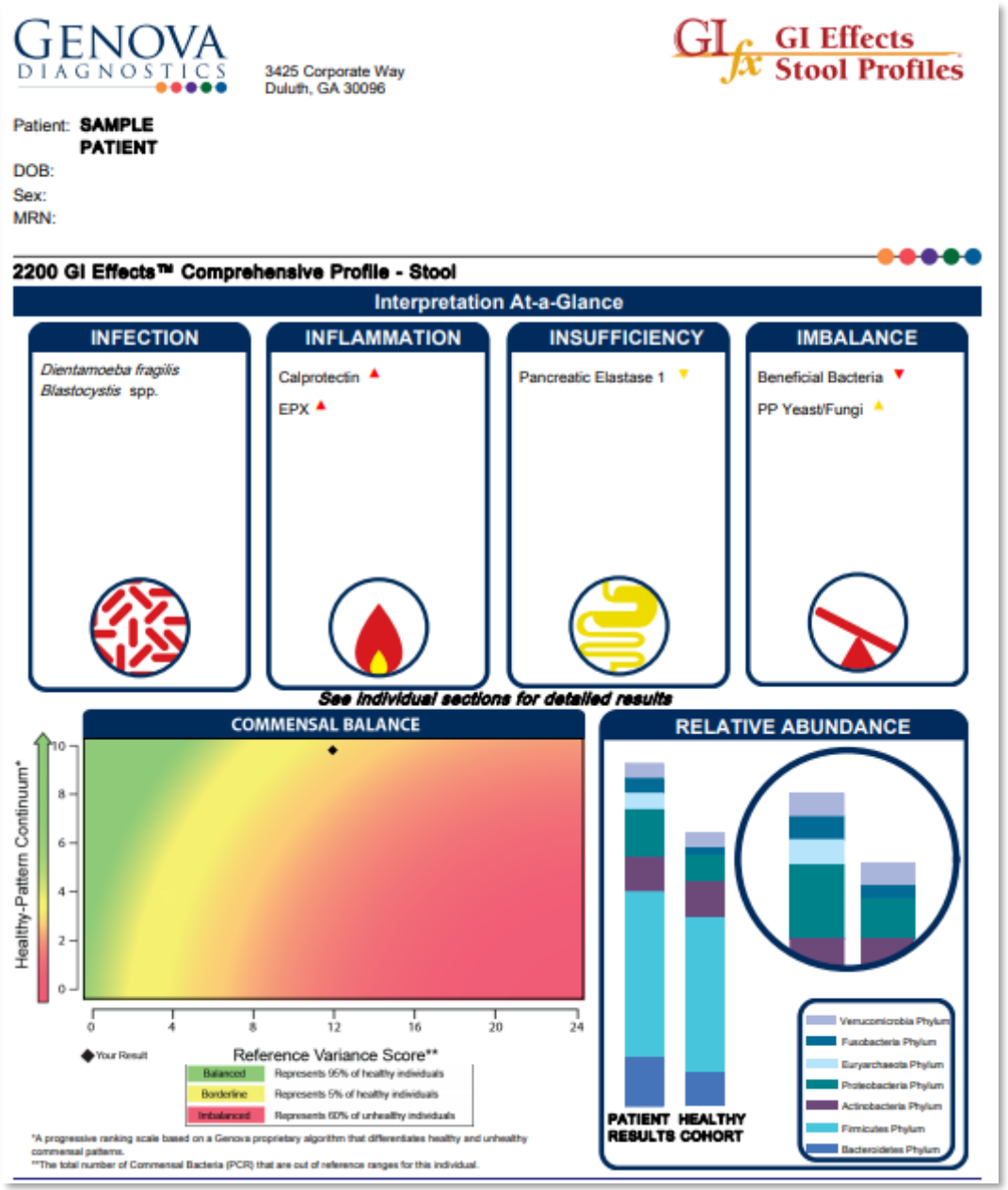
Vatanen T, et al. *Cell*. 2016 May 5; 165(4): 842–853.

LPS-producing Gut Bacteria

Campylobacter
E. Coli
Klebsiella
Enterobacter
Salmonella
Shigella

Detected either through PCR, culture, or Enzyme ImmunoAssay (EIA)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Duluth, GA 30096

GI fx GI Effects Stool Profiles

Patient: SAMPLE PATIENT
DOB:
Sex:
MRN:

2200 GI Effects™ Comprehensive Profile - Stool

Interpretation At-a-Glance

INFECTION
Dientamoeba fragilis
Blastocystis spp.

INFLAMMATION
Calprotectin ▲
EPX ▲

INSUFFICIENCY
Pancreatic Elastase 1 ▼

IMBALANCE
Beneficial Bacteria ▼
PP Yeast/Fungi ▲

See individual sections for detailed results

COMMENSAL BALANCE
Healthy-Pattern Continuum*
Reference Variance Score**
Your Result
Balanced — Represents 95% of healthy individuals
Borderline — Represents 5% of healthy individuals
Imbalanced — Represents 60% of unhealthy individuals
*A progressive ranking scale based on a Genova proprietary algorithm that differentiates healthy and unhealthy commensal patterns.
**The total number of Commensal Bacteria (PCR) that are out of reference ranges for this individual.

RELATIVE ABUNDANCE
PATIENT RESULTS
HEALTHY COHORT
Verrucomicrobia Phylum
Fusobacteria Phylum
Euryarchaeota Phylum
Proteobacteria Phylum
Actinobacteria Phylum
Firmicutes Phylum
Bacteroidetes Phylum

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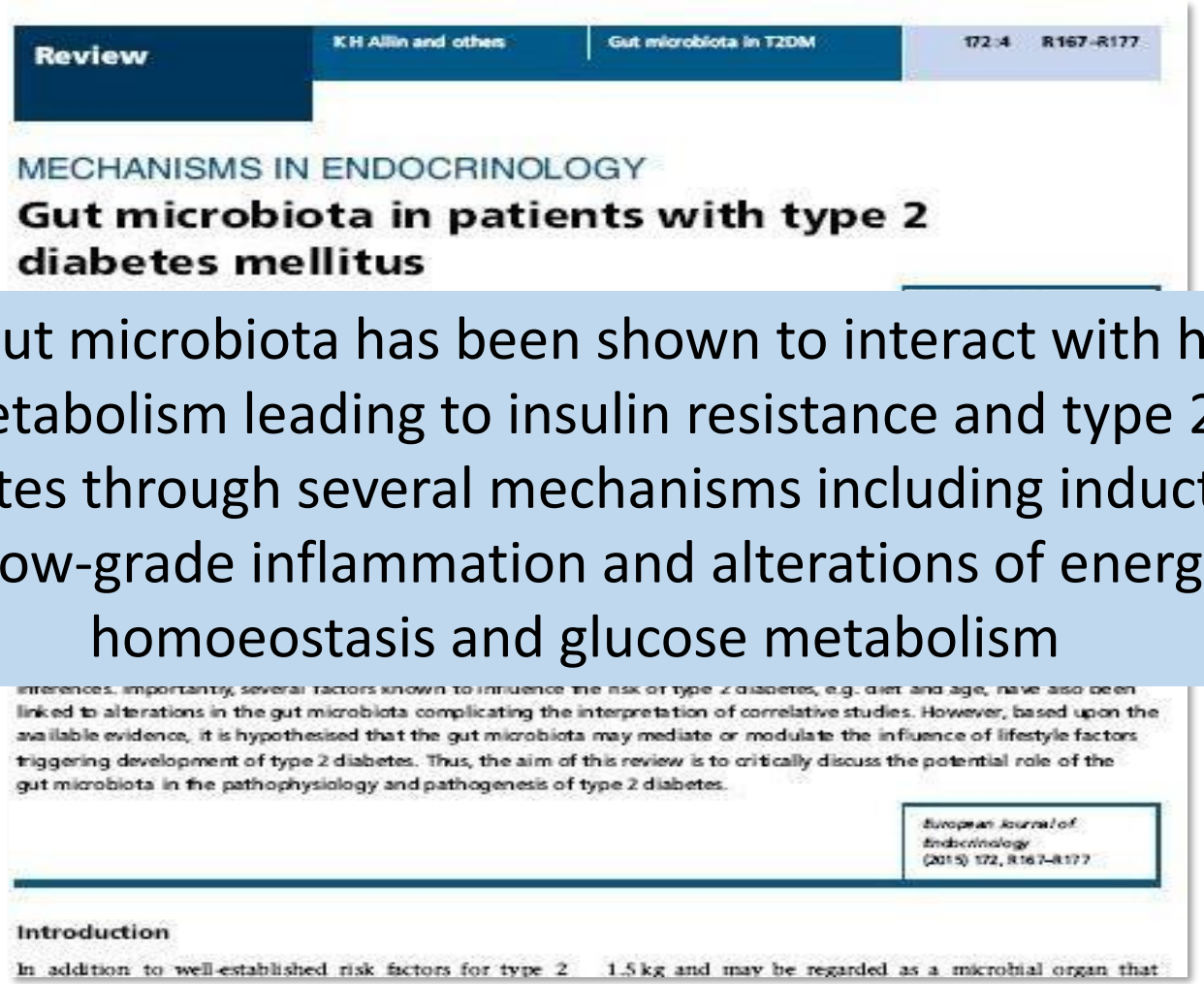
MIcrobiota and Type 2



The gut microbiota has been shown to interact with host metabolism leading to insulin resistance and type 2 diabetes through several mechanisms including induction of low-grade inflammation and alterations of energy homoeostasis and glucose metabolism

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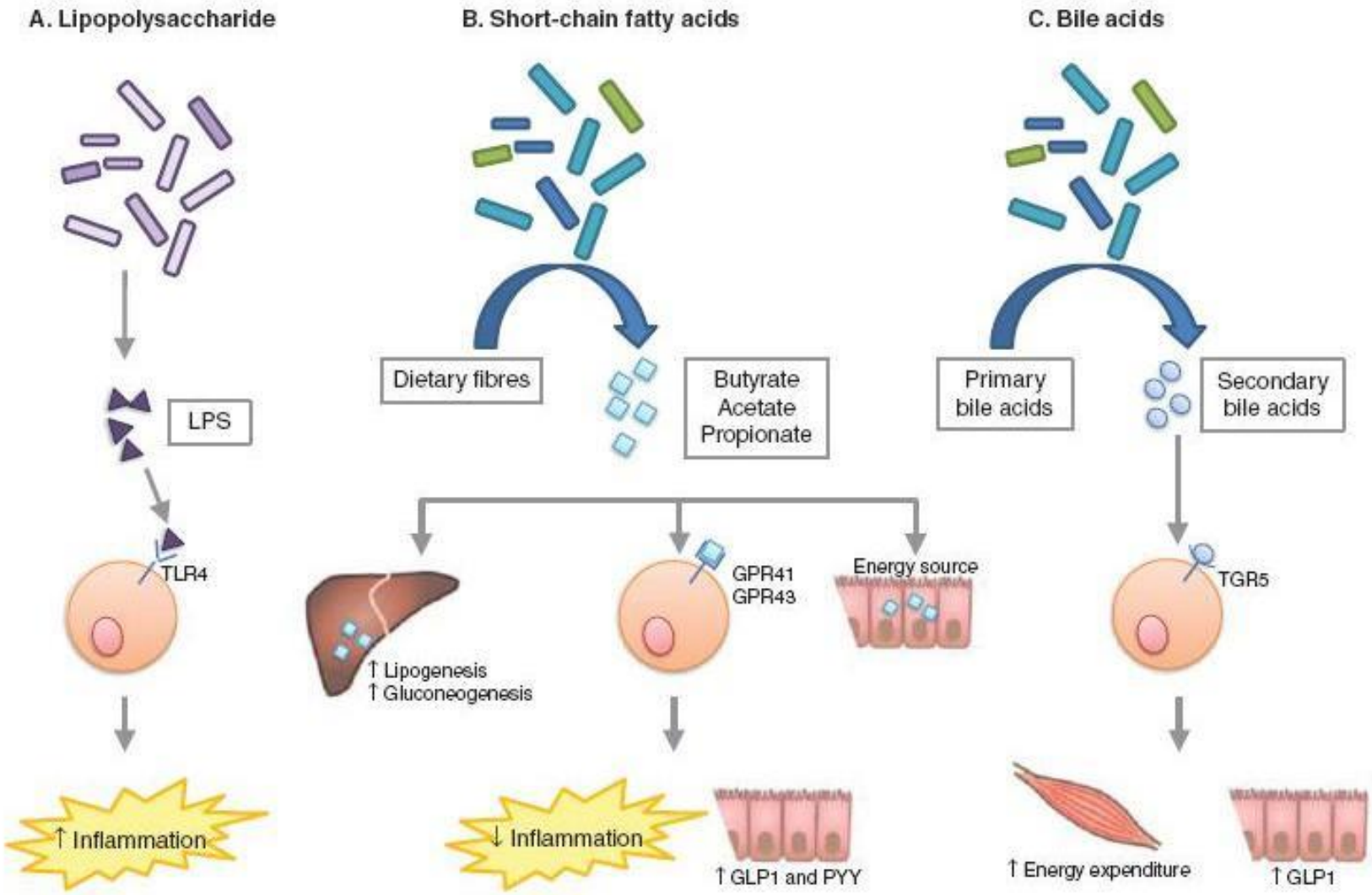
Allin KH, et al. *Eur J Endocrinol*. 2015 Apr;172(4):R167-77.



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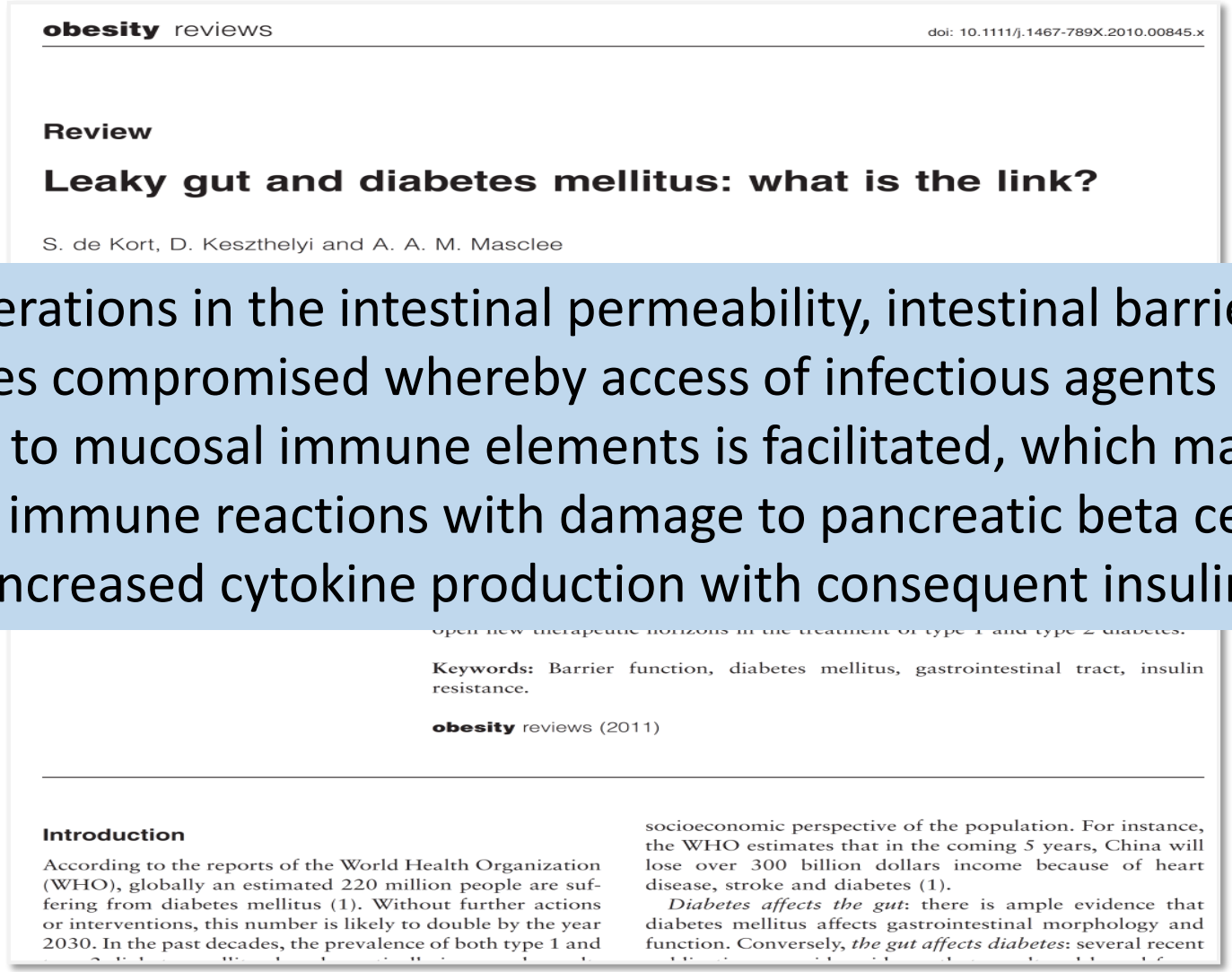
Allin KH, et al. *Eur J Endocrinol*. 2015 Apr;172(4):R167-77.

Leaky Gut and DM



obesity reviews doi: 10.1111/j.1467-789X.2010.00845.x

Review

Leaky gut and diabetes mellitus: what is the link?

S. de Kort, D. Keszthelyi and A. A. M. Masclee

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.

Keywords: Barrier function, diabetes mellitus, gastrointestinal tract, insulin resistance.

obesity reviews (2011)

Introduction

According to the reports of the World Health Organization (WHO), globally an estimated 220 million people are suffering from diabetes mellitus (1). Without further actions or interventions, this number is likely to double by the year 2030. In the past decades, the prevalence of both type 1 and

socioeconomic perspective of the population. For instance, the WHO estimates that in the coming 5 years, China will lose over 300 billion dollars income because of heart disease, stroke and diabetes (1).

Diabetes affects the gut: there is ample evidence that diabetes mellitus affects gastrointestinal morphology and function. Conversely, *the gut affects diabetes*: several recent

GENOVA DIAGNOSTICS

De Kort S, et al. *Obes Rev*. 2011 Jun;12(6):449-58.

Toxins and DM: Perfluoroalkyl acids (PFAAs)

PLoS One. 2014 Jan 31;9(1):e87137. doi: 10.1371/journal.pone.0087137. eCollection 2014.

Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring.

Wan HT, Zhao YG, Leung PY, Wong CK.

Author information

Abstract

Perfluoroalkyl acids (PFAAs) are globally present in the environment and are widely distributed in human populations and wildlife. The chemicals are ubiquitous in human body fluids and have a long serum elimination half-life. The notorious member of PFAAs, perfluorooctane sulfonate (PFOS) is prioritized as a global concerning chemical at the Stockholm Convention in 2009, due to its harmful effects in mammals and aquatic organisms. PFOS is known to affect lipid metabolism in adults and was found to be able to cross human placenta. However the effects of in utero exposure to the susceptibility of metabolic disorders in offspring have not yet been elucidated. In this study, pregnant CD-1 mice (F0) were fed with 0, 0.3 or 3 mg PFOS/kg body weight/day in corn oil by oral gavage daily throughout gestational and lactation periods. We investigated the immediate effects of perinatal exposure to PFOS on glucose metabolism in both maternal and offspring after weaning (PND 21). To determine if the perinatal exposure predisposes the risk for metabolic disorder to the offspring, weaned animals without further PFOS exposure, were fed with either standard or high-fat diet until PND 63. Fasting glucose and insulin levels were measured while HOMA-IR index and glucose AUCs were reported. Our data illustrated the first time the effects of the environmental equivalent dose of PFOS exposure on the disturbance of glucose metabolism in F1 pups and F1 adults at PND 21 and 63, respectively. Although the biological effects of PFOS on the elevated levels of fasting serum glucose and insulin levels were observed in both pups and adults of F1, the phenotypes of insulin resistance and glucose intolerance were only evident in the F1 adults. The effects were exacerbated under HFD, highlighting the synergistic action at postnatal growth on the development of metabolic disorders.

PMID: 24498028 [PubMed - in process] **Free full text**

GENOVA DIAGNOSTICS

Wan HT, et al. *PLoS One*. 2014 Jan 31;9(1):e87137.

Arsenic Exposure and Prevalence of Type 2 Diabetes in US Adults

Ana Navas-Acien, MD, PhD; Ellen K. Silbergeld, PhD; Roberto Pastor-Barriuso, PhD; et al

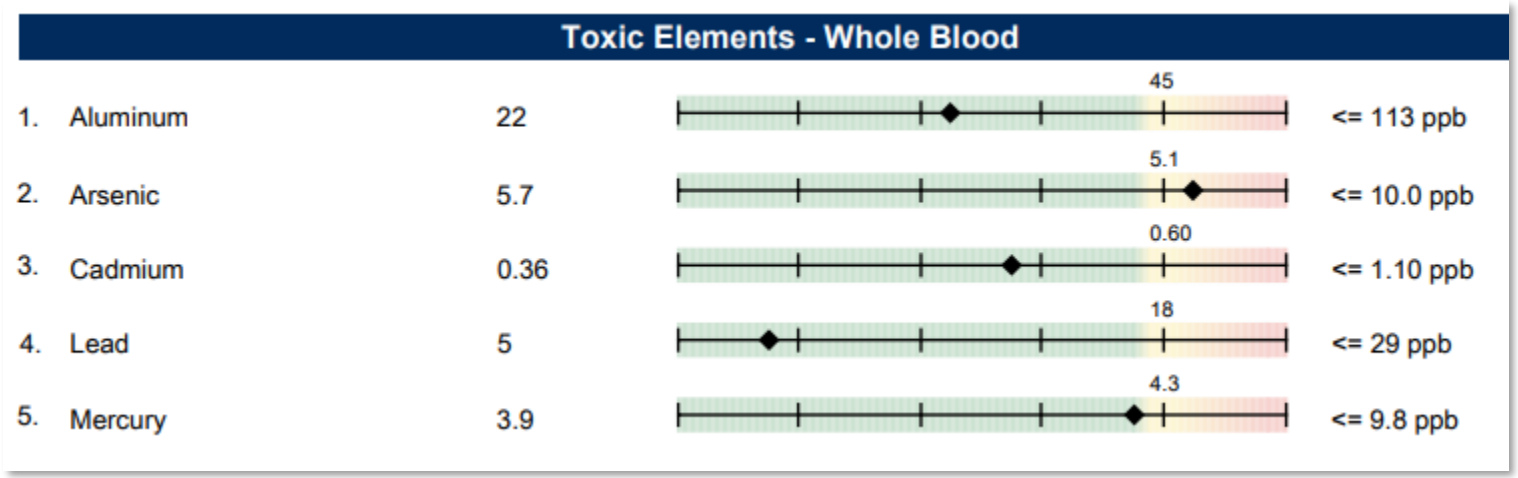
» Author Affiliations | Article Information

JAMA. 2008;300(7):814-822. doi:10.1001/jama.300.7.814

"Low-level arsenic exposure reported to be associated with insulin resistance."

Abstract

Context High chronic exposure to inorganic arsenic in drinking water has been related to diabetes development, but the effect of exposure to low to moderate levels of inorganic arsenic on diabetes risk is unknown. In contrast, arsenobetaine, an organic arsenic compound derived from seafood intake, is considered nontoxic.



GENOVA DIAGNOSTICS

Navas-Acien A, et al. *JAMA*. 2008 Aug 20;300(7):814-22.

Toxins and DM: PCB Exposure

J Toxicol Environ Health A. 2013;76(12):701-15. doi: 10.1080/15287394.2013.796503.

Chronic Exposure to PCBs (Aroclor 1254) Exacerbates Obesity-Induced Insulin Resistance and Hyperinsulinemia in Mice.

Gray SL, Shaw AC, Gagne AX, Chan HM.

a Northern Medical Program, University of Northern British Columbia , Prince George , British Columbia , Canada.

Abstract

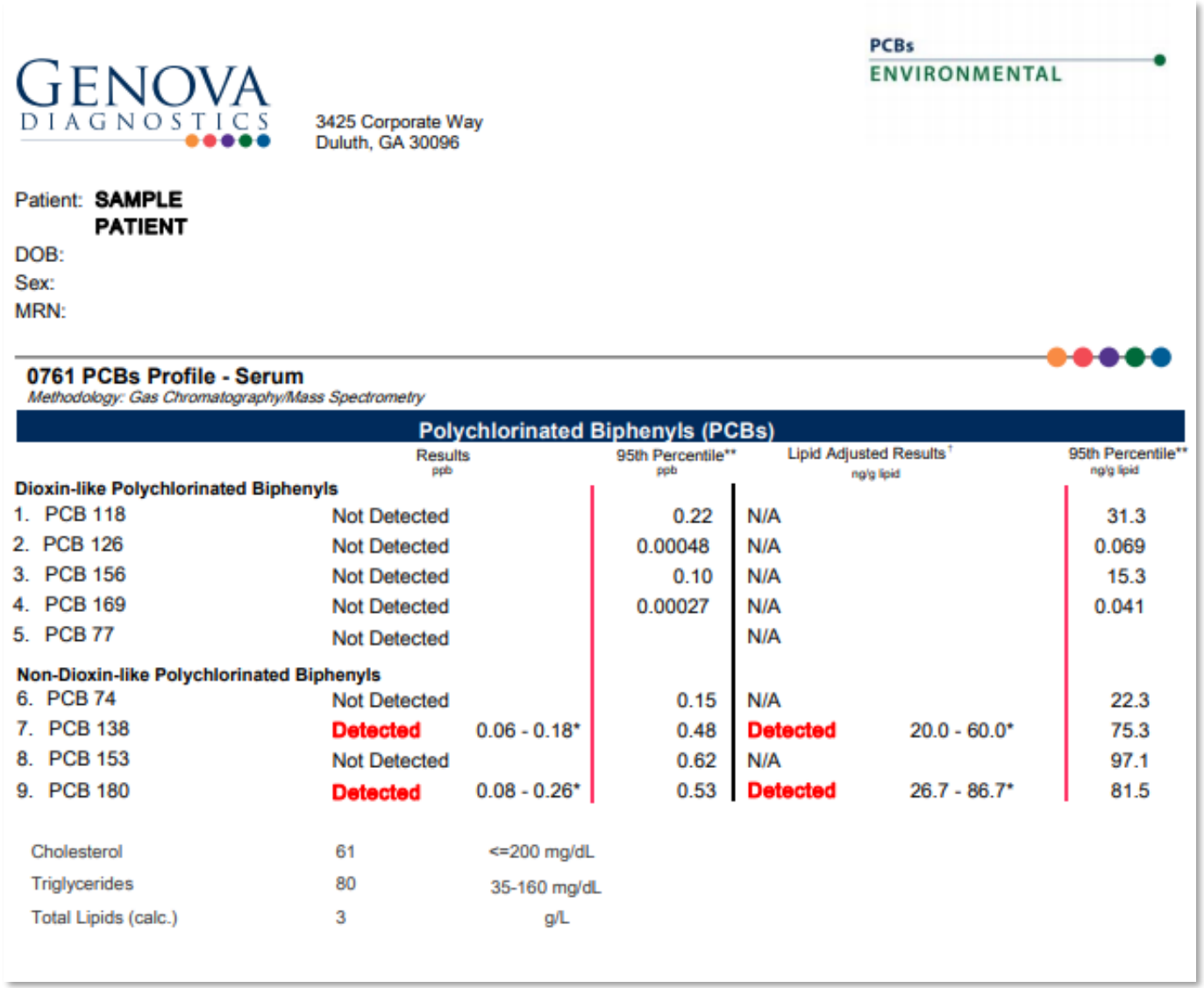
Our results demonstrate a causative association between **PCB** exposure and obesity-induced insulin resistance and hyperinsulinemia independent of body weight changes.

metabolic homeostasis. Chronic exposure of diabetes-prone C57B/6 mice to a polychlorinated biphenyl (PCB) mixture (Aroclor 1254, 36 mg/kg/wk, 20 wk) alone or in combination with high-fat diet impairs carbohydrate metabolism was compared to vehicle-treated control animals. Specifically, PBC exposure was found to produce hyperinsulinemia in both lean and diet-induced obese mice and exacerbated whole-body insulin resistance in obese mice. These changes in carbohydrate metabolism in response to Aroclor 1254 occurred without marked effect on body weight in both lean and obese mice. Our results demonstrate a causative association between PCB exposure and obesity-induced insulin resistance and hyperinsulinemia independent of body weight changes, an observation that contributes to a growing body of evidence suggesting that exposure to environmental pollutants represents a novel risk factor contributing to the diabetes epidemic.

GENOVA DIAGNOSTICS

Gray SL, et al. *J Toxicol Environ Health A*. 2013;76(12):701-15.

Testing for PCB Exposure



GENOVA DIAGNOSTICS

3425 Corporate Way
Duluth, GA 30096

PCBs
ENVIRONMENTAL

Patient: **SAMPLE PATIENT**
DOB:
Sex:
MRN:

0761 PCBs Profile - Serum
Methodology: Gas Chromatography/Mass Spectrometry

Polychlorinated Biphenyls (PCBs)

	Results ppb		95th Percentile** ppb	Lipid Adjusted Results† ng/g lipid		95th Percentile** ng/g lipid
Dioxin-like Polychlorinated Biphenyls						
1. PCB 118	Not Detected		0.22	N/A		31.3
2. PCB 126	Not Detected		0.00048	N/A		0.069
3. PCB 156	Not Detected		0.10	N/A		15.3
4. PCB 169	Not Detected		0.00027	N/A		0.041
5. PCB 77	Not Detected			N/A		
Non-Dioxin-like Polychlorinated Biphenyls						
6. PCB 74	Not Detected		0.15	N/A		22.3
7. PCB 138	**Detected**	0.06 - 0.18*	0.48	**Detected**	20.0 - 60.0*	75.3
8. PCB 153	Not Detected		0.62	N/A		97.1
9. PCB 180	**Detected**	0.08 - 0.26*	0.53	**Detected**	26.7 - 86.7*	81.5

Cholesterol	61	<=200 mg/dL
Triglycerides	80	35-160 mg/dL
Total Lipids (calc.)	3	g/L

GENOVA DIAGNOSTICS

Hypercortisolism is Associated With Insulin Resistance (IR) and Diabetes Mellitus (DM)

Psychoneuroendocrinology 62 (2015) 327–335

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Diurnal salivary cortisol, glycemia and insulin resistance: The multi-ethnic study of atherosclerosis

Joshua J. Joseph[a], Xu Wang[b], Elias Spanakis[c], Teresa Seeman[d], Gary Wand[a], Belinda Needham[e], Sherita Hill Golden[a,f,*]

[a] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[b] School of Public Health, Drexel University, Philadelphia, PA, United States
[c] Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, United States
[d] Division of Geriatrics, David Geffen School of Medicine, University of California, Los Angeles, CA, United States
[e] Department of Epidemiology, University of Michigan, Ann Arbor, MI, United States
[f] Department of Epidemiology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, United States

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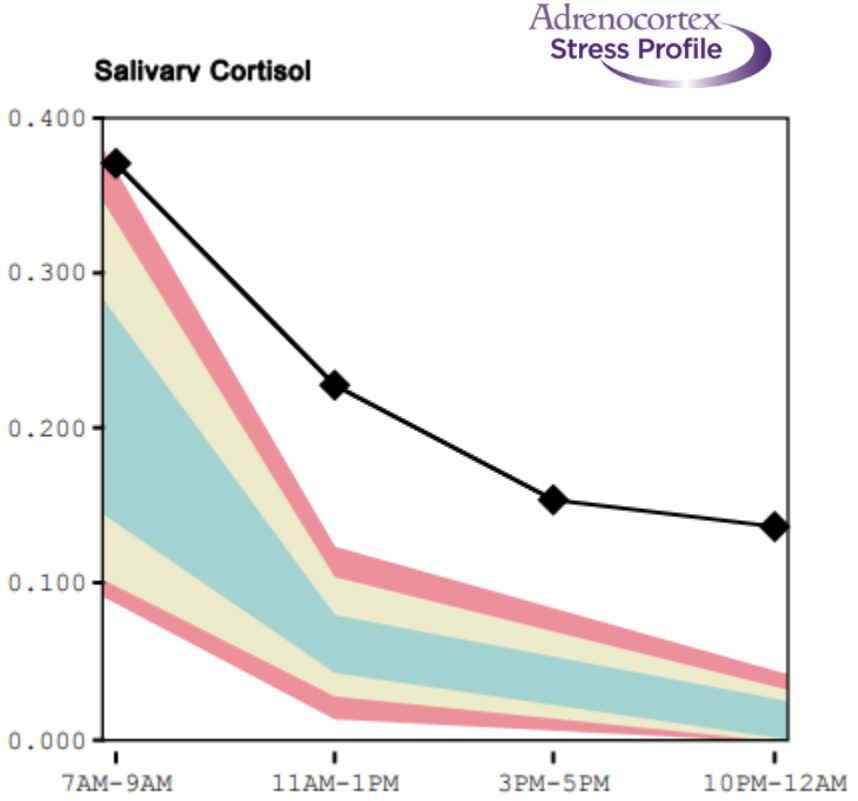
Keywords:
Cortisol
Glycemia
Insulin resistance
Type 2 Diabetes mellitus
Hypothalamic-pituitary-adrenal axis

ABSTRACT

Hypercortisolism is associated with insulin resistance (IR) and diabetes mellitus (DM); however, to our knowledge prior studies have not examined the association of diurnal cortisol curve features with measures of glycemia or IR in a population-based setting. Using log-transformed salivary cortisol data on 850 ethnically diverse men and women from the Multi-Ethnic Study of Atherosclerosis, we investigated the cross-sectional association of cortisol curve features with (1) glycemia in those with and without DM and (2) IR, in non-diabetic subjects. The log-transformed salivary cortisol curve features included wake-up cortisol, cortisol awakening response (CAR), early decline slope (30 min to 2 h post-awakening), late decline slope (2 h post-awakening to bedtime), overall decline slope (0 min to bedtime, excluding 30 min cortisol), bedtime cortisol and total area under the curve (AUC). Overall, following multivariable adjustment, among those with diabetes mellitus (DM), early decline slope, overall decline slope, bedtime cortisol, and AUC were significantly and positively associated with a 5.4% (95% CI: 1.3, 9.7), 54.7% (95% CI: 12.4, 112.9), 4.0% (95% CI: 1.6,6.4), and 6.8% (95% CI: 3.3,10.4) higher HbA1c per 1 unit increase in log cortisol feature, respectively. Cortisol curve features were not associated with HbA1c among non-diabetic participants; however, wake-up cortisol and AUC were associated with a 8.2% lower (95% CI: −13.3,−2.7) and 7.9% lower (95% CI: −14.6, −0.6) log HOMA-IR, respectively. This was attenuated by adjustment for waist circumference. Among participants with DM, cortisol curve parameters suggestive of higher hypothalamic-pituitary-adrenal (HPA) axis activity and dysfunction were associated with higher HbA1c. In non-diabetic participants, greater HPA activity was paradoxically associated with lower insulin resistance.



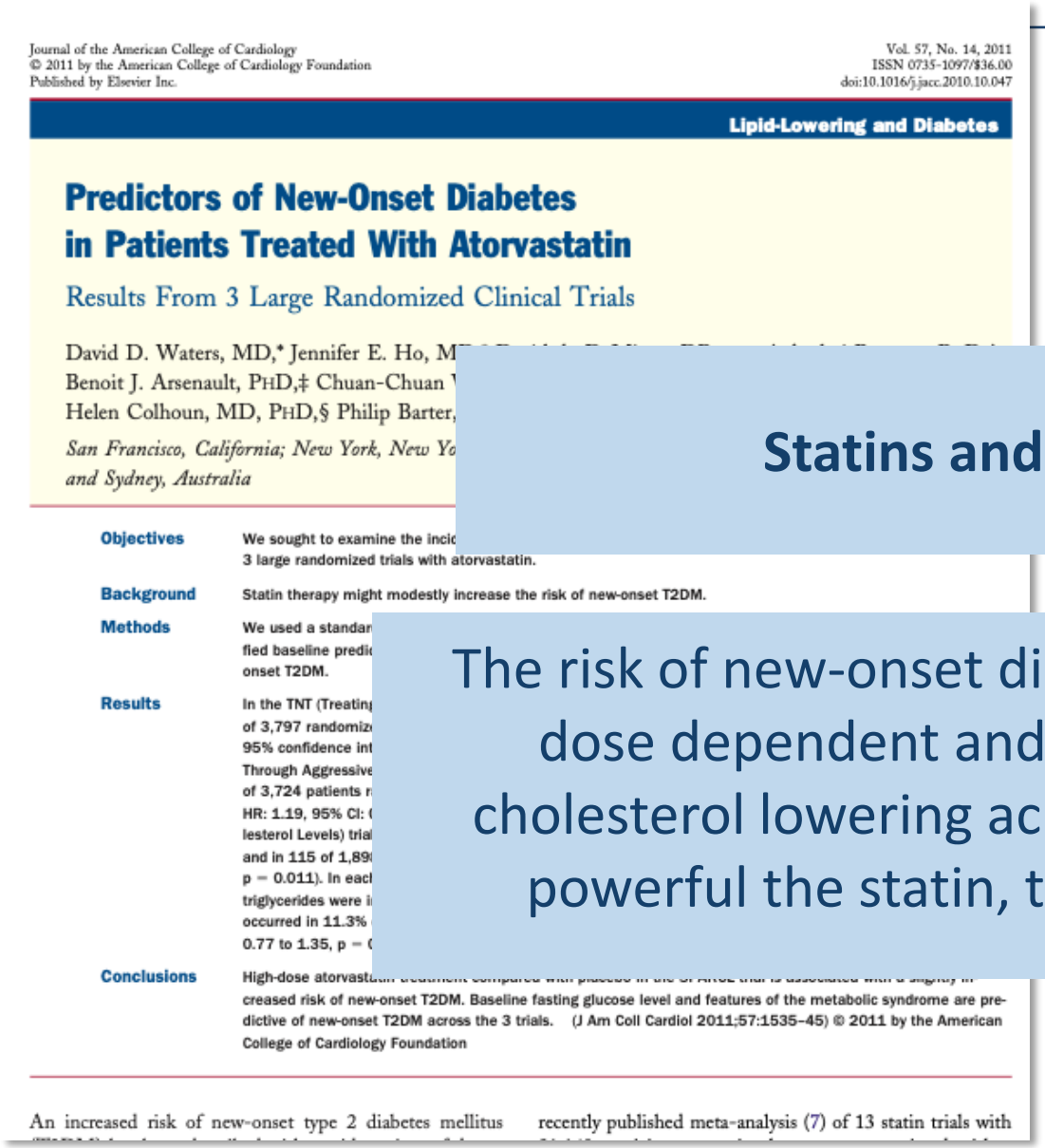
Joseph, JJ et al. *Psychoneuroendocrinology*. 2015 Dec;62:327-35.2015 Dec;62:327-35.

Sleep and Insulin Resistance

"Sleep deprivation may lead to **insulin resistance** and, subsequently, to diabetes mellitus."

GENOVA DIAGNOSTICS

Aldabal L, Bahammam AS. *Open Respir Med J*. 2011;5:31-43.



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ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.10.047

Lipid-Lowering and Diabetes

Predictors of New-Onset Diabetes in Patients Treated With Atorvastatin

Results From 3 Large Randomized Clinical Trials

David D. Waters, MD,* Jennifer E. Ho, M
Benoit J. Arsenault, PHD,‡ Chuan-Chuan
Helen Colhoun, MD, PHD,§ Philip Barter,

San Francisco, California; New York, New Yo
and Sydney, Australia

Objectives We sought to examine the incid
3 large randomized trials with atorvastatin.

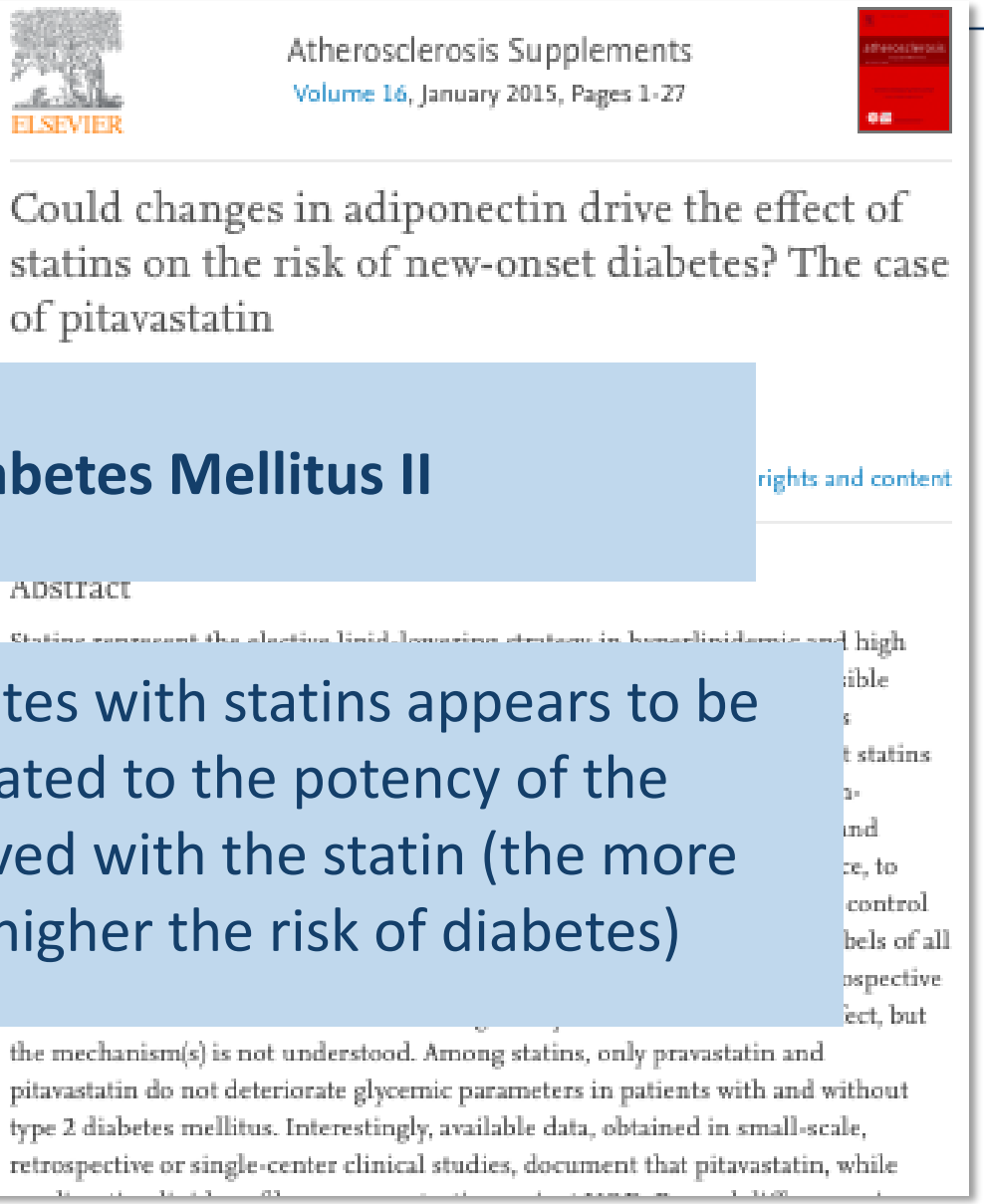
Background Statin therapy might modestly increase the risk of new-onset T2DM.

Methods We used a standar
fied baseline predic
onset T2DM.

Results In the TNT (Treating
of 3,797 randomize
95% confidence int
Through Aggressive
of 3,724 patients r
HR: 1.19, 95% CI: (
lesterol Levels) trial
and in 115 of 1,89
p = 0.011). In each
triglycerides were i
occurred in 11.3%
0.77 to 1.35, p = (

Conclusions High-dose atorvastatin treatment compared with placebo in the SPARCL trial is associated with a slightly increased risk of new-onset T2DM. Baseline fasting glucose level and features of the metabolic syndrome are predictive of new-onset T2DM across the 3 trials. (J Am Coll Cardiol 2011;57:1535–45) © 2011 by the American College of Cardiology Foundation

An increased risk of new-onset type 2 diabetes mellitus recently published meta-analysis (7) of 13 statin trials with



Atherosclerosis Supplements
Volume 16, January 2015, Pages 1-27

Could changes in adiponectin drive the effect of statins on the risk of new-onset diabetes? The case of pitavastatin

rights and content

Abstract

Statins represent the elective lipid-lowering strategy in hypercholesterolemic and high
ible
s
t statins
a-
nd
ce, to
control
bels of all
ospective
ect, but

the mechanism(s) is not understood. Among statins, only pravastatin and pitavastatin do not deteriorate glycemic parameters in patients with and without type 2 diabetes mellitus. Interestingly, available data, obtained in small-scale, retrospective or single-center clinical studies, document that pitavastatin, while

Statins and Diabetes Mellitus II

The risk of new-onset diabetes with statins appears to be dose dependent and related to the potency of the cholesterol lowering achieved with the statin (the more powerful the statin, the higher the risk of diabetes)

GENOVA DIAGNOSTICS

Waters DD, et al. *J Am Coll Cardiol*. 2011 Apr 5;57(14):1535-45.
Arnaboldi L, Corsini A. *Atheroscler Suppl*. 2015 Jan;16:1-27.

Get the History!

GENOVA DIAGNOSTICS

Chronic Conditions Linked to the Pathophysiology of Insulin Resistance

- Obstructive sleep apnea
- Hypertension
- Polycystic ovary syndrome
- Cancer (breast, colon, other)
- Nonalcoholic fatty liver disease (NAFLD) and non-alcoholic steato-hepatitis (NASH)
- Elevated liver enzymes (AST/ALT) &/or GGT
- Inflammation
- Thyroid problems
- Cardiovascular disease
- Cushings or Addison's Disease

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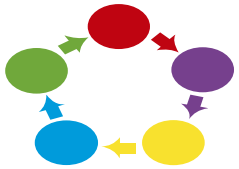


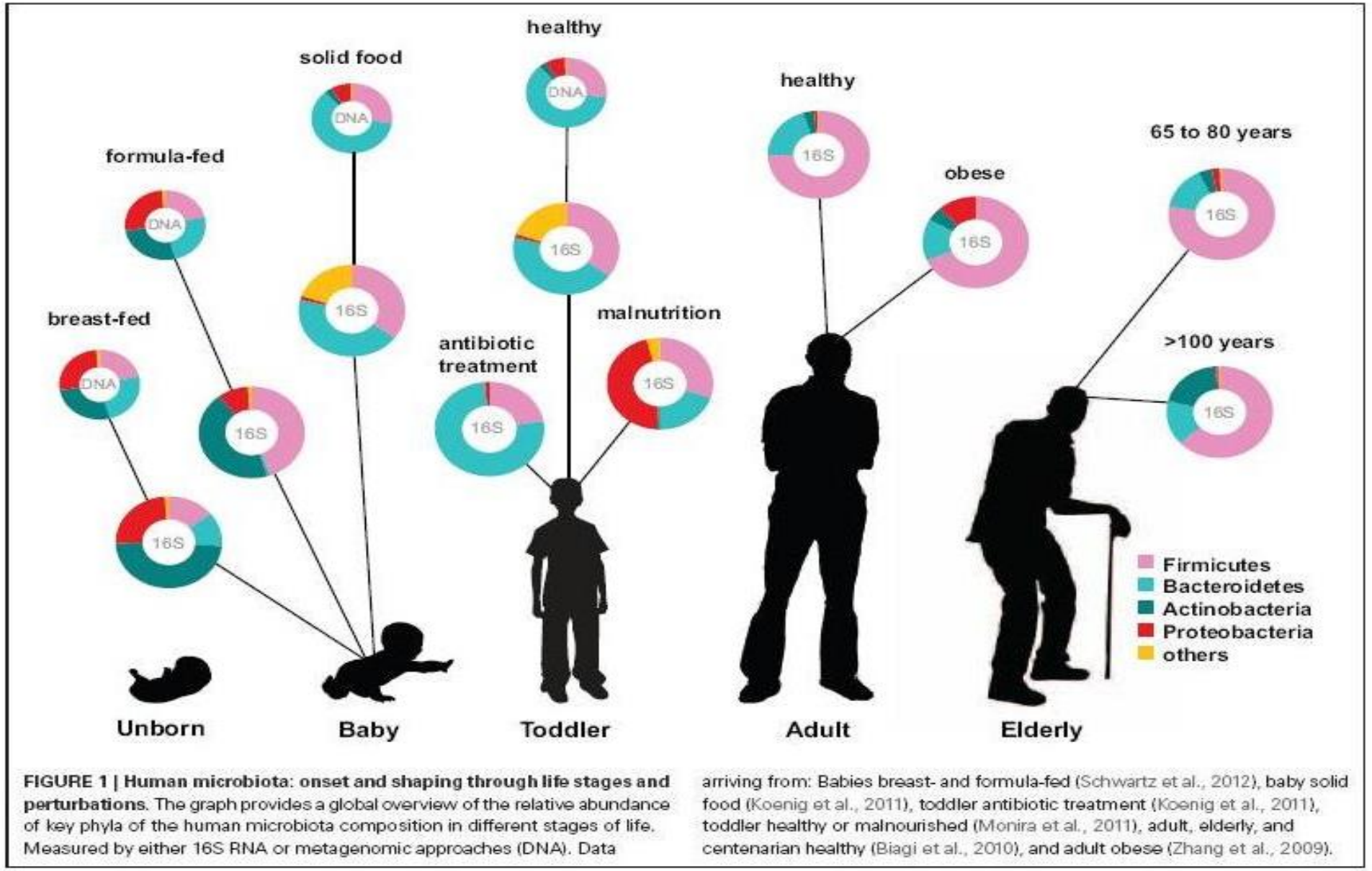
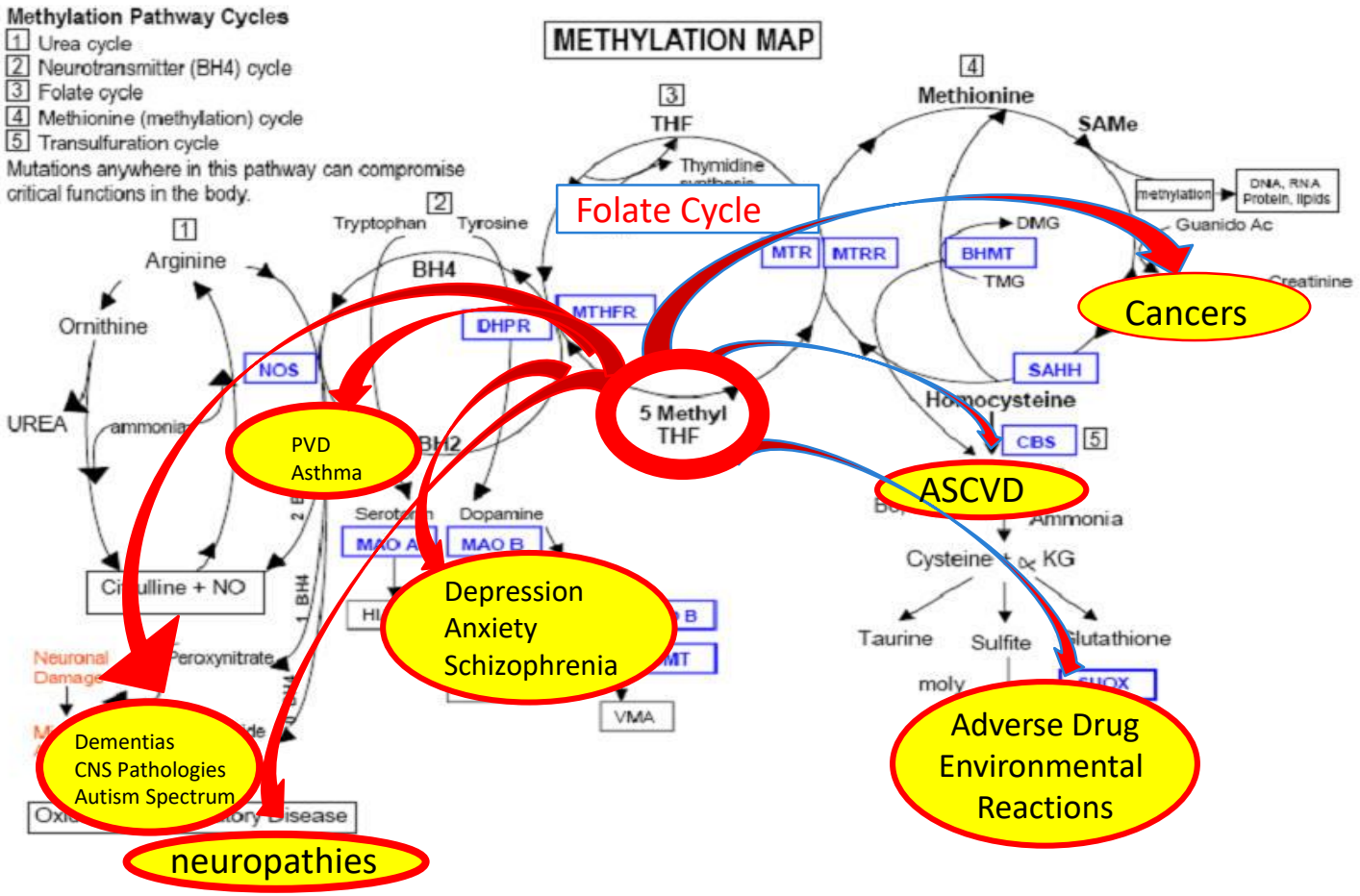


FIGURE 1 | Human microbiota: onset and shaping through life stages and perturbations. The graph provides a global overview of the relative abundance of key phyla of the human microbiota composition in different stages of life. Measured by either 16S RNA or metagenomic approaches (DNA). Data arriving from: Babies breast- and formula-fed (Schwartz et al., 2012), baby solid food (Koenig et al., 2011), toddler antibiotic treatment (Koenig et al., 2011), toddler healthy or malnourished (Monira et al., 2011), adult, elderly, and centenarian healthy (Biagi et al., 2010), and adult obese (Zhang et al., 2009).

GENOVA DIAGNOSTICS

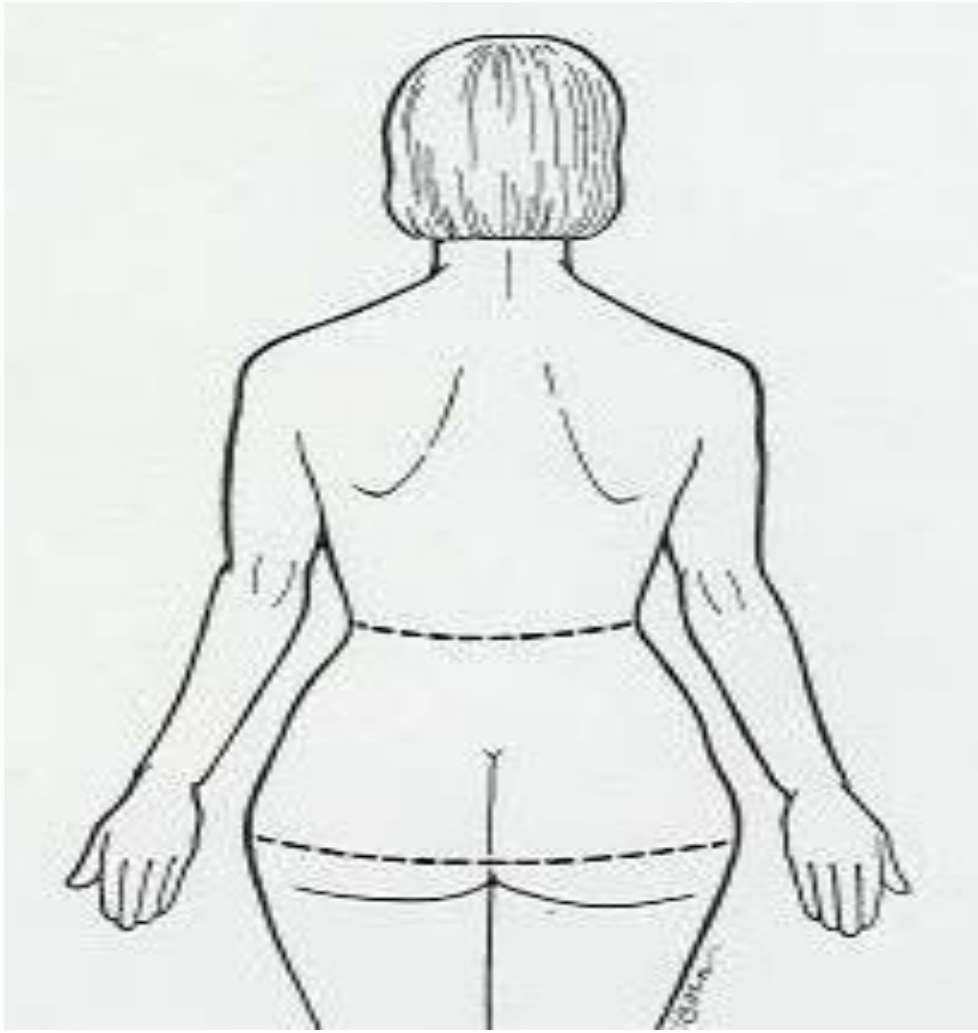
Ottman N, et al. *Front Cell Infect Microbiol*. 2012 Aug 9;2:104.

B-Vitamin Status and Methylation



Physical Exam Findings

- Body shape
- Acanthosis nigricans
- Skin tags / melasma
- Hirsutism
- Hair loss
- Waist circumference
- Abdominal exam
- Nails
- Hair
- Muscle bulk



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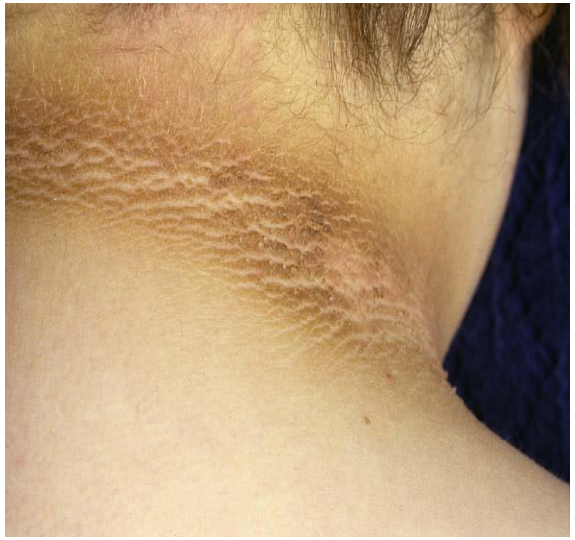
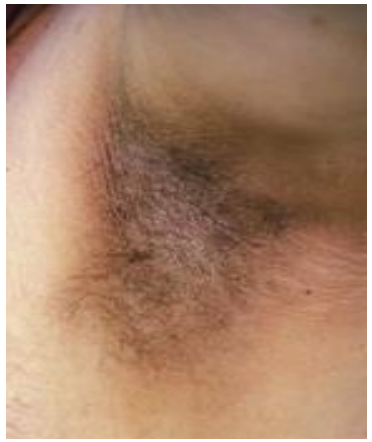
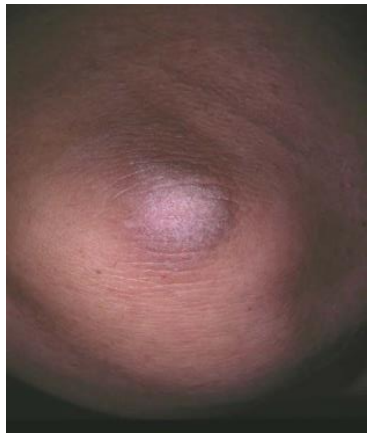
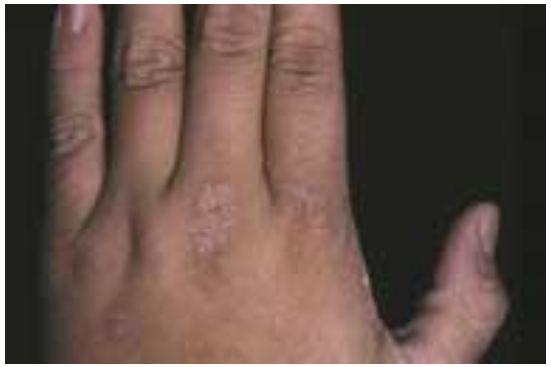


Acanthosis nigricans

- Smooth, velvet-like, hyperkeratotic plaques in intertriginous areas (e.g., groin, axillae, neck)
- Generally **caused by hyperinsulin-emia**







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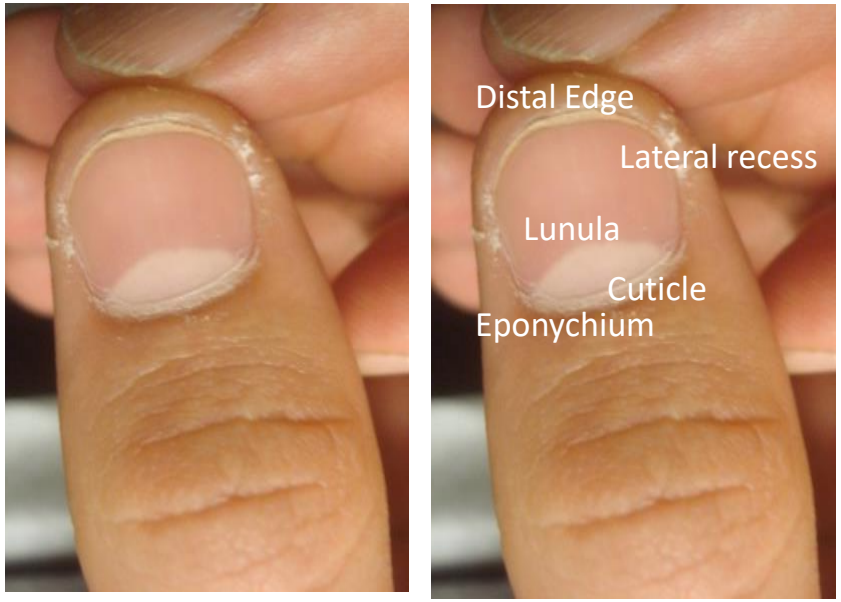
Look at the Nails



- Shape
- Color
- Pattern of color
- Texture and strength
- Growth pattern
- Surrounding tissue

GENOVA DIAGNOSTICS

Summary: Common Findings

- **Acanthosis nigricans**
  - Insulin resistance
- **White spots on nails**
  - Zinc
- **Hyperkeratosis pilaris**
  - Omega 3 deficiency
- **Tongue fissuring**
  - Up-regulated GALT
- **New onset abdominal girth**
  - Cortisol steal
- **Taste bud atrophy**
  - B2, B3, B12, iron

GENOVA DIAGNOSTICS

Suggested Initial Laboratory Work-Up

- Adiponectin
- Proinsulin
- HgbA1c
- Fasting insulin, and 30-min insulin after 75g glucose load, 1-hr and 2-hr insulin level
- Fasting glucose, 1-hr and 2-hr glucose after 75g load
- NMR lipoprotein profile
- Comprehensive metabolic panel
- GGTP
- Uric acid
- Comprehensive stool test
- Breath test for hydrogen and methane

GI fx GI Effects Stool Profiles

Small Intestinal Bacterial Overgrowth (SIBO)
GASTROINTESTINAL

GENOVA DIAGNOSTICS

HbA1c

Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk)

Kay-Tee Khaw, Nicholas Wareham, Robert Luben, Sheila Bingham, Suzy Oakes, Ailsa Welch, Nicholas Day

Abstract

Objectiv haemogl blood gl from ca **Design** **Setting** Investiga (EPIC-N **Subjects** glycated survey in 1993–7 who were followed up to December 1999.

Main outcome measures Mortality from all causes, cardiovascular disease, ischaemic heart disease, and other causes.

Results Men with known diabetes had increased mortality from all causes, cardiovascular disease, and ischaemic disease (relative risks 2.2, 3.3, and 4.2, respectively, $P < 0.001$ independent of age and other risk factors) compared with men without known

efforts need to consider not just those with established diabetes but whether it is possible to reduce the

Various blood glucose thresholds for the diagnosis of diabetes have been proposed,[4–7] based on the relation to risk of microvascular complications of diabetes, particularly retinopathy.[8] However, people with diabetes are also at increased risk of macrovascular diseases such as coronary heart disease and stroke,[9] and it is uncertain whether the relation between blood glucose concentration and such diseases has a threshold or is a continuum.

Glycated haemoglobin (HbA_{1c}) concentration is an

Department of Public Health and Primary Care, ...e of Public ... University ...bridge ... of Clinical ...ine, ...ridge ...SR

...e Khaw ...or of clinical ...logy

...las Wareham ...l Research ...l clinician

Robert Luben *research associate, computing and biostatistics*

Suzy Oakes *research associate*

Ailsa Welch *research associate, nutrition*

Nicholas Day *Medical Research Council research*

> "The predictive value of HbA1c for total mortality was *stronger* than that documented for *cholesterol* concentration, *body mass index* and *blood pressure*."

Khaw KT, et al. *BMJ*, 2001. 322(7277): p. 15-8.

Adiponectin

- *Protective*, adipose-derived protein
- Plays an important role in regulating glucose and lipid metabolism
  - Moderates fat tissue
  - Promotes insulin sensitivity
  - Is inversely related to glucose & insulin
  - Decreases hepatic glucose & lipid production
  - Protects against atherosclerosis by suppressing vascular inflammation (anti-inflammatory)

Proinsulin

J Diabetes Sci Technol. 2015 Sep 29;9(6):1307-12. doi: 10.1177/1932296815607862.

Elevated Intact Proinsulin Levels During an Oral Glucose Challenge Indicate Progressive ß-Cell Dysfunction and May Be Predictive for Development of Type 2 Diabetes.

Pfützner A[1], Hermanns I[2], Ramljak S[3], Demircik F[3], Pfützner AH[4], Kann PH[5], Weber MM[6].

Author information

Abstract

BACKGROUND: Elevated fasting intact proinsulin is a biomarker of late-stage ß-cell-dysfunction associated with clinically relevant insulin resistance. In this pilot investigation, we explored the potential value of measuring intact proinsulin as a functional predictor of ß-cell

Elevated proinsulin is viewed as symptoms of a functionally compromised ß-cell, most often arising from the over-stimulation of chronic hyperglycemia or in later disease stage from therapeutic intervention.

mg/dL, intact proinsulin: 3 ± 2 pmol/L/10 ± 7 pmol/L/10 ± 5 pmol/L); IGT: glucose: 102 ± 9 mg/dL/158 ± 57 mg/dL/149 ± 34 mg/dL, intact proinsulin: 7 ± 4 pmol/L/23 ± 8 pmol/L/28 ± 6 pmol/L; T2DM: glucose: 121 ± 20 mg/dL/230 ± 51 mg/dL/213 ± 34 mg/dL; intact proinsulin: 7 ± 7 pmol/L/26 ± 9 pmol/L/27 ± 10 pmol/L). Five years later, all of the IGT and 2 of the healthy subjects had developed T2DM and one had devloped IGT. All of them had elevated 2-hour proinsulin values in the initial OGTT, while patients with normal intact proinsulin results did not develop diabetes.

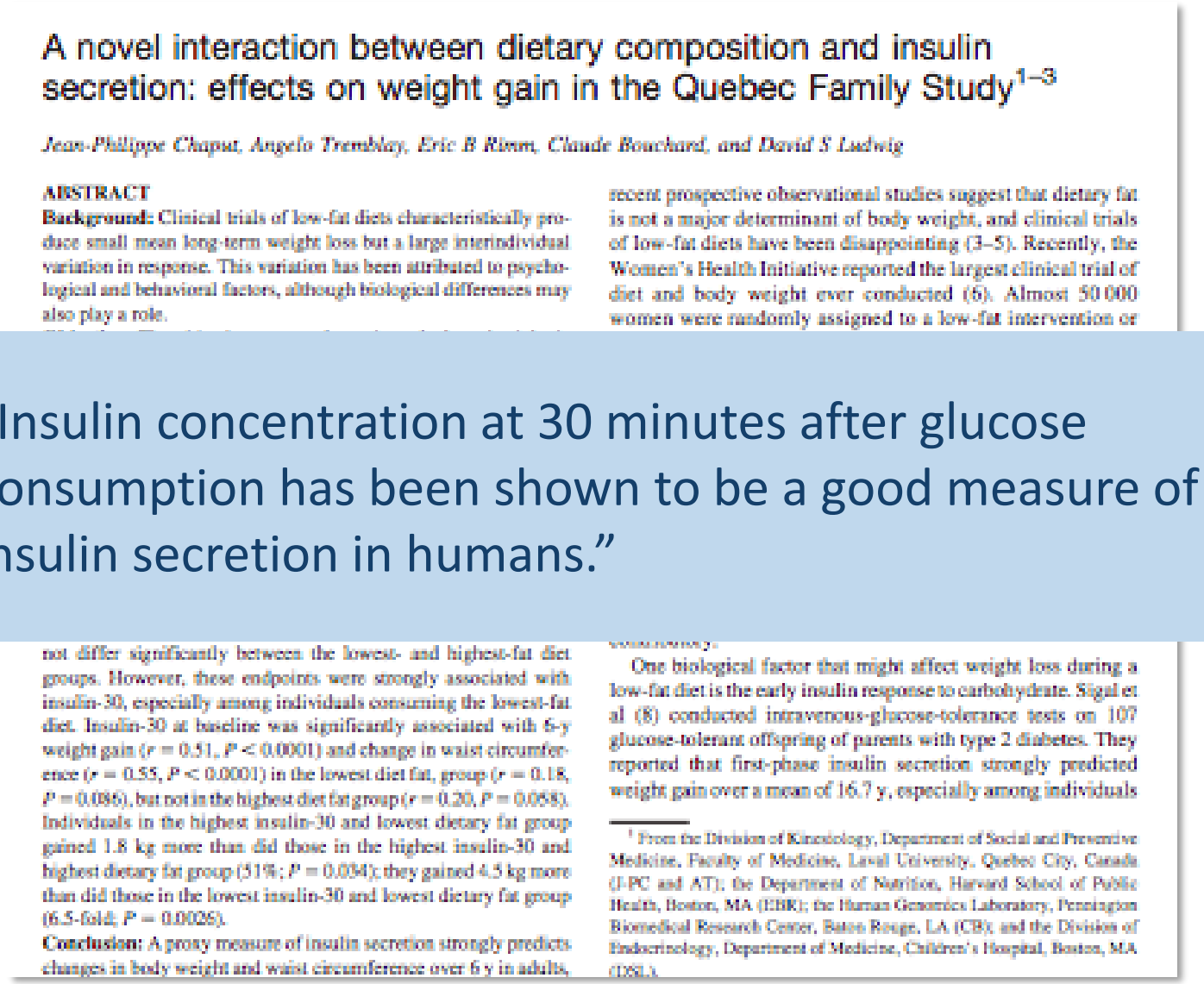
CONCLUSIONS: Elevated 2-hour intact proinsulin levels during OGTT were predictive for later type 2 diabetes development. Further studies need to confirm our findings in larger populations.

KEYWORDS: diabetes prediction; insulin resistance; intact proinsulin; oral glucose challenge; ß-cell dysfunction

GENOVA DIAGNOSTICS

Pfutzner A, et al. *J Diabetes Sci Technol*. 2015 Sep 29;9(6):1307-12.

Insulin



A novel interaction between dietary composition and insulin secretion: effects on weight gain in the Quebec Family Study[1–3]

Jean-Philippe Chaput, Angelo Tremblay, Eric B Rimm, Claude Bouchard, and David S Ludwig

ABSTRACT

Background: Clinical trials of low-fat diets characteristically produce small mean long-term weight loss but a large interindividual variation in response. This variation has been attributed to psychological and behavioral factors, although biological differences may also play a role.

recent prospective observational studies suggest that dietary fat is not a major determinant of body weight, and clinical trials of low-fat diets have been disappointing (3–5). Recently, the Women's Health Initiative reported the largest clinical trial of diet and body weight ever conducted (6). Almost 50 000 women were randomly assigned to a low-fat intervention or

not differ significantly between the lowest- and highest-fat diet groups. However, these endpoints were strongly associated with insulin-30, especially among individuals consuming the lowest-fat diet. Insulin-30 at baseline was significantly associated with 6-y weight gain ($r = 0.51$, $P < 0.0001$) and change in waist circumference ($r = 0.55$, $P < 0.0001$) in the lowest diet fat, group ($r = 0.18$, $P = 0.086$), but not in the highest diet fat group ($r = 0.20$, $P = 0.058$). Individuals in the highest insulin-30 and lowest dietary fat group gained 1.8 kg more than did those in the highest insulin-30 and highest dietary fat group (51%; $P = 0.034$); they gained 4.5 kg more than did those in the lowest insulin-30 and lowest dietary fat group (6.5-fold; $P = 0.0026$).

Conclusion: A proxy measure of insulin secretion strongly predicts changes in body weight and waist circumference over 6 y in adults,

One biological factor that might affect weight loss during a low-fat diet is the early insulin response to carbohydrate. Sigal et al (8) conducted intravenous-glucose-tolerance tests on 107 glucose-tolerant offspring of parents with type 2 diabetes. They reported that first-phase insulin secretion strongly predicted weight gain over a mean of 16.7 y, especially among individuals

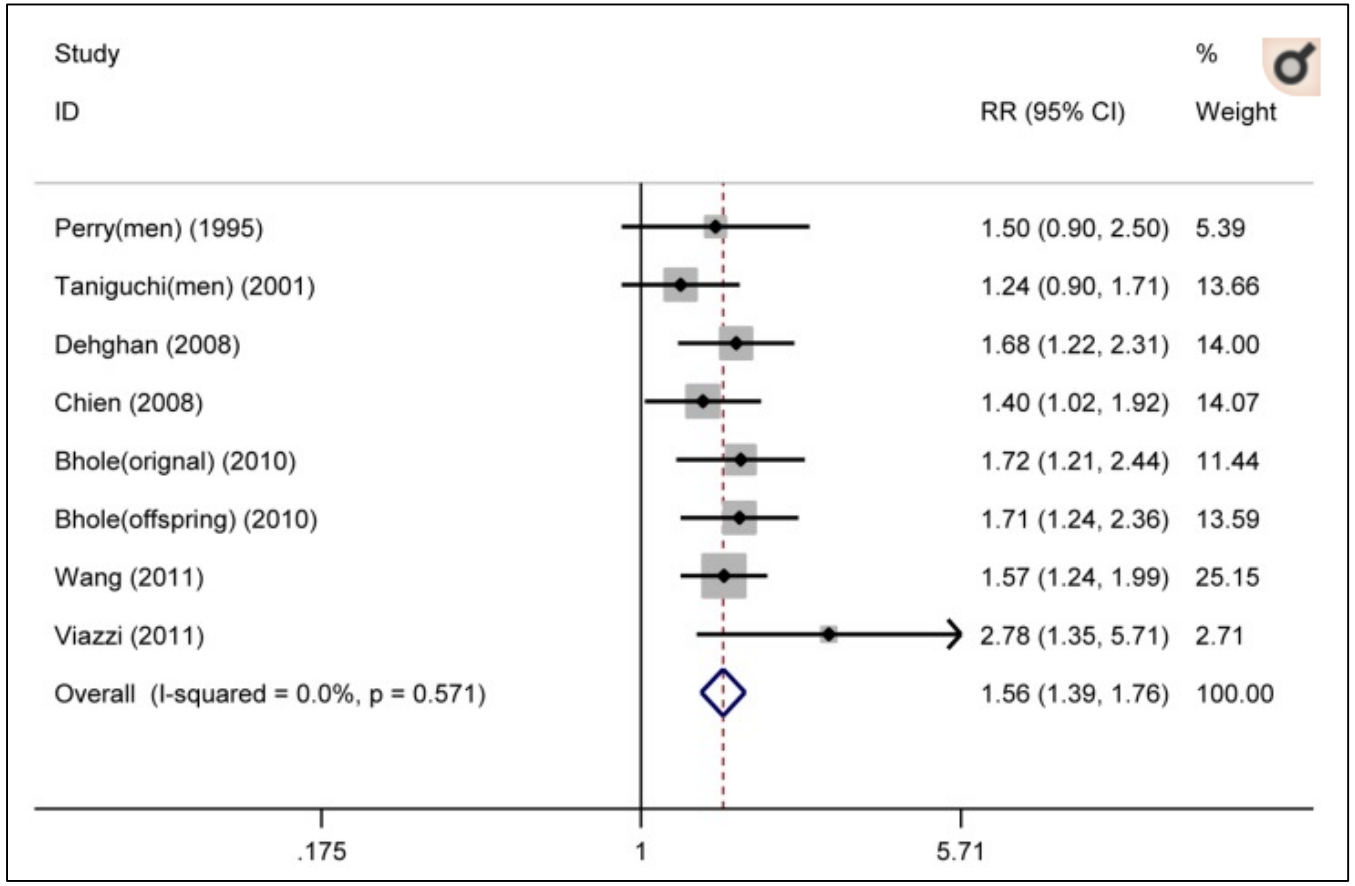
[1] From the Division of Kinesiology, Department of Social and Preventive Medicine, Faculty of Medicine, Laval University, Quebec City, Canada (J-PC and AT); the Department of Nutrition, Harvard School of Public Health, Boston, MA (EBR); the Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA (CB); and the Division of Endocrinology, Department of Medicine, Children's Hospital, Boston, MA (DSL).

"Insulin concentration at 30 minutes after glucose consumption has been shown to be a good measure of insulin secretion in humans."

Ludwig D, et al. *AJCN.* Feb 2008; 87:303-309.

Uric Acid and DM

- Meta-analysis
- High level of serum uric acid is independent of other established risk factors…for developing type 2 diabetes.



Serum uric acid and risk of incident type 2 diabetes.

GENOVA DIAGNOSTICS

Lv Q, et al. PLoS One. 2013;8(2):e56864.

Leptin and Adiponectin

PLoS One. 2017 Apr 27;12(4):e0176430. doi: 10.1371/journal.pone.0176430. eCollection 2017.

Circulating leptin and adiponectin are associated with insulin resistance in healthy postmenopausal women with hot flashes.

Huang WY[1], Chang CC[2], Chen DR[3], Kor CT[4], Chen TY[5], Wu HM[5,6,7].

Author information

Abstract

INTRODUCTION: Hot flashes have been postulated to be linked to the development of metabolic disorders. This study aimed to evaluate the relationship between hot flashes, adipocyte-derived hormones, and insulin resistance in healthy, non-obese postmenopausal women.

PARTICIPANTS AND DESIGN: In this cross-sectional study, a total of 151 women aged 45-60 years were stratified into one of three groups according to hot-flash status over the past three months: never experienced hot flashes (Group N), mild-to-moderate hot flashes (Group M), and severe hot flashes (Group S). Variables measured in this study included clinical parameters, hot flash experience, fasting levels of circulating glucose, lipid profiles, plasma insulin, and adipocyte-derived hormones. Multiple linear regression analysis was used to evaluate the associations of hot flashes with adipocyte-derived hormones, and with insulin resistance.

SETTINGS: The study was performed in a hospital medical center.

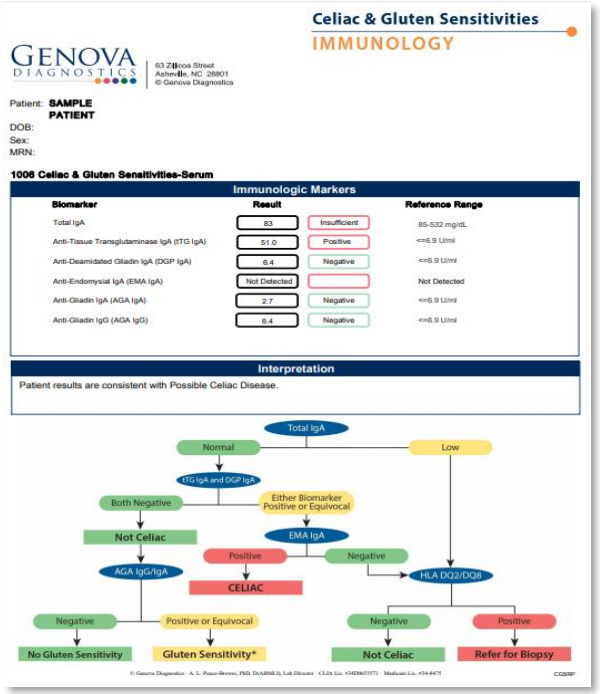
RESULTS: The mean (standard deviation) of body-mass index was 22.8(2.7) for Group N, 22.6(2.6) for Group M, and 23.5(2.4) for Group S, respectively. Women in Group S displayed statistically significantly higher levels of leptin, fasting glucose, and insulin, and lower levels of adiponectin than those in Groups M and N. Multivariate linear regression analysis revealed that hot-flash severity was significantly associated with higher leptin levels, lower adiponectin levels, and higher leptin-to-adiponectin ratio. Univariate linear regression analysis revealed that hot-flash severity was strongly associated with a higher HOMA-IR index (% difference, 58.03%; 95% confidence interval, 31.00-90.64; $p < 0.001$). The association between hot flashes and HOMA-IR index was attenuated after adjusting for leptin or adiponectin and was no longer significant after simultaneously adjusting for leptin and adiponectin.

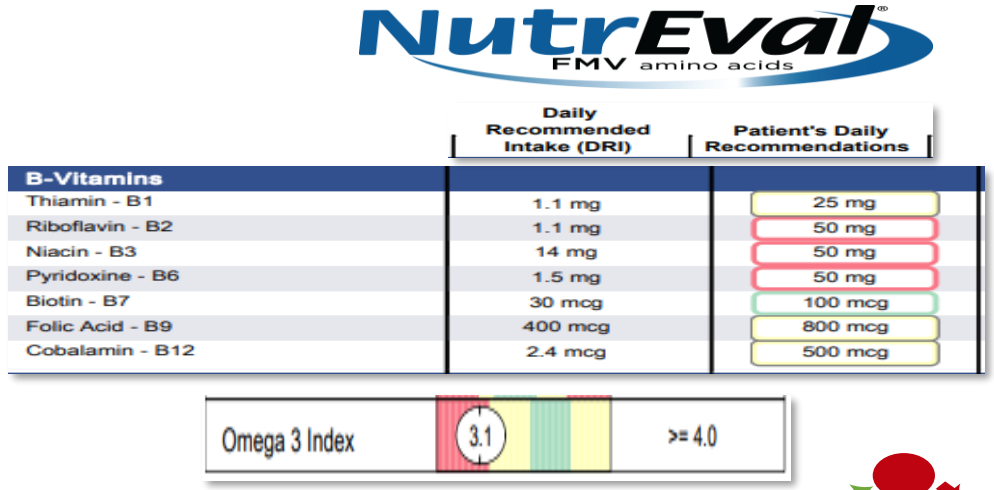
CONCLUSION: The present study provides evidence that hot flashes are associated with insulin resistance in postmenopausal women. It further suggests that hot flash association with insulin resistance is dependent on the combination of leptin and adiponectin variables.

GENOVA DIAGNOSTICS

Additional Labs

- 25-OH Vitamin D
- Homocysteine
- Lipoprotein (a)
- CRP-HS
- Apolipoprotein B and Apoliproprotein A1
- Gliadin antibody
- Celiac Panel
- Celiac Genetic panel (HLA-DQ2 and DQ8)
- Nutrient Analysis
- LpPLA2
- PAI-1
- Inflammatory Cytokines: IL-6, IL-8, TNF-alpha
- Resistin?

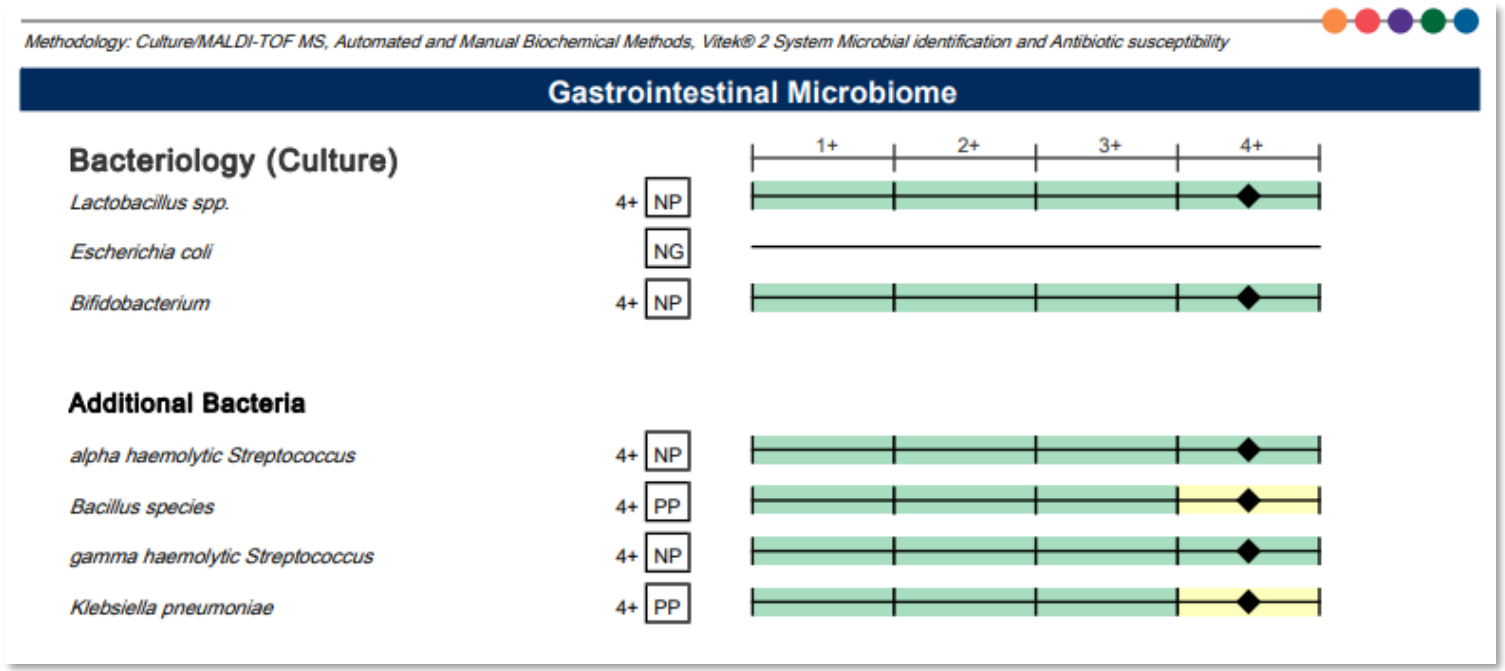




Luo Z, et al. *Endocrine*. 2009 May 8.

Additional Labs (continued)

- GAD 65 antibodies
- GFAP antibodies
- Hormone Panels
- Toxic Profiles
- Infections
  - Bacterial
    - Atypical Bacteria
    - Potential Pathogens
  - Parasitic
  - Fungal
  - Viral
    - Reactivated
- Marker of Oxidative Stress



Methodology: Culture/MALDI-TOF MS, Automated and Manual Biochemical Methods, Vitek® 2 System Microbial identification and Antibiotic susceptibility

Gastrointestinal Microbiome

Bacteriology (Culture)

			1+	2+	3+	4+
Lactobacillus spp.	4+	NP				◆
Escherichia coli		NG				
Bifidobacterium	4+	NP				◆

Additional Bacteria

			1+	2+	3+	4+
alpha haemolytic Streptococcus	4+	NP				◆
Bacillus species	4+	PP				◆
gamma haemolytic Streptococcus	4+	NP				◆
Klebsiella pneumoniae	4+	PP				◆

GENOVA DIAGNOSTICS

Treatment: Address the Triggers and Mediators

- Diet/nutrition protocol
  - Sugar
  - Trans and saturated fats
  - Polyunsaturated omega 6 oils (except GLA)
  - Toxins
  - Low fiber
- Food allergies/sensitivities (consider Elimination Diet (gluten, dairy, soy, corn, nightshade family)
- Dysbiosis/Altered Gut Microbiota/Leaky Gut
- Toxins in environment/home
- Hormone imbalance
- Stress from toxic relationships at work/home
- Nutrient deficiencies
- Unhealthy habits
- Infections (consider occult dental)

GENOVA DIAGNOSTICS

Treatment: My Approach

- Nutritional support: wholesome food (fresh, whole, unprocessed, organic, colorful, high fiber, with nuts, seeds) omega 3s, fermented foods
- Digestion
- Elimination diet (personalized)
- Decrease insulin stimulation
- Address the underlying cause/causes
- Lifestyle modification
- Exercise/movement
- Sleep
- Stress
- Modify/address gut microbiota
- Targeted supplementation
  - Food is the foundation
- Mind-body-spirit connection
- Support

Management for the Patient with Insulin Resistance

- Decrease insulin stimulation
  - Dietary modifications which decrease insulin release:
    - Fiber
    - 'Good' (vs. 'bad') fat
    - 'Good' (vs. 'bad') carbohydrates
    - Protein at every meal
    - Elimination of most inflammatory food:
      - Wheat, dairy, soy, corn, nightshades…
- Modify gut microbiota
  - Food first
  - Fermented foods
  - Probiotics/prebiotics
- Increase cellular responsiveness to insulin
- Exercise and lifestyle modification
- Agents that modify insulin responsiveness at the cellular level:
  - Spices
  - Herbs
  - Chromium
  - Vitamin D
  - Magnesium
  - Omega-3
- Balance Hormones
  - Adrenal, Thyroid, Sex

The “Westernized” Standard American Diet (S.A.D.)

High in saturated and trans fatty acids

Shifts Fatty Acid composition toward inflammation- Sinopoulus AP. *J Am Coll Nutr 2002; 21:495-505*

Low in fiber/high refined grains

Alters glycemic load/shifts metabolic function toward diseases of inflammation- Rifai n et al. *Curr Opin Lipidol 2002;13:383-9*

High sodium/low fruit and vegetables

Supports sodium dominance /low potassium and other micronutrients- Antonios TF et al. *Lancet 1996: 348:250-1.*

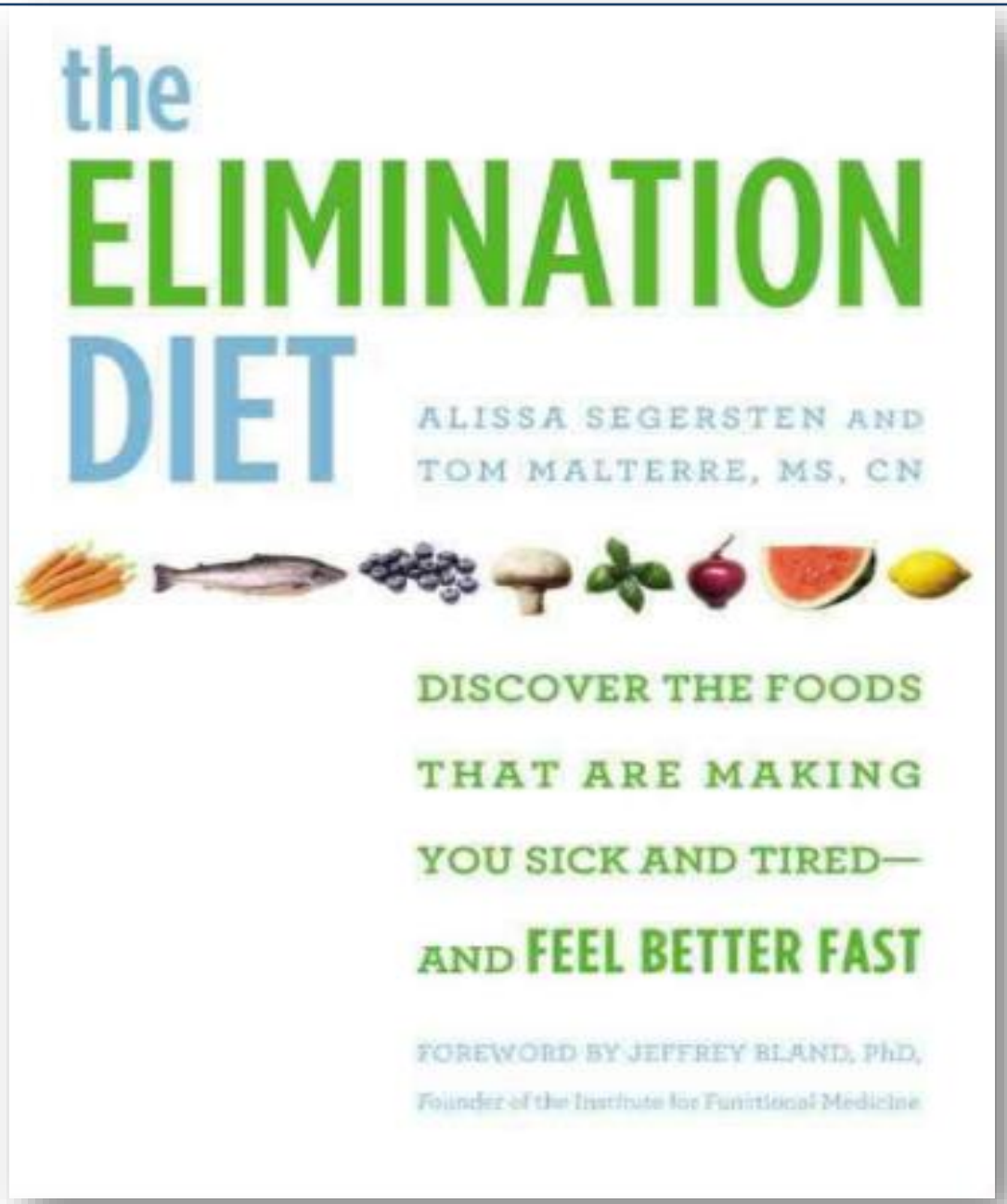
High in refined sugars

Alters glycemic load/shifts metabolic function toward diseases of inflammation Lui S, Williet WC. *Curr Atheroscler Report 2002:4:454-61.*

“Super Sized” – high quantity/poor quality

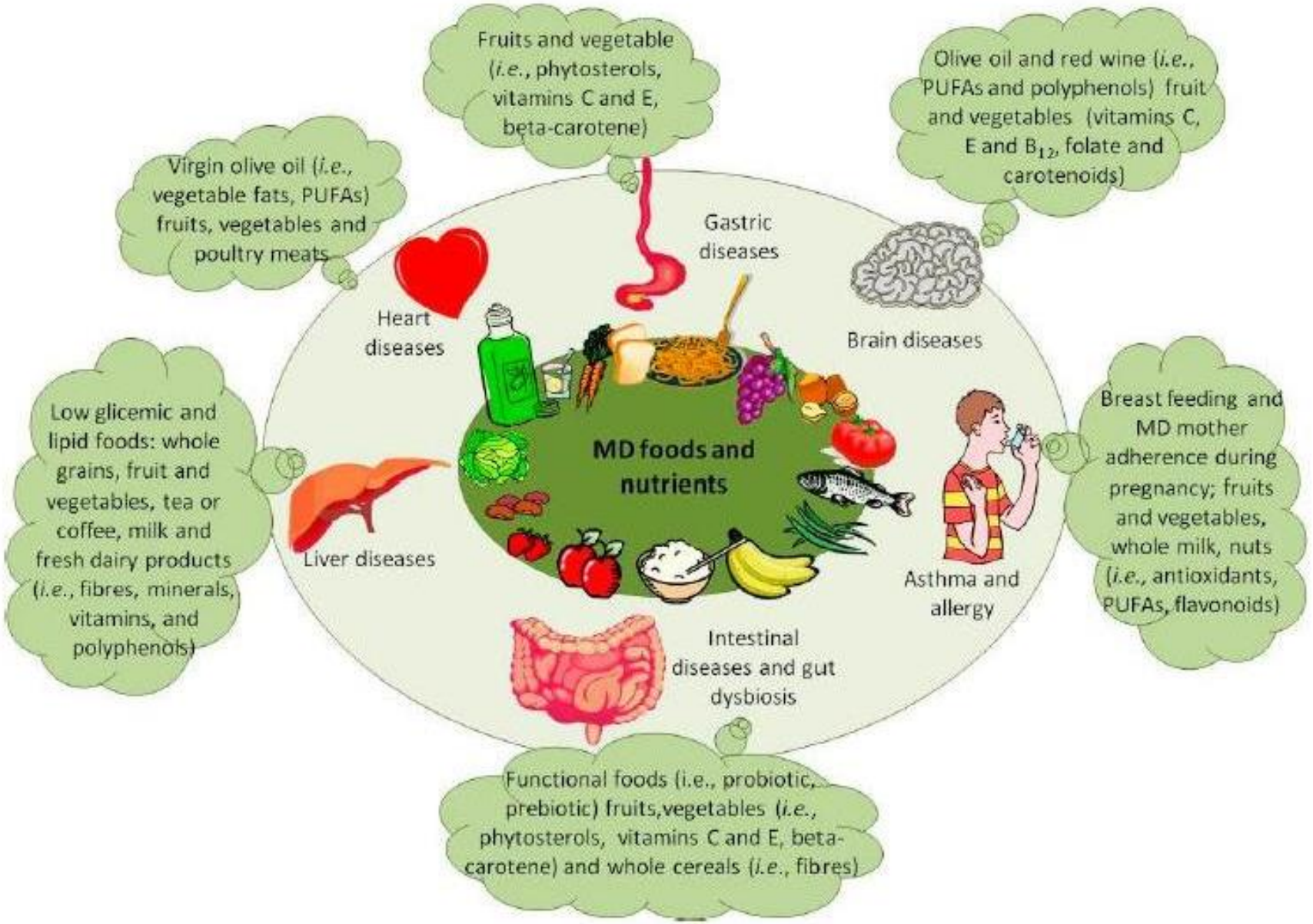
Supports imbalances in Macronutrient Composition and Micronutrient density- *Franzo E. US Dept. of Agr*i 1999

GENOVA DIAGNOSTICS



GENOVA DIAGNOSTICS

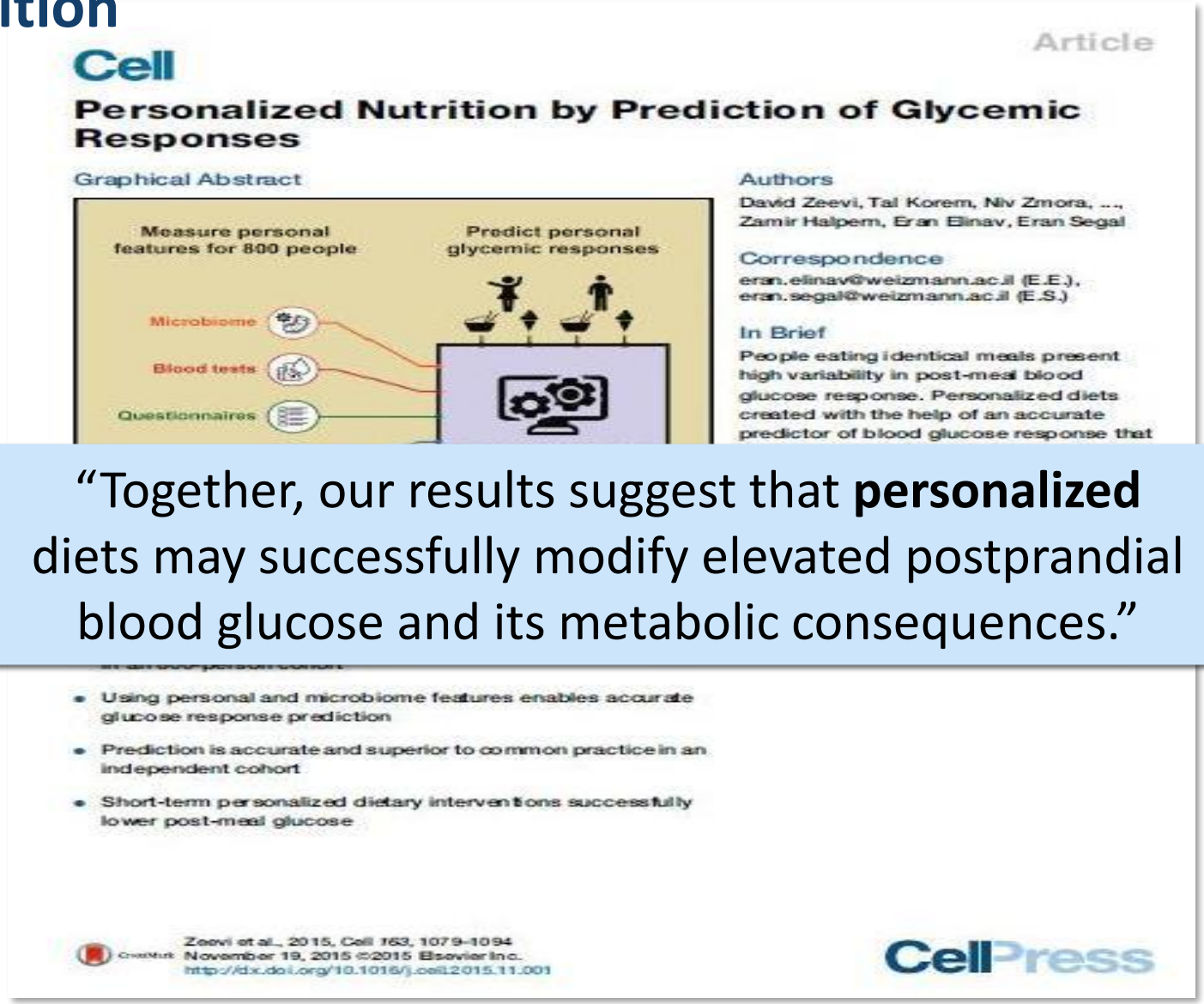
Figure 2. MD-related positive effects on diseases.



GENOVA DIAGNOSTICS

Del Chierico F, et al. Int J Mol Sci. 2014 Jul 1;15(7):11678-99.

Personalized Nutrition



Article

Cell

Personalized Nutrition by Prediction of Glycemic Responses

Graphical Abstract

Authors

David Zeevi, Tal Korem, Niv Zmora, ..., Zamir Halpern, Eran Elinav, Eran Segal

Correspondence

eran.elinav@weizmann.ac.il (E.E.), eran.segal@weizmann.ac.il (E.S.)

In Brief

People eating identical meals present high variability in post-meal blood glucose response. Personalized diets created with the help of an accurate predictor of blood glucose response that

- Using personal and microbiome features enables accurate glucose response prediction
- Prediction is accurate and superior to common practice in an independent cohort
- Short-term personalized dietary interventions successfully lower post-meal glucose

Zeevi et al., 2015, Cell 163, 1079-1094
November 19, 2015 ©2015 Elsevier Inc.
http://dx.doi.org/10.1016/j.cell.2015.11.001

CellPress

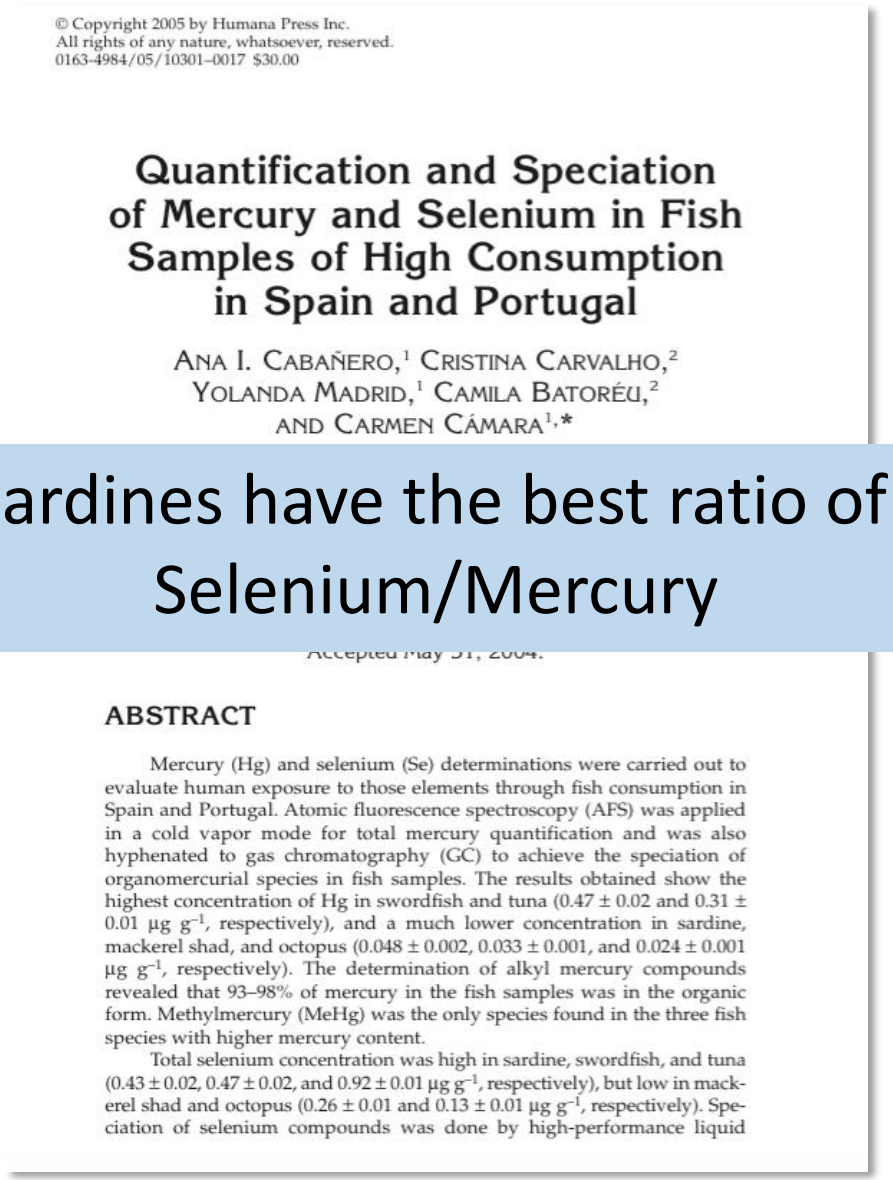
"Together, our results suggest that **personalized** diets may successfully modify elevated postprandial blood glucose and its metabolic consequences."

Zeevi D, et al. *Cell*. 2015 Nov 19;163(5):1079-1094.

Low GL Dietary Suggestions

- Total GL <80/daily
- Each meal should have a GL of 20 or less
- Each snack should have a GL of 10 or less
- The addition of other food categories (animal protein, non starchy vegetables, fat/oils, nuts/seeds, non-carbohydrate beverages and condiments) will not affect the GL
- These other categories should be modified and limited as necessary for specific health concerns

Sardines



0163-4984/05/10301–0017 $30.00

Quantification and Speciation of Mercury and Selenium in Fish Samples of High Consumption in Spain and Portugal

ANA I. CABAÑERO,[1] CRISTINA CARVALHO,[2] YOLANDA MADRID,[1] CAMILA BATORÉU,[2] AND CARMEN CÁMARA[1,*]

Sardines have the best ratio of Selenium/Mercury

Accepted May 31, 2004.

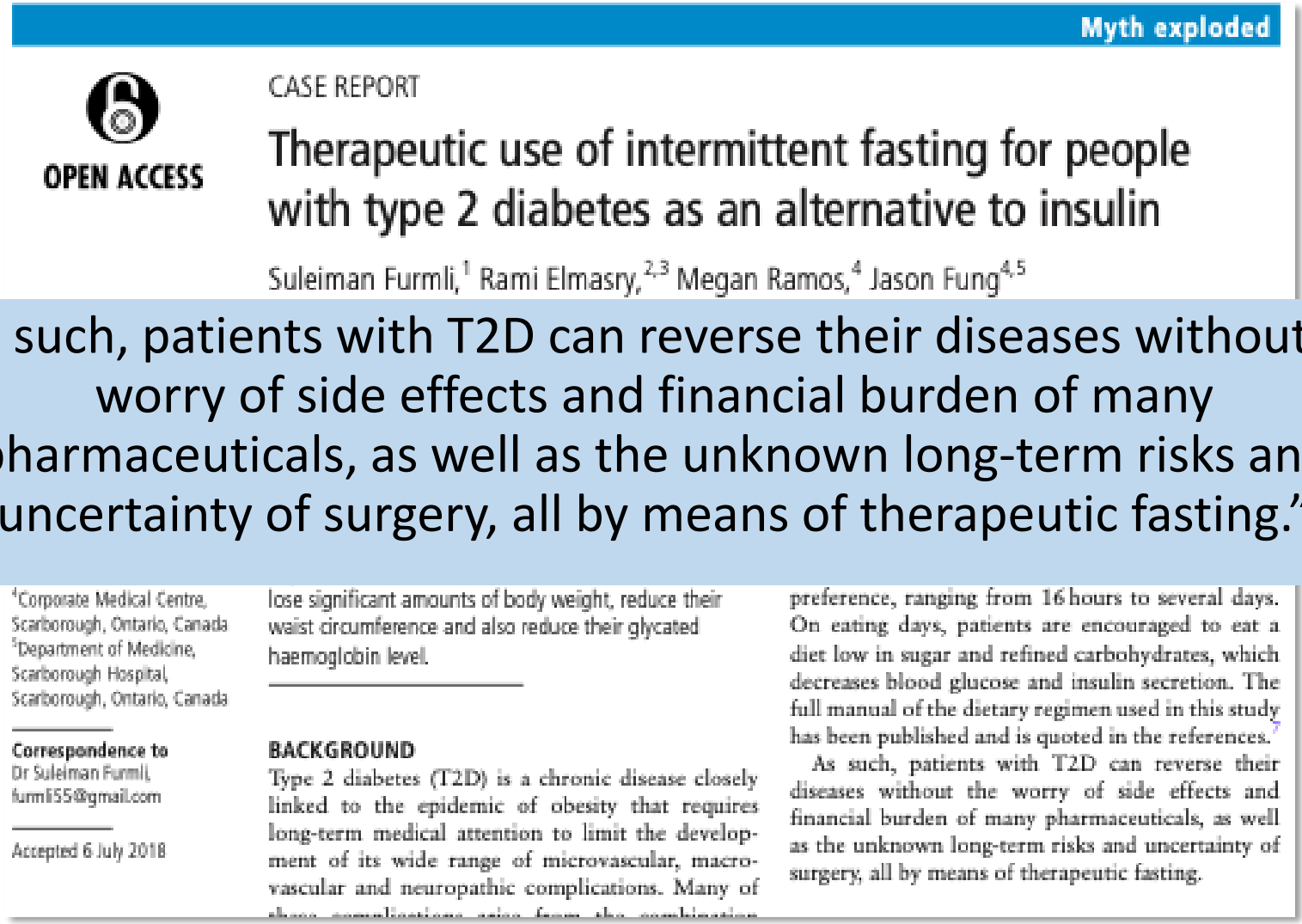
ABSTRACT

Mercury (Hg) and selenium (Se) determinations were carried out to evaluate human exposure to those elements through fish consumption in Spain and Portugal. Atomic fluorescence spectroscopy (AFS) was applied in a cold vapor mode for total mercury quantification and was also hyphenated to gas chromatography (GC) to achieve the speciation of organomercurial species in fish samples. The results obtained show the highest concentration of Hg in swordfish and tuna (0.47 ± 0.02 and 0.31 ± 0.01 μg g^{-1}, respectively), and a much lower concentration in sardine, mackerel shad, and octopus (0.048 ± 0.002, 0.033 ± 0.001, and 0.024 ± 0.001 μg g^{-1}, respectively). The determination of alkyl mercury compounds revealed that 93–98% of mercury in the fish samples was in the organic form. Methylmercury (MeHg) was the only species found in the three fish species with higher mercury content.

Total selenium concentration was high in sardine, swordfish, and tuna (0.43 ± 0.02, 0.47 ± 0.02, and 0.92 ± 0.01 μg g^{-1}, respectively), but low in mackerel shad and octopus (0.26 ± 0.01 and 0.13 ± 0.01 μg g^{-1}, respectively). Speciation of selenium compounds was done by high-performance liquid

Cabanero AI, et al. *Biol Trace Elem Res*. 2005 Jan;103(1):17-35.

Intermittent Fasting



Myth exploded

OPEN ACCESS

CASE REPORT

Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin

Suleiman Furmli,[1] Rami Elmasry,[2,3] Megan Ramos,[4] Jason Fung[4,5]

" As such, patients with T2D can reverse their diseases without the worry of side effects and financial burden of many pharmaceuticals, as well as the unknown long-term risks and uncertainty of surgery, all by means of therapeutic fasting."

[1]Corporate Medical Centre, Scarborough, Ontario, Canada
[2]Department of Medicine, Scarborough Hospital, Scarborough, Ontario, Canada

Correspondence to
Dr Suleiman Furmli, furmli55@gmail.com

Accepted 6 July 2018

lose significant amounts of body weight, reduce their waist circumference and also reduce their glycated haemoglobin level.

BACKGROUND

Type 2 diabetes (T2D) is a chronic disease closely linked to the epidemic of obesity that requires long-term medical attention to limit the development of its wide range of microvascular, macrovascular and neuropathic complications. Many of

preference, ranging from 16 hours to several days. On eating days, patients are encouraged to eat a diet low in sugar and refined carbohydrates, which decreases blood glucose and insulin secretion. The full manual of the dietary regimen used in this study has been published and is quoted in the references.[7]

As such, patients with T2D can reverse their diseases without the worry of side effects and financial burden of many pharmaceuticals, as well as the unknown long-term risks and uncertainty of surgery, all by means of therapeutic fasting.

GENOVA DIAGNOSTICS

Furmli S, et al. *Case Reports*. 2018;**2018**:bcr-2017-221854.

Hypocaloric Diet

Nutr Hosp. 2014 May 1;29(n05):1103-1108.

HYPOCALORIC DIET ASSOCIATED WITH THE CONSUMPTION OF JAM ENRICHED WITH MICROENCAPSULATED FISH OIL DECREASES INSULIN RESISTANCE.

Soares de Oliveira Carvalho AP[1], Kimi Uehara S[2], Nogueria Netto JF[3], Rosa G[4].

Author information

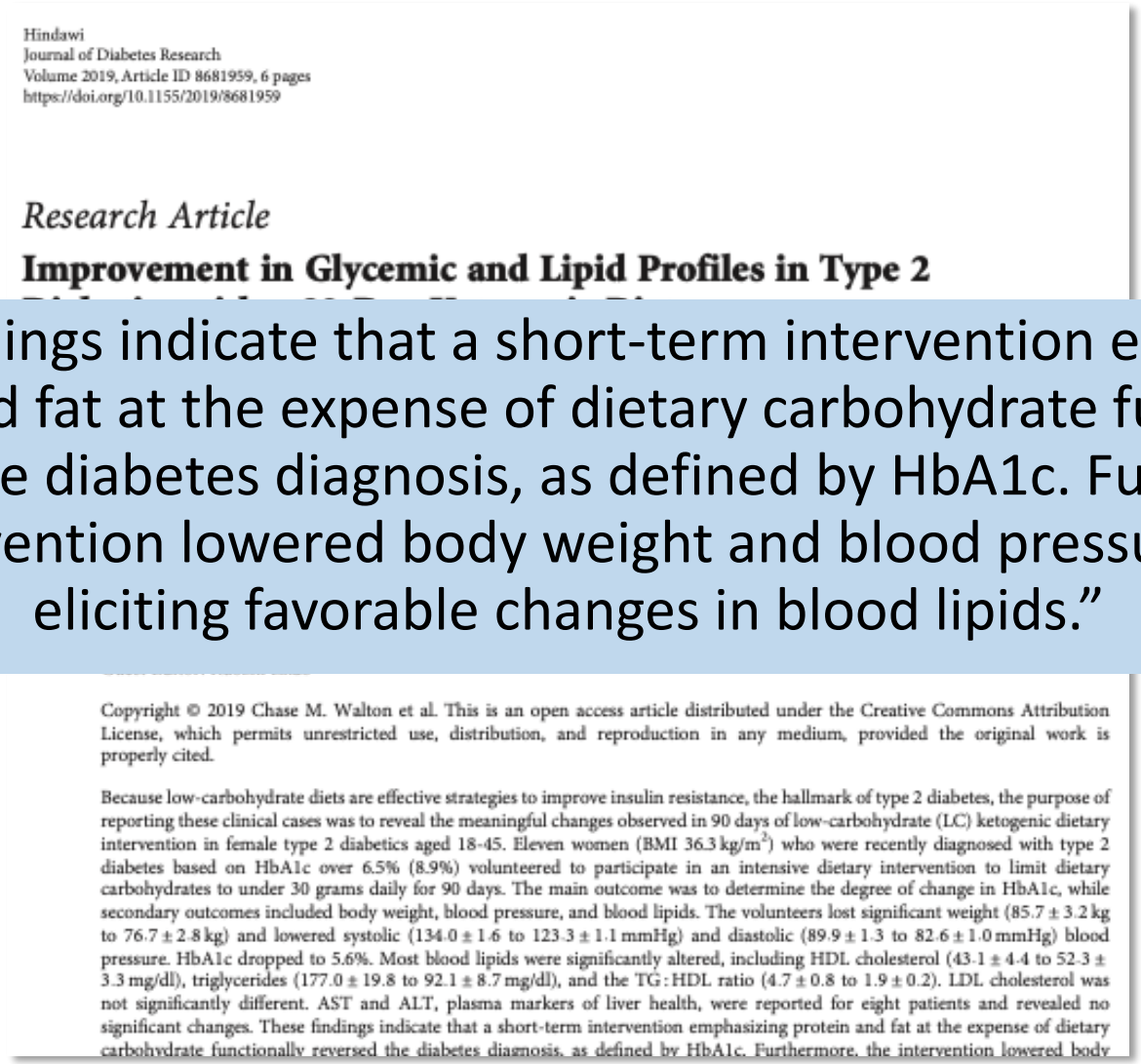
Abstract in **English**, Spanish

A hypocaloric diet associated with the consumption of microencapsulated fish oil was effective in reducing blood glucose, insulinemia and insulin resistance in women with MS.

placebo group (n = 15) and microencapsulated fish oil group (n = 15) (3 g/day of microencapsulated fish oil containing 0.41 g/day of eicosapentaenoic acid and decosahexaneoic acid). Anthropometric, body composition, clinical and laboratory parameters were assessed before and after the intervention. Paired t-test was used for comparisons within groups and Student's t-test for comparison between groups. We considered $p < 0.05$ as significant values. Results: The comparison between groups revealed a significant reduction of blood glucose, insulinemia and the homeostasis model assessment in the microencapsulated fish oil group after 90 days, as opposed to the placebo group. We also observed reduction of the systolic arterial pressure in the microencapsulated fish oil group. Conclusion: A hypocaloric diet associated with the consumption of microencapsulated fish oil was effective in reducing blood glucose, insulinemia and insulin resistance in women with MS.

GENOVA DIAGNOSTICS

Ketogenic Diet



Hindawi
Journal of Diabetes Research
Volume 2019, Article ID 8681959, 6 pages
https://doi.org/10.1155/2019/8681959

Research Article

Improvement in Glycemic and Lipid Profiles in Type 2

Because low-carbohydrate diets are effective strategies to improve insulin resistance, the hallmark of type 2 diabetes, the purpose of reporting these clinical cases was to reveal the meaningful changes observed in 90 days of low-carbohydrate (LC) ketogenic dietary intervention in female type 2 diabetics aged 18-45. Eleven women (BMI 36.3 kg/m^2) who were recently diagnosed with type 2 diabetes based on HbA1c over 6.5% (8.9%) volunteered to participate in an intensive dietary intervention to limit dietary carbohydrates to under 30 grams daily for 90 days. The main outcome was to determine the degree of change in HbA1c, while secondary outcomes included body weight, blood pressure, and blood lipids. The volunteers lost significant weight (85.7 ± 3.2 kg to 76.7 ± 2.8 kg) and lowered systolic (134.0 ± 1.6 to 123.3 ± 1.1 mmHg) and diastolic (89.9 ± 1.3 to 82.6 ± 1.0 mmHg) blood pressure. HbA1c dropped to 5.6%. Most blood lipids were significantly altered, including HDL cholesterol (43.1 ± 4.4 to 52.3 ± 3.3 mg/dl), triglycerides (177.0 ± 19.8 to 92.1 ± 8.7 mg/dl), and the TG : HDL ratio (4.7 ± 0.8 to 1.9 ± 0.2). LDL cholesterol was not significantly different. AST and ALT, plasma markers of liver health, were reported for eight patients and revealed no significant changes. These findings indicate that a short-term intervention emphasizing protein and fat at the expense of dietary carbohydrate functionally reversed the diabetes diagnosis, as defined by HbA1c. Furthermore, the intervention lowered body

"These findings indicate that a short-term intervention emphasizing protein and fat at the expense of dietary carbohydrate functionally reversed the diabetes diagnosis, as defined by HbA1c. Furthermore, the intervention lowered body weight and blood pressure, while eliciting favorable changes in blood lipids."

Walton CM, et al. *J Diabetes Res*. 2019 Aug 14;2019:8681959.

Gut Microbiota

Genes Nutr (2011) 6:241–260
DOI 10.1007/s12263-011-0230-1

REVIEW

Obesity and the gut microbiota: does up-regulating colonic fermentation protect against obesity and metabolic disease?

Lorenza Conterno · Francesca Fava · Roberto Viola · Kieran M. Tuohy

"Most studies suggest that the gut microbiota differs in composition between lean and obese individuals and that diet, especially the high-fat low-fiber Western-style diet, dramatically impacts on the gut microbiota."

hand, the adoption of "western"-style diets and low-energy expenditure lifestyles around the world. Recent studies report an aberrant gut microbiota in obese subjects and that gut microbial metabolic activities, especially carbohydrate fermentation and bile acid metabolism, can impact on a number of mammalian physiological functions linked to obesity. The aim of this review is to present the evidence for a characteristic "obese-type" gut microbiota and to discuss studies linking microbial metabolic activities with mammalian regulation of lipid and glucose metabolism, thermogenesis, satiety, and chronic systemic inflammation. We focus in particular on short-chain fatty acids (SCFA) produced upon fiber fermentation in the colon. Although SCFA are reported to be elevated in the feces of

dietary modulation of associated disease risk.

Keywords Obesity · Microbiota · SCFA · Fiber · Prebiotics · Probiotics

Introduction

Obesity is now considered among the top public health issues worldwide. In many countries, obesity rates reported before 1980 were below 10%, whereas nearly half of the Organization for Economic Co-operation and Development (OECD) countries now report 50% or more of the population as being overweight, with the percentage obese

GENOVA DIAGNOSTICS

Conterno L, et al. *Genes Nutr*. 2011 Aug;6(3):241-60.

Gut Microbiota

Cell. 2016 Nov 17;167(5):1339-1353.e21. doi: 10.1016/j.cell.2016.10.043.

A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility.

Desai MS[1], Seekatz AM[2], Koropatkin NM[2], Kamada N[2], Hickey CA[3], Wolter M[4], Pudlo NA[2], Kitamoto S[2], Terrapon N[5], Muller A[6], Young VB[2], Henrissat B[5], Wilmes P[7], Stappenbeck TS[3], Núñez G[2], Martens EC[8].

Author information

Abstra
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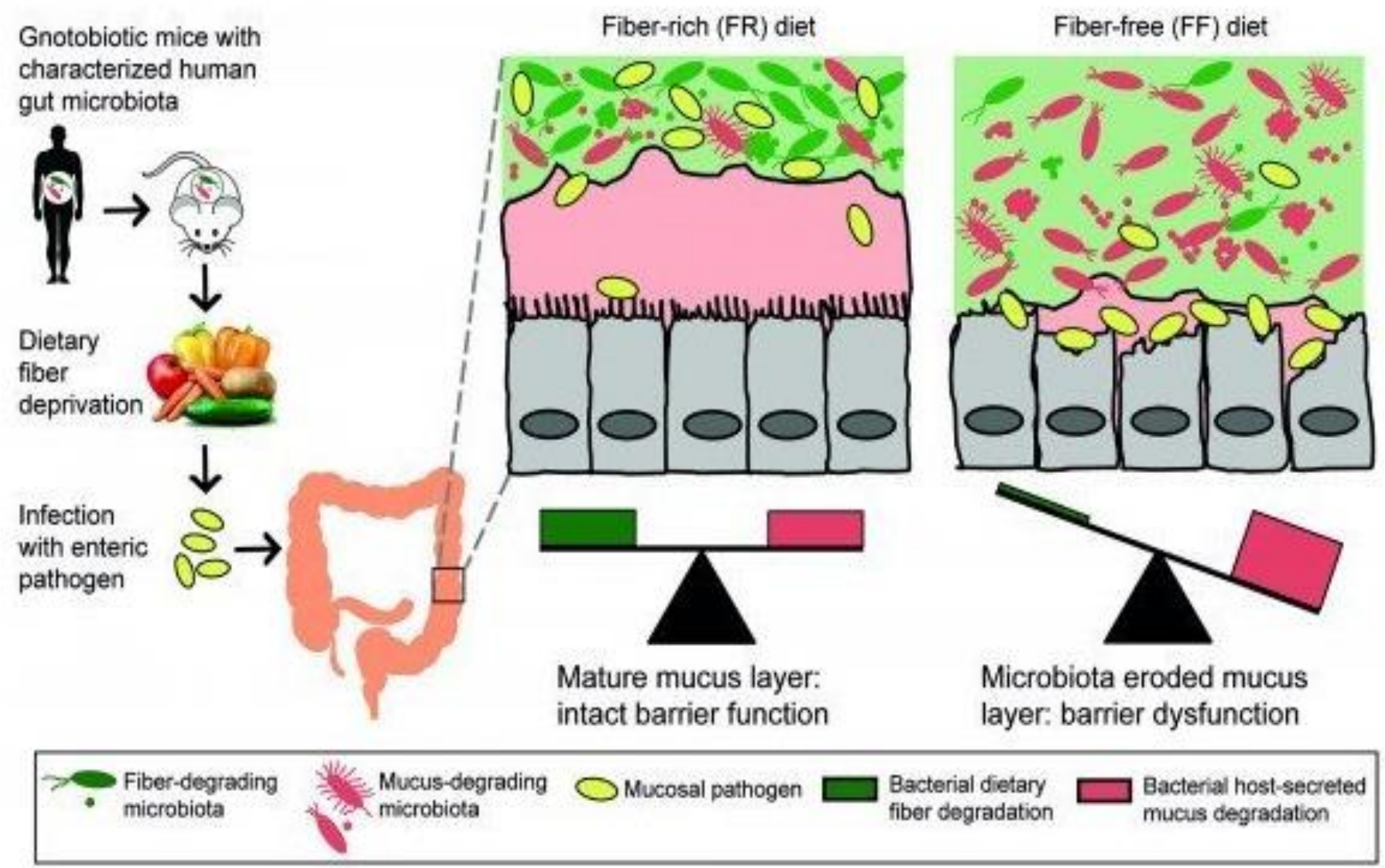
during chronic or intermittent dietary fiber deficiency, the gut microbiota resorts to host-secreted mucus glycoproteins as a nutrient source, leading to erosion of the colonic mucus barrier. Dietary fiber deprivation, together with a fiber-deprived, mucus-eroding microbiota, promotes greater epithelial access and lethal colitis by the mucosal pathogen, Citrobacter rodentium. Our work reveals intricate pathways linking diet, the gut microbiome, and intestinal barrier dysfunction, which could be exploited to improve health using dietary therapeutics.

During chronic or intermittent dietary fiber deficiency, the gut microbiota resorts to host-secreted mucus glycoproteins as a nutrient source, leading to erosion of the colonic mucus barrier.

GENOVA DIAGNOSTICS

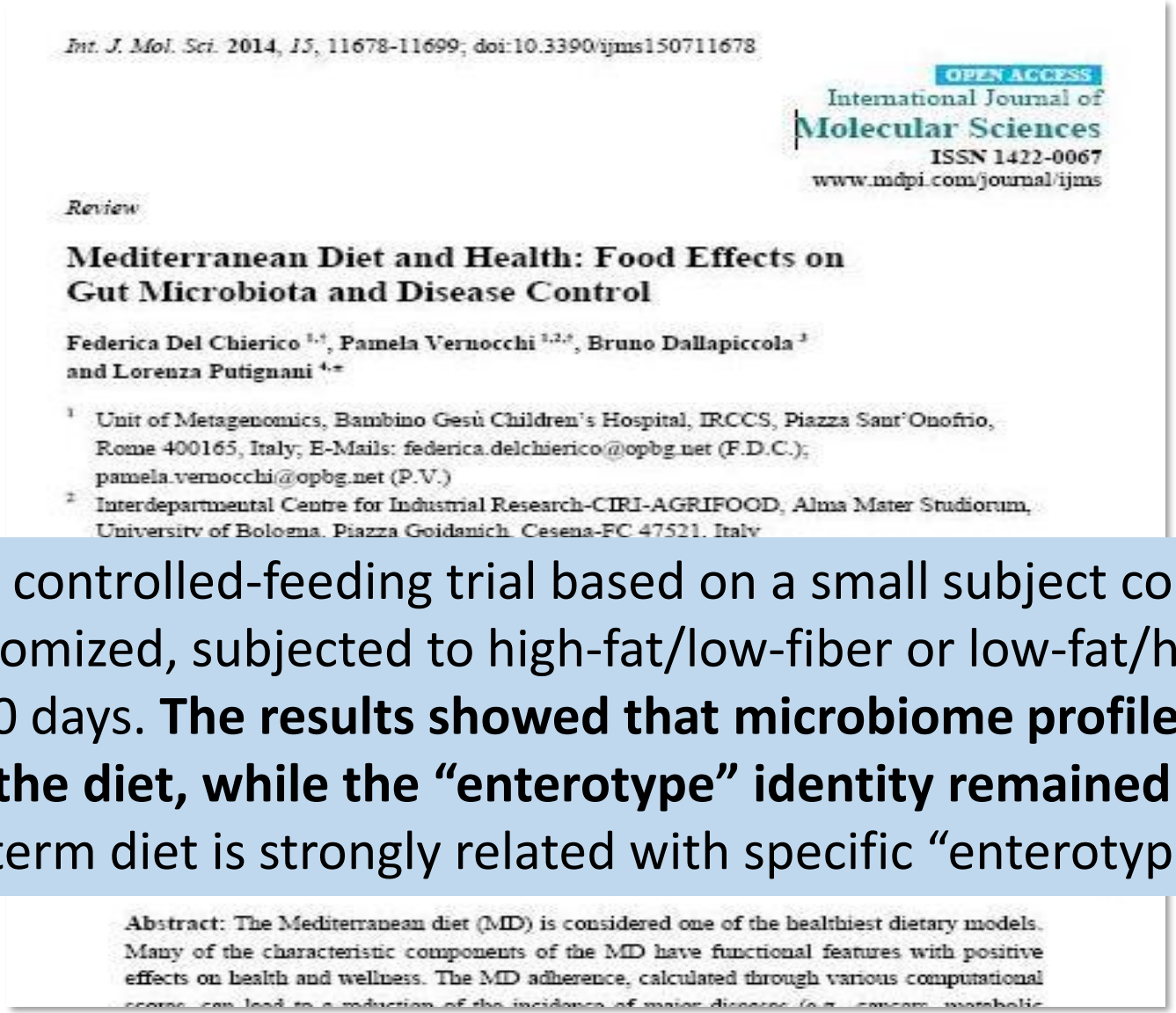
Desai MS, et al. *Cell*. 2016 Nov 17;167(5):1339-1353.e21.



Desai MS, et al. *Cell*. 2016 Nov 17;167(5):1339-1353.e21.

Three main variants or "enterotypes" in adults represented by:

1. *Bacteroides*
2. *Prevotella*
3. *Ruminococcus*



Int. J. Mol. Sci. 2014, *15*, 11678-11699; doi:10.3390/ijms150711678

OPEN ACCESS
International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

Mediterranean Diet and Health: Food Effects on Gut Microbiota and Disease Control

Federica Del Chierico [1,†], Pamela Vernocchi [1,2,†], Bruno Dallapiccola [1] and Lorenza Putignani [1,*]

[1] Unit of Metagenomics, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio, Rome 400165, Italy; E-Mails: federica.delchierico@opbg.net (F.D.C.); pamela.vernocchi@opbg.net (P.V.)

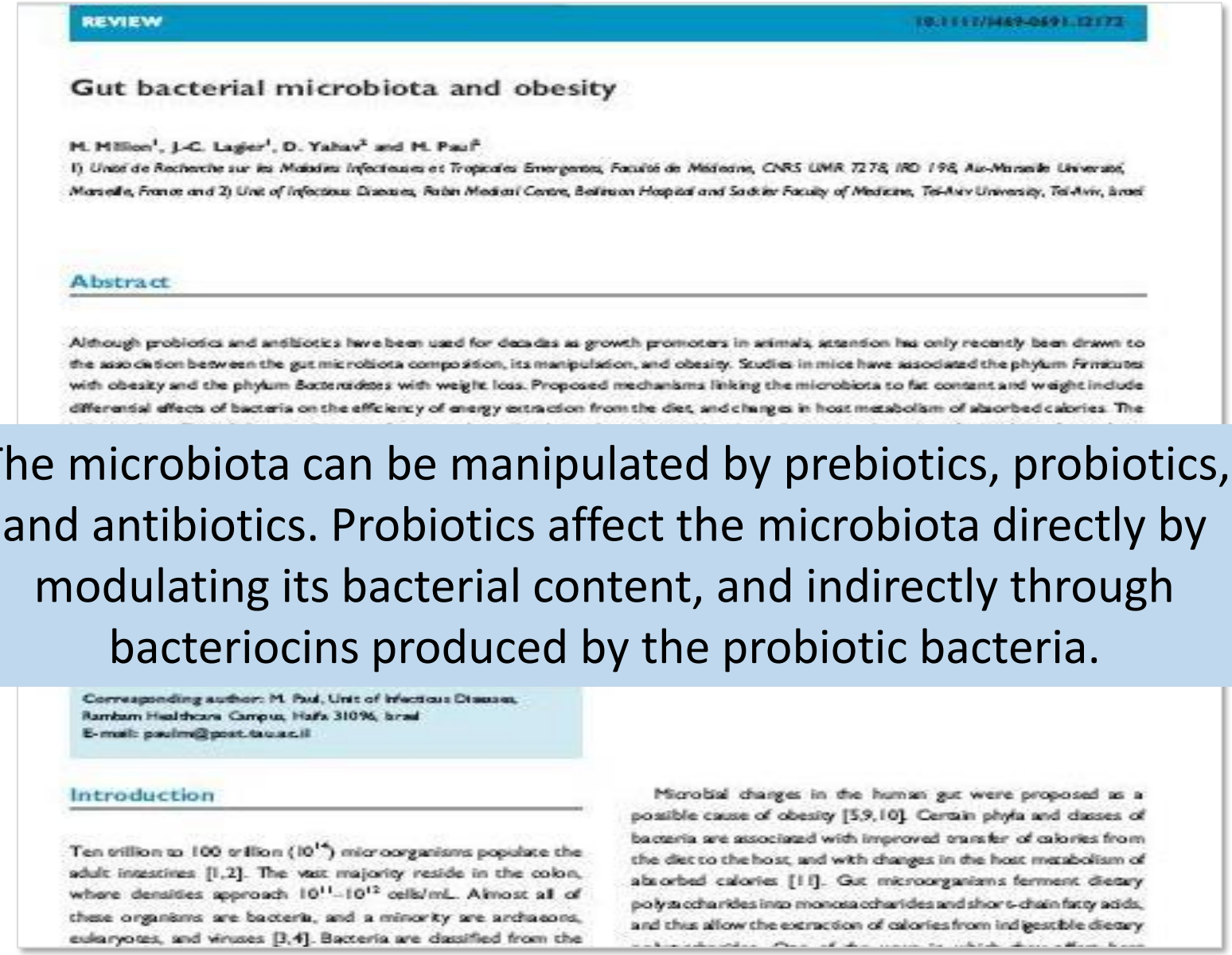
[2] Interdepartmental Centre for Industrial Research-CIRI-AGRIFOOD, Alma Mater Studiorum, University of Bologna, Piazza Goidanich, Cesena-FC 47521, Italy

Abstract: The Mediterranean diet (MD) is considered one of the healthiest dietary models. Many of the characteristic components of the MD have functional features with positive effects on health and wellness. The MD adherence, calculated through various computational

The authors performed a controlled-feeding trial based on a small subject cohort (10 subjects), which was randomized, subjected to high-fat/low-fiber or low-fat/high-fiber diets and sampled over 10 days. **The results showed that microbiome profiles clearly changed within 24 h of the diet, while the "enterotype" identity remained stable**, indicating that long-term diet is strongly related with specific "enterotypes."

GENOVA DIAGNOSTICS

Del Chierico F, et al. *Int. J. Mol. Sci.* 2014, *15*(7), 11678-11699.



REVIEW

Gut bacterial microbiota and obesity

M. Million[1], J.-C. Lagier[1], D. Yahav[2] and M. Paul[2]
1) Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, Faculté de Médecine, CNRS UMR 7278, IRD 198, Aix-Marseille Université, Marseille, France and 2) Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Abstract

Although probiotics and antibiotics have been used for decades as growth promoters in animals, attention has only recently been drawn to the association between the gut microbiota composition, its manipulation, and obesity. Studies in mice have associated the phylum *Firmicutes* with obesity and the phylum *Bacteroidetes* with weight loss. Proposed mechanisms linking the microbiota to fat content and weight include differential effects of bacteria on the efficiency of energy extraction from the diet, and changes in host metabolism of absorbed calories. The

The microbiota can be manipulated by prebiotics, probiotics, and antibiotics. Probiotics affect the microbiota directly by modulating its bacterial content, and indirectly through bacteriocins produced by the probiotic bacteria.

Corresponding author: M. Paul, Unit of Infectious Diseases, Rambam Healthcare Campus, Haifa 31096, Israel
E-mail: paulm@post.tau.ac.il

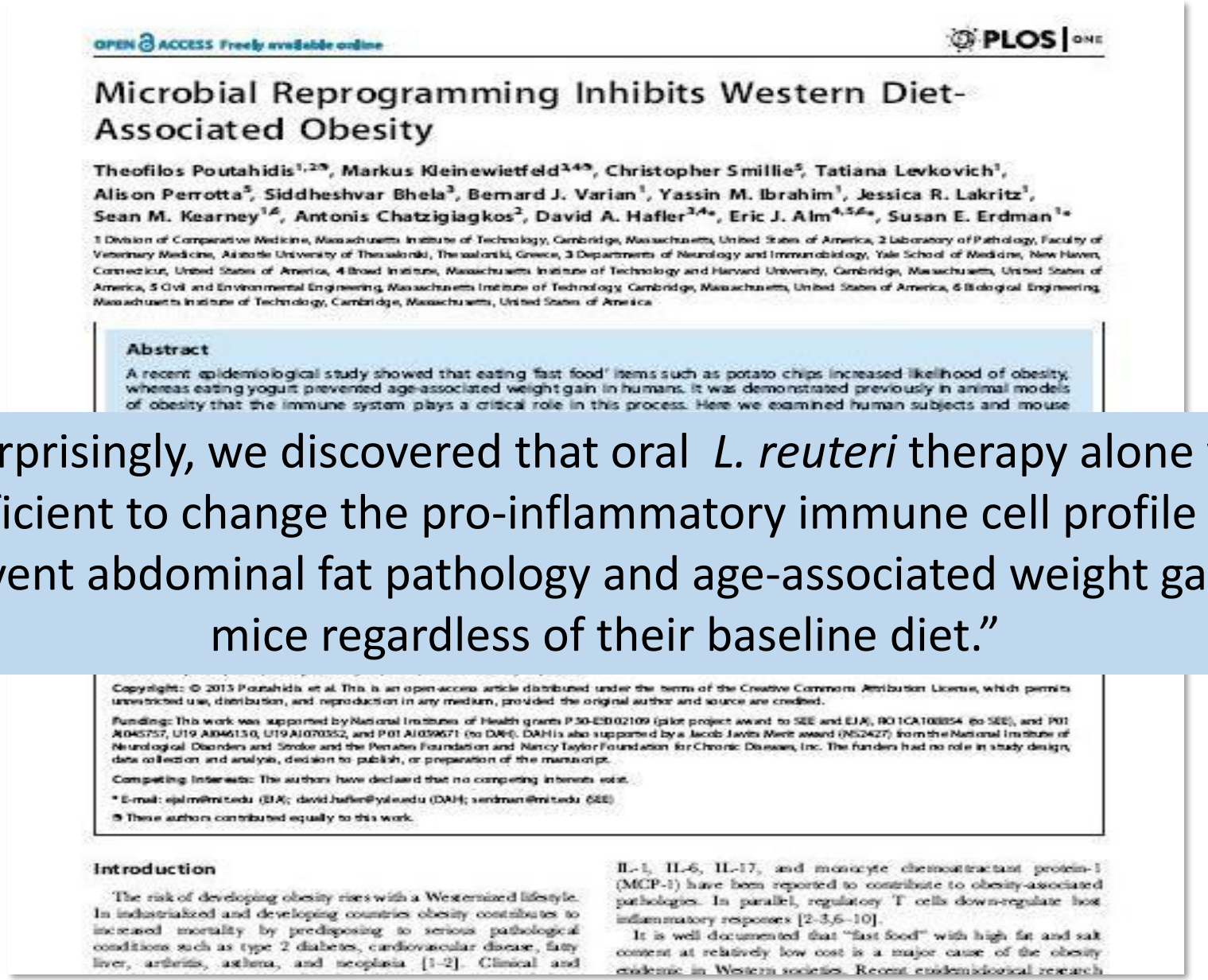
Introduction

Ten trillion to 100 trillion (10^{14}) microorganisms populate the adult intestines [1,2]. The vast majority reside in the colon, where densities approach 10^{11}–10^{12} cells/mL. Almost all of these organisms are bacteria, and a minority are archaeons, eukaryotes, and viruses [3,4]. Bacteria are classified from the

Microbial changes in the human gut were proposed as a possible cause of obesity [5,9,10]. Certain phyla and classes of bacteria are associated with improved transfer of calories from the diet to the host, and with changes in the host metabolism of absorbed calories [11]. Gut microorganisms ferment dietary polysaccharides into monosaccharides and short-chain fatty acids, and this allow the extraction of calories from indigestible dietary

GENOVA DIAGNOSTICS

Million M, et al. *Clin Microbiol Infect*. 2013 Apr;19(4):305-13.



OPEN ACCESS Freely available online

PLOS ONE

Microbial Reprogramming Inhibits Western Diet-Associated Obesity

Theofilos Poutahidis[1,2☯], Markus Kleinewietfeld[3,4☯], Christopher Smillie[5], Tatiana Levkovich[1], Alison Perrotta[5], Siddheshvar Bhela[3], Bernard J. Varian[1], Yassin M. Ibrahim[1], Jessica R. Lakritz[1], Sean M. Kearney[1,6], Antonis Chatzigiagkos[2], David A. Hafler[3,4*], Eric J. Alm[4,5,6*], Susan E. Erdman[1*]

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Abstract

A recent epidemiological study showed that eating 'fast food' items such as potato chips increased likelihood of obesity, whereas eating yogurt prevented age-associated weight gain in humans. It was demonstrated previously in animal models of obesity that the immune system plays a critical role in this process. Here we examined human subjects and mouse

"Surprisingly, we discovered that oral *L. reuteri* therapy alone was sufficient to change the pro-inflammatory immune cell profile and prevent abdominal fat pathology and age-associated weight gain in mice regardless of their baseline diet."

Funding: This work was supported by National Institutes of Health grants P30-ES02109 (pilot project award to SEE and EJA), RO1CA108854 (to SEE), and P01 AI045757, U19 AI046130, U19 AI070352, and P01 AI039671 (to DAH). DAH is also supported by a Jacob Javits Merit award (NS24427) from the National Institute of Neurological Disorders and Stroke and the Peraton Foundation and Nancy Taylor Foundation for Chronic Diseases, Inc. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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☯ These authors contributed equally to this work.

Introduction

The risk of developing obesity rises with a Westernized lifestyle. In industrialized and developing countries obesity contributes to increased mortality by predisposing to serious pathological conditions such as type 2 diabetes, cardiovascular disease, fatty liver, arthritis, asthma, and neoplasia [1–2]. Clinical and

IL-1, IL-6, IL-17, and monocyte chemoattractant protein-1 (MCP-1) have been reported to contribute to obesity-associated pathologies. In parallel, regulatory T cells down-regulate host inflammatory responses [2-3,6–10].

It is well documented that "fast food" with high fat and salt content at relatively low cost is a major cause of the obesity epidemic in Western societies. Recent epidemiological research

GENOVA DIAGNOSTICS

Poutahidis T, et al. *PLoS One*. 2013 Jul 10;8(7):e68596.

Korean J Fam Med. 2013;34:80-89 http://dx.doi.org/10.4082/kjfm.2013.34.2.80

Effect of *Lactobacillus gasseri* BNR17 on Overweight and Obese Adults: A Randomized, Double-Blind Clinical Trial

Original Article

Seung-Pil Jung*, Keun-Mi Lee, Ji-Hee Kang[1], Sung-Il Yun[1], Han-Oh Park[1], Yong Moon[2], Jong-Yeon Kim[3]

participated in a placebo controlled, randomized, and double-blind trial. For 12 weeks, 57 participants were given either placebo or BNR17 and were tested by measuring body fat, body weight, various biochemical parameters, vital signs, and computed tomography at the start of the study and at weeks 4, 8, and 12. The subjects assumed usual daily activities without having to make behavioral or dietary modifications during the course of the study.

Results: At the 12th week, a slight reduction in body weight was noted in the BNR17 group, but there were no significant weight changes between groups. Decrease of waist and hip circumferences in the BNR17 group was more pronounced than those in the placebo group. The two groups had no special or severe adverse reactions.

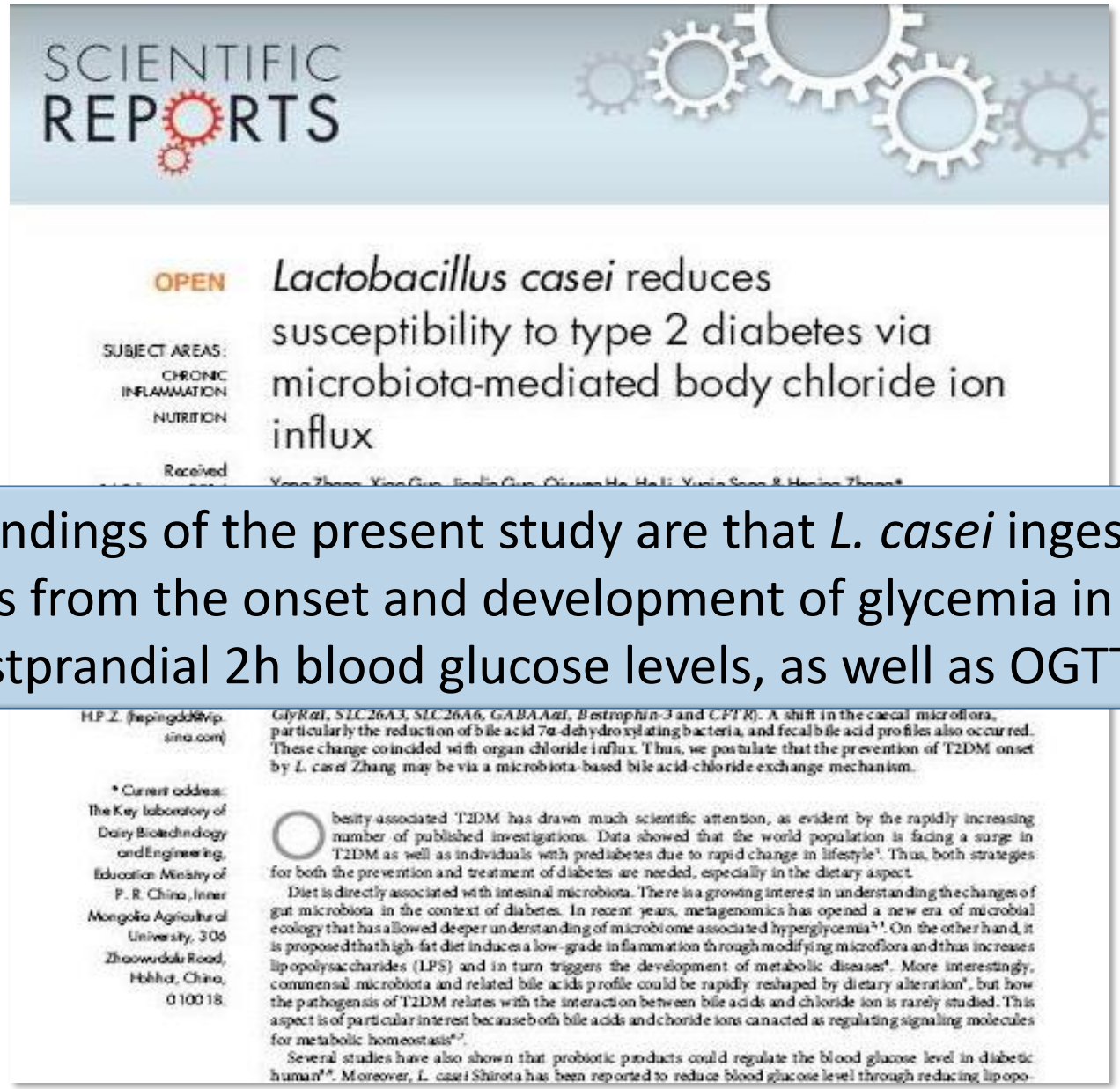
Conclusion: Despite there being no change in behavior or diet, administration of only the supplement of BNR17 reduced weight and waist and hip circumference. However, there were no significant differences between the two groups. These findings warrant a subsequent longer-term prospective clinical investigation with a large population.

Keywords: Probiotics; Obesity; Metabolic Disorders; Human Breast Milk

"Despite there being no change in behavior or diet, administration of only the supplement of BNR17 reduced weight and waist and hip circumference. However, there were no significant differences between the two groups. These findings warrant a subsequent longer-term prospective clinical investigation with a large population."

GENOVA DIAGNOSTICS

Jung SP, et al. *Korean J Fam Med*. 2013 Mar;34(2):80-9.



SCIENTIFIC REPORTS

OPEN

Lactobacillus casei reduces susceptibility to type 2 diabetes via microbiota-mediated body chloride ion influx

SUBJECT AREAS:
CHRONIC INFLAMMATION
NUTRITION

Received

GlyRα1, SLC26A3, SLC26A6, GABAAα1, Beistrophin-3 and *CFTR*). A shift in the caecal microflora, particularly the reduction of bile acid 7α-dehydroxylating bacteria, and fecal bile acid profiles also occurred. These change coincided with organ chloride influx. Thus, we postulate that the prevention of T2DM onset by *L. casei* Zhang may be via a microbiota-based bile acid-chloride exchange mechanism.

Obesity associated T2DM has drawn much scientific attention, as evident by the rapidly increasing number of published investigations. Data showed that the world population is facing a surge in T2DM as well as individuals with prediabetes due to rapid change in lifestyle[1]. Thus, both strategies for both the prevention and treatment of diabetes are needed, especially in the dietary aspect.

Diet is directly associated with intestinal microbiota. There is a growing interest in understanding the changes of gut microbiota in the context of diabetes. In recent years, metagenomics has opened a new era of microbial ecology that has allowed deeper understanding of microbiome associated hyperglycemia[2,3]. On the other hand, it is proposed that high-fat diet induces a low-grade inflammation through modifying microflora and thus increases lipopolysaccharides (LPS) and in turn triggers the development of metabolic diseases[4]. More interestingly, commensal microbiota and related bile acids profile could be rapidly reshaped by dietary alteration[5], but how the pathogenesis of T2DM relates with the interaction between bile acids and chloride ion is rarely studied. This aspect is of particular interest because both bile acids and choride ions can acted as regulating signaling molecules for metabolic homeostasis[6,7].

Several studies have also shown that probiotic products could regulate the blood glucose level in diabetic human[8,9]. Moreover, *L. casei* Shirota has been reported to reduce blood glucose level through reducing lipopo-

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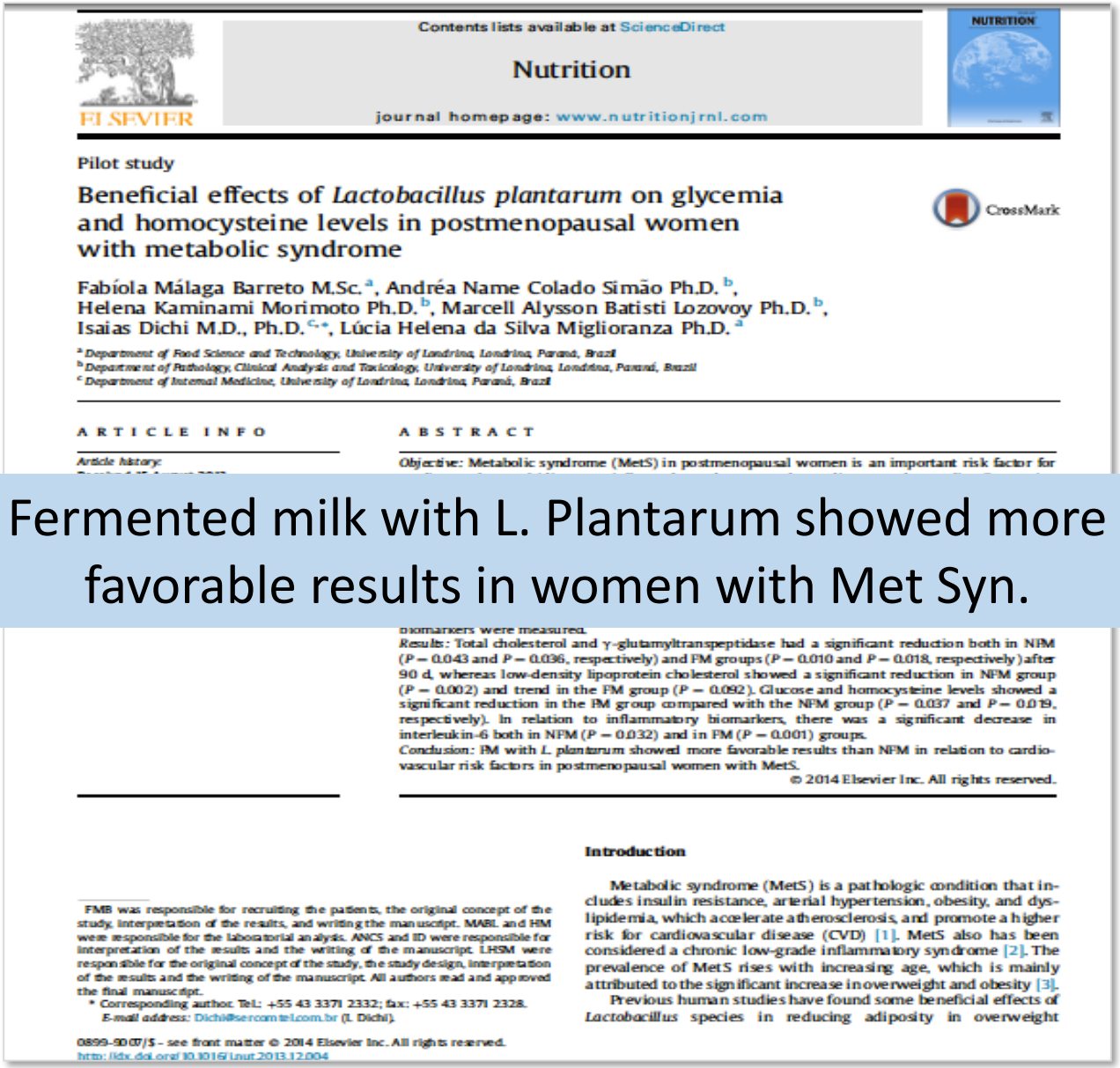
* Current address: The Key laboratory of Dairy Biotechnology and Engineering, Education Ministry of P. R. China, Inner Mongolia Agricultural University, 306 Zhaowudalu Road, Hohhot, China, 010018.

The primary findings of the present study are that *L. casei* ingestion markedly prevents rats from the onset and development of glycemia in both fasting and postprandial 2h blood glucose levels, as well as OGTT levels.

Zhang Y, et al. *Sci Rep* 4, 5654 (2015).



Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Pilot study

Beneficial effects of *Lactobacillus plantarum* on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome

Fabíola Málaga Barreto M.Sc.[a], Andréa Name Colado Simão Ph.D.[b], Helena Kaminami Morimoto Ph.D.[b], Marcell Alysson Batisti Lozovoy Ph.D.[b], Isaías Dichi M.D., Ph.D.[c,*], Lúcia Helena da Silva Miglioranza Ph.D.[a]

[a] Department of Food Science and Technology, University of Londrina, Londrina, Paraná, Brazil
[b] Department of Pathology, Clinical Analysis and Toxicology, University of Londrina, Londrina, Paraná, Brazil
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ARTICLE INFO

Article history:

ABSTRACT

Objective: Metabolic syndrome (MetS) in postmenopausal women is an important risk factor for

biomarkers were measured.

Results: Total cholesterol and γ-glutamyltranspeptidase had a significant reduction both in NFM ($P = 0.043$ and $P = 0.036$, respectively) and FM groups ($P = 0.010$ and $P = 0.018$, respectively) after 90 d, whereas low-density lipoprotein cholesterol showed a significant reduction in NFM group ($P = 0.002$) and trend in the FM group ($P = 0.092$). Glucose and homocysteine levels showed a significant reduction in the FM group compared with the NFM group ($P = 0.037$ and $P = 0.019$, respectively). In relation to inflammatory biomarkers, there was a significant decrease in interleukin-6 both in NFM ($P = 0.032$) and in FM ($P = 0.001$) groups.

Conclusion: FM with *L. plantarum* showed more favorable results than NFM in relation to cardiovascular risk factors in postmenopausal women with MetS.

Introduction

Metabolic syndrome (MetS) is a pathologic condition that includes insulin resistance, arterial hypertension, obesity, and dyslipidemia, which accelerate atherosclerosis, and promote a higher risk for cardiovascular disease (CVD) [1]. MetS also has been considered a chronic low-grade inflammatory syndrome [2]. The prevalence of MetS rises with increasing age, which is mainly attributed to the significant increase in overweight and obesity [3].

Previous human studies have found some beneficial effects of *Lactobacillus* species in reducing adiposity in overweight

FMB was responsible for recruiting the patients, the original concept of the study, interpretation of the results, and writing the manuscript. MABL and HM were responsible for the laboratorial analysis. ANCS and ID were responsible for interpretation of the results and the writing of the manuscript. LHSM were responsible for the original concept of the study, the study design, interpretation of the results and the writing of the manuscript. All authors read and approved the final manuscript.

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E-mail address: Dichi@sercomtel.com.br (I. Dichi).

0899-9007/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nut.2013.12.004

Fermented milk with L. Plantarum showed more favorable results in women with Met Syn.

Barreto FM, et al. *Nutrition*. 2014 Jul-Aug;30(7-8):939-42.

Akkermansia spp.

Gut. 2014 May;63(5):727-35. doi: 10.1136/gutjnl-2012-303839. Epub 2013 Jun 26.

An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice.

Shin NR[1], Lee JC, Lee HY, Kim MS, Whon TW, Lee MS, Bae JW.

Author information

"Modulation of the gut microbiota (by an increase in the *Akkermansia* spp. population) may contribute to the antidiabetic effects of metformin, thereby providing a new mechanism for the therapeutic effect of metformin in patients with T2D."

Adipose tissue inflammation was examined by flow cytometric analysis of the immune cells present in visceral adipose tissue (VAT).

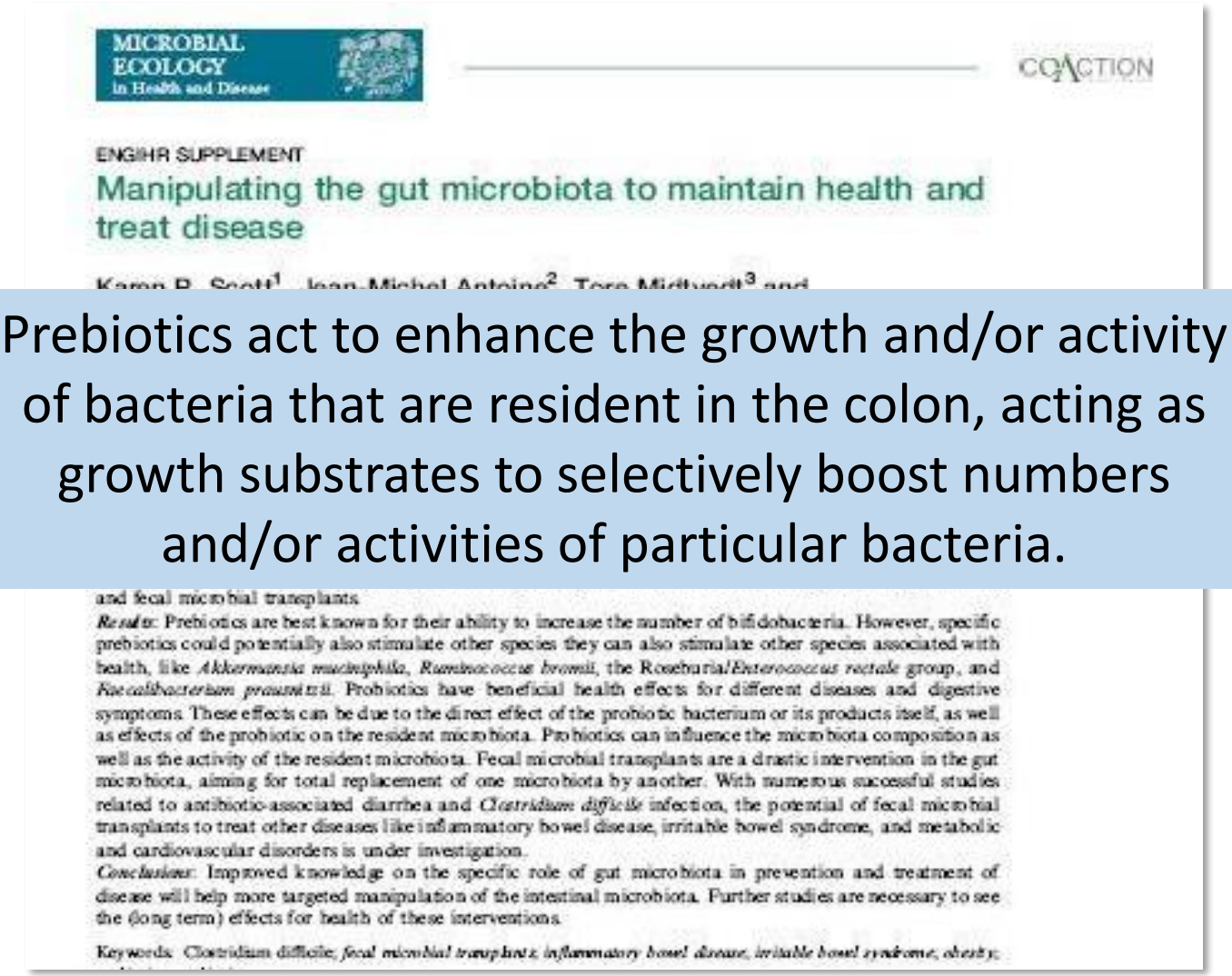
RESULTS: Metformin treatment significantly improved the glycaemic profile of HFD-fed mice. HFD-fed mice treated with metformin showed a higher abundance of the mucin-degrading bacterium Akkermansia than HFD-fed control mice. In addition, the number of mucin-producing goblet cells was significantly increased by metformin treatment ($p<0.0001$). Oral administration of Akkermansia muciniphila to HFD-fed mice without metformin significantly enhanced glucose tolerance and attenuated adipose tissue inflammation by inducing Foxp3 regulatory T cells (Tregs) in the VAT.

CONCLUSIONS: Modulation of the gut microbiota (by an increase in the Akkermansia spp. population) may contribute to the antidiabetic effects of metformin, thereby providing a new mechanism for the therapeutic effect of metformin in patients with T2D. This suggests that pharmacological manipulation of the gut microbiota in favour of Akkermansia may be a potential treatment for T2D.

GENOVA DIAGNOSTICS

Shin NR, et al. *Gut*. 2014 May;63(5):727-35.

Gut Microbiota



MICROBIAL ECOLOGY in Health and Disease

COACTION

ENGIHR SUPPLEMENT

Manipulating the gut microbiota to maintain health and treat disease

Karen P. Scott[1], Jean-Michel Antoine[2], Tore Midtvedt[3] and

Prebiotics act to enhance the growth and/or activity of bacteria that are resident in the colon, acting as growth substrates to selectively boost numbers and/or activities of particular bacteria.

and fecal microbial transplants.

Results: Prebiotics are best known for their ability to increase the number of bifidobacteria. However, specific prebiotics could potentially also stimulate other species they can also stimulate other species associated with health, like *Akkermansia muciniphila*, *Ruminococcus bromii*, the Roseburia/*Enterococcus rectale* group, and *Faecalibacterium prausnitzii*. Probiotics have beneficial health effects for different diseases and digestive symptoms. These effects can be due to the direct effect of the probiotic bacterium or its products itself, as well as effects of the probiotic on the resident microbiota. Probiotics can influence the microbiota composition as well as the activity of the resident microbiota. Fecal microbial transplants are a drastic intervention in the gut microbiota, aiming for total replacement of one microbiota by another. With numerous successful studies related to antibiotic-associated diarrhea and *Clostridium difficile* infection, the potential of fecal microbial transplants to treat other diseases like inflammatory bowel disease, irritable bowel syndrome, and metabolic and cardiovascular disorders is under investigation.

Conclusions: Improved knowledge on the specific role of gut microbiota in prevention and treatment of disease will help more targeted manipulation of the intestinal microbiota. Further studies are necessary to see the (long term) effects for health of these interventions.

Keywords: Clostridium difficile; *fecal microbial transplants; inflammatory bowel disease, irritable bowel syndrome, obesity;*

GENOVA DIAGNOSTICS

Scott KP, et al. *Microb Ecol Health Dis*. 2015 Feb 2;26:25877.

Slow Down & Chew Your Food

Clin Nutr. 2013 Apr;32(2):232-5. doi: 10.1016/j.clnu.2012.06.013. Epub 2012 Jul 15.

Fast eating and the risk of type 2 diabetes mellitus: a case-control study.

Radzevičienė L[1], Ostrauskas R.

Author information

Abstract

BACKGROUND & A … 2 diabetes mellitus.

SUBJECTS AND ME … non diabetic controls. A specifica… es. The speed of eating was self-repo… The odds ratios (OR), and 95% conf…

More than two-fold increased risk of type 2 diabetes was determined for subjects eating faster vs. subjects eating slower.

RESULTS: Variables such as a family history on diabetes, body mass index, waist circumference, educational level, morning exercise, smoking and plasma triglycerides level were retained in multivariate logistic regression models as confounders because their inclusion changed the value of the OR by more than 5% in any exposure category. After adjustment for possible confounders more than two-fold increased risk of type 2 diabetes was determined for subjects eating faster (OR = 2.52; 95% CI 1.56-4.06) vs. subjects eating slower.

CONCLUSIONS: Our data support a possible relationship between faster eating speed and the increased risk of type 2 diabetes mellitus.

PMID: 22800734 DOI: 10.1016/j.clnu.2012.06.013

GENOVA DIAGNOSTICS

Radzevičienė L, et al. *Clin Nutr*. 2013 Apr;32(2):232-5.

Drinking Soda and Diabetes Risk

Diabetologia. 2013 Jul;56(7):1520-30. doi: 10.1007/s00125-013-2899-8. Epub 2013 Apr 26.

Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPIC-InterAct.

InterAct Consortium, Romaguera D, Norat T, Wark PA, Vergnaud AC, Schulze MB, van Woudenbergh GJ, Drogan D, Amiano P, Molina-Montes E, Sánchez MJ, Balkau B, Barricarte A, Beulens JW, Clavel-Chapelon F, Crispim SP, Fagherazzi G, Franks PW, Grote VA, Huybrechts I, Kaaks R, Key TJ, Khaw KT, Nilsson P, Overvad K, Palli D, Panico S, Quirós JR, Rolandsson O, Sacerdote C, Sieri S, Slimani N, Spijkerman AM, Tjonneland A, Tormo MJ, Tumino R, van den Berg SW, Wermeling PR, Zamara-Ros R, Feskens EJ, Langenberg C, Sharp SJ, Forouhi NG, Riboli E, Wareham NJ.

Abstract

AIMS/

diabet … e 2

drinks … soft

METH

Drinking one 12-ounce sugar sweetened soft drink a day can increase the risk of type 2 diabetes by 22%

participants selected from eight European cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. After exclusions, the final sample size included 11,684 incident cases and a subcohort of 15,374 participants. Cox proportional hazards regression models (modified for the case-cohort design) and random-effects meta-analyses were used to estimate the association between sweet beverage consumption (obtained from validated dietary questionnaires) and type 2 diabetes incidence.

RESULTS: In adjusted models, one 336 g (12 oz) daily increment in sugar-sweetened and artificially sweetened soft drink consumption was associated with HRs for type 2 diabetes of 1.22 (95% CI 1.09, 1.38) and 1.52 (95% CI 1.26, 1.83), respectively. After further adjustment for energy intake and BMI, the association of sugar-sweetened soft drinks with type 2 diabetes persisted (HR 1.18, 95% CI 1.06, 1.32), but the association of artificially sweetened soft drinks became statistically not significant (HR 1.11, 95% CI 0.95, 1.31). Juice and nectar consumption was not associated with type 2 diabetes incidence.

CONCLUSIONS/INTERPRETATION: This study corroborates the association between increased incidence of type 2 diabetes and high consumption of sugar-sweetened soft drinks in European adults.

GENOVA DIAGNOSTICS

Romaguera D, et al. *Diabetologia*. 2013 Jul;56(7):1520-30.

Television and DM

Arch Pediatr Adolesc Med. 2010 Jul;164(7):643-9. doi: 10.1001/archpediatrics.2010.88.

Screen time and metabolic risk factors among adolescents.

Hardy LL[1], Denney-Wilson E, Thrift AP, Okely AD, Baur LA.

⊕ Author information

Abstract

OBJECTIVE: To examine the association between screen time (ST) (ie, television/DVD/video and computer use) guidelines and risk fact

DE

SE

PA

MAIN EXPOSURES: Body mass index, waist circumference, cardiorespiratory endurance, dietary factors, socioeconomic status, and pubertal status.

MAIN OUTCOME MEASURES: Screen time was categorized as less than 2 hours per day or 2 or more hours per day and calculated for weekday, weekend, and the entire week. Fasting blood samples were analyzed for levels of high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, insulin, and glucose; homeostasis model assessment of insulin resistance (HOMA-IR); levels of alanine aminotransferase, gamma-glutamyltransferase, and high-sensitivity C-reactive protein; and blood pressure. Abnormal results were categorized according to published guidelines.

Television, Computer Viewing of More Than 2 Hours per Day May Increase Metabolic Syndrome Risk in Teenage Boys

GENOVA DIAGNOSTICS

Hardy LL, et al. *Arch Pediatr Adolesc Med*. 2010 Jul;164(7):643-9.

Passive Smoking and DM

PLoS One. 2013 Jul 26;8(7):e69915. doi: 10.1371/journal.pone.0069915. Print 2013.

Passive smoking and risk of type 2 diabetes: a meta-analysis of prospective cohort studies.

Wang Y[1], Ji J, Liu YJ, Deng X, He QQ.

⊕ Author information

Abstract

BACKGROUNDS/OBJECTIVE: The prevalence of diabetes is increasing rapidly all over the world. However, studies on passive smoking and type 2 diab…whether an association exists between…

METHODS: We…tify prospective cohort studies that ass…e overall relative risk (RR).

RESULT: 4 prospective cohort studies were included for analysis, with a total of 112,351 participants involved. The pooled RR was 1.28 (95% confidence interval (CI) 1.14 to 1.44) comparing those who were exposed to passive smoking with those who were not. Subgroup, sensitivity analysis and publication bias test suggested the overall result of this analysis was robust.

CONCLUSIONS: Passive smoking is associated with a significantly increased risk of type 2 diabetes. Further well-designed studies are warranted to confirm this association.

Passive smoking is associated with a significantly increased risk of type 2 diabetes

GENOVA DIAGNOSTICS

Wang Y, et al. *PLoS One*. 2013 Jul 26;8(7):e69915.

Prayer, Meditation and Yoga

- **Religious participation** predicted steeper ("healthier") cortisol slopes at the 10-year f/u[1]
- **Prospective 12 week study exploring yoga, meditation and lifestyle intervention (YMLI)**[2]
  - Looking cellular markers affecting aging (8-OH2dG, ROS, cortisol telomere attrition and TAC, β-endorphin, IL-6, BDNF and sirtuin-1)
  - There was decrease in oxidative stress markers and cortisol, and TAC, telomerase activity, β-endorphin, BDNF and sirtuin-1 increased

GENOVA DIAGNOSTICS

1. Tobin ET, Slatcher RB. *Health Psychol*. 2016 Dec;35(12):1356-1363.
2. Tolahunase M, et al. *Oxid Med Cell Longev*. 2017:2784153.

Laughter and Diabetes

Laughter lowered the increase in postprandial blood glucose.

In 19 **diabetic patients,** (mean age 63, mean BMI 23.5, mean HbA1c 7.2, not on insulin) the mean **blood sugar 2 hr after a 500 kcal meal rose 121 mg/dl above FBS in those who had attended a 40 minute dry lecture vs. a rise of 77 mg/dl after attending a comedy show during which their laughter level was 4-5/5**.

GENOVA DIAGNOSTICS

Hayashi K, et al. *Diabetes Care*. 2003 May;26(5):1651-2.

Exercise

- Alters skeletal muscle metabolism and improves glucose uptake
- Reduces low-density lipoprotein, raises HDL
- Lowers blood pressure
- Reduces inflammation and oxidative stress

GENOVA DIAGNOSTICS

Klein S, et al. *Am J Clin Nutr.*2004;80(2):257-263.

Importance of Lifestyle

- *Diabetes Prevention Program Research Group* – 2002 study
- 3234 prediabetics were randomized to placebo, metformin, or lifestyle modification (≥7% weight loss and ≥150 min/wk of physical activity) for 2.8 years
- Results: Compared to placebo:
  - Lifestyle intervention decreased incidence of type 2 DM by 58%
  - Metformin decreased type 2 DM by only 31%

GENOVA DIAGNOSTICS

Knowler WC. *N Engl J Med*. 2002; 346(6):393-403.

GENOVA DIAGNOSTICS

Sleep and Diabetes

Nutr Diabetes. 2017 May 8;7(5):e266. doi: 10.1038/nutd.2017.19.

Inadequate sleep as a contributor to type 2 diabetes in children and adolescents.

Dutil C[1], Chaput JP[1].

Author information

Abstract

There is a link between inadequate sleep and type 2 diabetes in children and adolescents.

studies). Notwithstanding the conflicting results found in these studies and despite being attenuated by adiposity level, maturity, sex and age, there is still some compelling evidence for an association between sleep duration (for both objective or subjective measurements of duration) and architecture with one or more T2D biomarkers in children and adolescents. The majority of the studies reviewed did focus on sleep duration and one or more T2D biomarkers in children and adolescents, but sleep architecture, more precisely the suppression of slow wave sleep and rapid eye movement sleep, has also been shown to be associated with insulin resistance. Only two studies looked at sleep quality, and the association between sleep quality and insulin resistance was not independent of level of adiposity. Future experimental studies will help to better understand the mechanisms linking insufficient sleep with T2D. Work also needs to be carried out on finding novel and effective strategies aimed at improving sleep hygiene and health outcomes of children and adolescents.

PMID: 28481337 PMCID: PMC5518801 DOI: 10.1038/nutd.2017.19

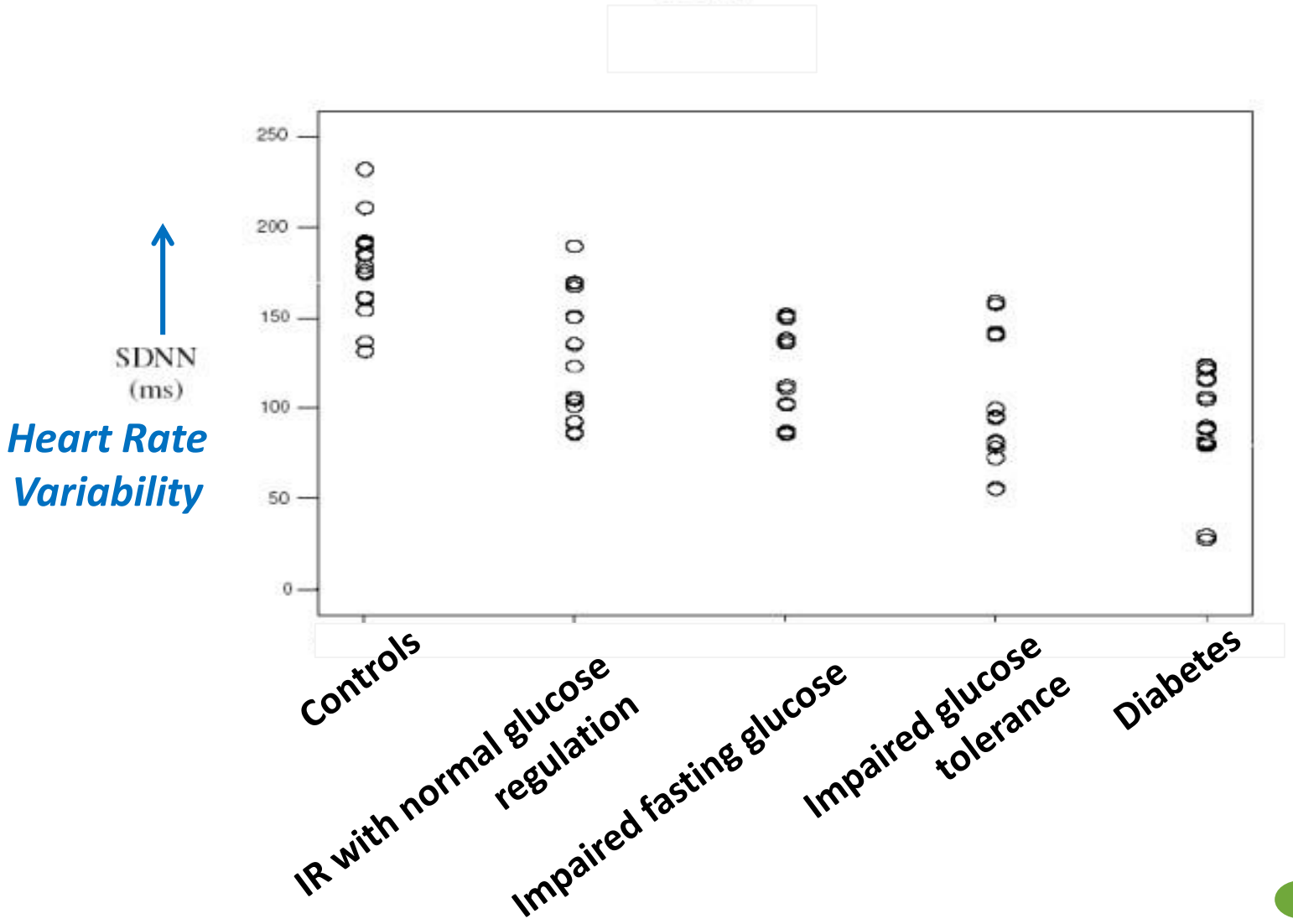
Free PMC Article

GENOVA DIAGNOSTICS

Dutil C, Chaput JP. *Nutr Diabetes*. 2017 May; 7(5): e266.

HRV & Glucose Regulation

Autonomic dysfunction increases in parallel with worsening glucose regulation



Perciaccante A, et al. *BMC Cardiovasc Disord.* 2006; 6:19.

Probiotic + Omega 3 & Glucose Regulation

Mediators Inflamm. 2014;2014:348959. doi: 10.1155/2014/348959. Epub 2014 Mar 26.

Effect of probiotic (VSL#3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial.

Rajkumar H[1], Mahmood N[1], Kumar M[1], Varikuti SR[1], Challa HR[1], Myakala SP[1].

Author information

Abstract

Addition of omega-3 fatty acid with VSL#3 had more pronounced effect on HDL, insulin sensitivity and hsCRP.

groups received, respectively, placebo, omega-3 fatty acid, probiotic VSL#3, or both omega-3 and probiotic, for 6 weeks. Blood and fecal samples were collected at baseline and after 6 weeks. The probiotic (VSL#3) supplemented group had significant reduction in total cholesterol, triglyceride, LDL, and VLDL and had increased HDL ($P < 0.05$) value. VSL#3 improved insulin sensitivity ($P < 0.01$), decreased hsCRP, and favorably affected the composition of gut microbiota. Omega-3 had significant effect on insulin sensitivity and hsCRP but had no effect on gut microbiota. Addition of omega-3 fatty acid with VSL#3 had more pronounced effect on HDL, insulin sensitivity and hsCRP. Subjects with low HDL, insulin resistance, and high hsCRP had significantly lower total lactobacilli and bifidobacteria count and higher E. coli and bacteroides count.

GENOVA DIAGNOSTICS

Hemalatha R, et al. *Mediators Inflamm*. 2014; 2014: 348959.

Nutrients Known to Modify Insulin Responsiveness

- Chromium
- Alpha-lipoic acid
- CoQ10
- Vitamin D
- Magnesium
- Vitamin C, vitamin E and other antioxidants
- Omega 3 fatty acids
- Curcumin
- Vanadium
- Serum kinase receptor modulators (SKRMs)

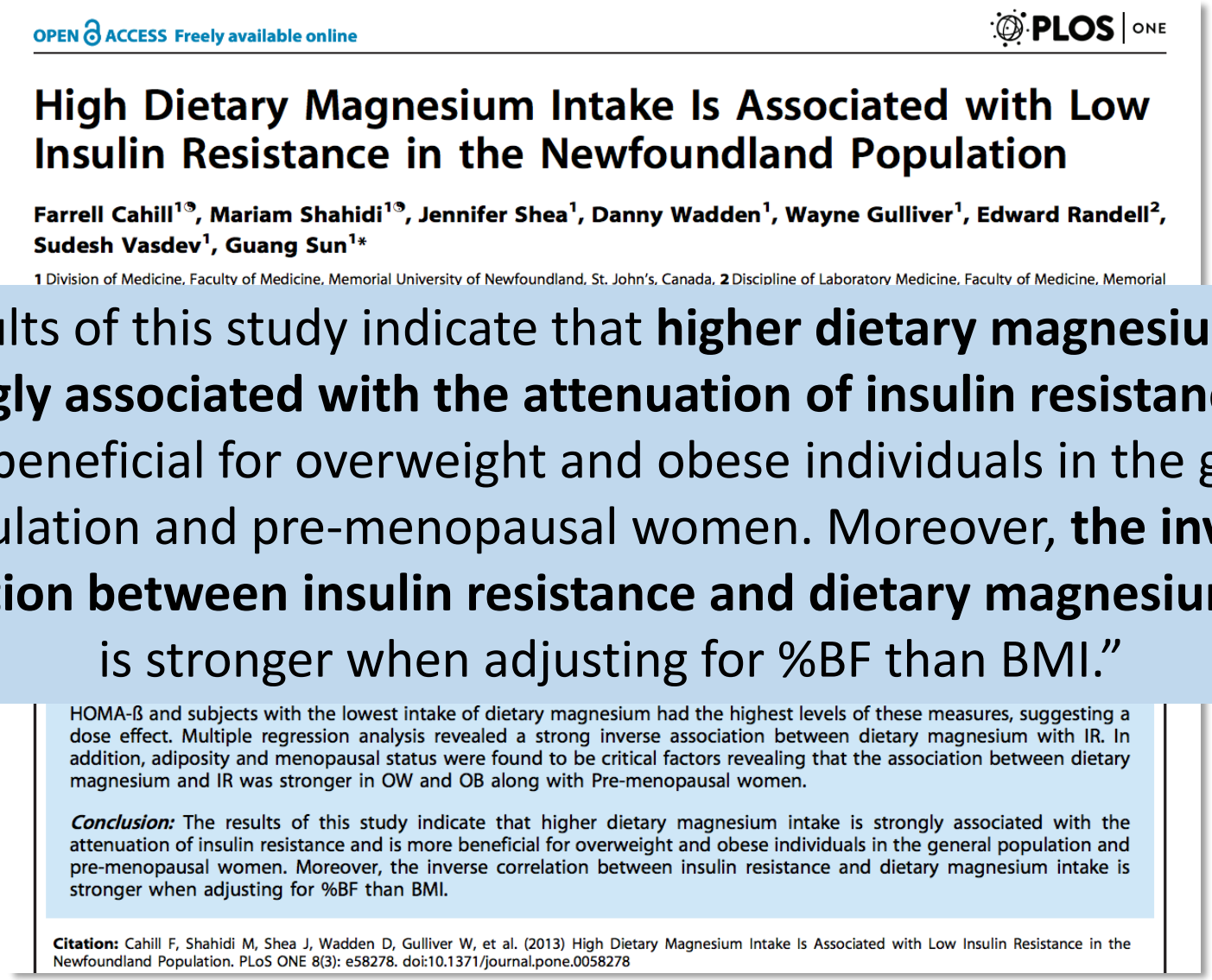
Magnesium

- Epidemiological studies show that high daily Mg intake is predictive of a lower incidence of NIDDM
- Poor intracellular Mg concentration are found in NIDDM and in hypertensive patients
- Daily Mg administration in NIDDM patients and in insulin resistant patients restores intracellular Mg concentration and contributes to improves insulin sensitivity and glucose uptake

GENOVA DIAGNOSTICS

Barbagallo M, et al. *Mol Aspects Med*. 2003 Feb-Jun;24(1-3): p. 39-52.
Guerrero-Romero F, et al. *Diabetes Metab* 2004 Jun;30(3):253-8.

Magnesium



OPEN ACCESS Freely available online

PLOS ONE

High Dietary Magnesium Intake Is Associated with Low Insulin Resistance in the Newfoundland Population

Farrell Cahill[1], Mariam Shahidi[1], Jennifer Shea[1], Danny Wadden[1], Wayne Gulliver[1], Edward Randell[2], Sudesh Vasdev[1], Guang Sun[1]*

1 Division of Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Canada, **2** Discipline of Laboratory Medicine, Faculty of Medicine, Memorial

"The results of this study indicate that **higher dietary magnesium intake is strongly associated with the attenuation of insulin resistance** and is more beneficial for overweight and obese individuals in the general population and pre-menopausal women. Moreover, **the inverse correlation between insulin resistance and dietary magnesium** intake is stronger when adjusting for %BF than BMI."

HOMA-ß and subjects with the lowest intake of dietary magnesium had the highest levels of these measures, suggesting a dose effect. Multiple regression analysis revealed a strong inverse association between dietary magnesium with IR. In addition, adiposity and menopausal status were found to be critical factors revealing that the association between dietary magnesium and IR was stronger in OW and OB along with Pre-menopausal women.

Conclusion: The results of this study indicate that higher dietary magnesium intake is strongly associated with the attenuation of insulin resistance and is more beneficial for overweight and obese individuals in the general population and pre-menopausal women. Moreover, the inverse correlation between insulin resistance and dietary magnesium intake is stronger when adjusting for %BF than BMI.

Citation: Cahill F, Shahidi M, Shea J, Wadden D, Gulliver W, et al. (2013) High Dietary Magnesium Intake Is Associated with Low Insulin Resistance in the Newfoundland Population. PLoS ONE 8(3): e58278. doi:10.1371/journal.pone.0058278

GENOVA DIAGNOSTICS

Farrell C, et al. PLoS One. 2013; 8(3): e58278.

Micronutrient Recommendations

- Chromium: If using generally give 200mcg/daily if insulin resistant. Likely most effective if deficient, but difficult to test.
- Vitamin D: Test 25(OH)D and supplement as appropriate (or supplement 2000-5000) IU/daily
- Magnesium: Generally give 200-400 mg. Likely most effective if deficient, accurate testing is cumbersome. Supplementation if signs and symptoms of deficiency/insufficiency.
- CoQ10 100-200 mg/day: Generally supplement in patients with metabolic syndrome or diabetes if also hypertensive.
- Alpha lipoic acid: 600 mg bid if diabetic or specifically if have peripheral neuropathy. Likely useful at lower dosages in insulin resistant.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