TYPE 2 DIABETES MELLITUS: PATHOPHYSIOLOGY, DIAGNOSIS, PREVENTION AND TREATMENT

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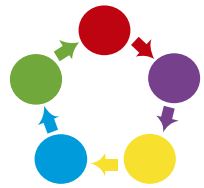
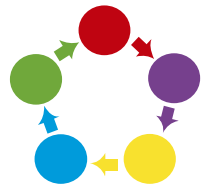
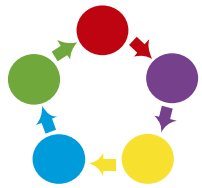


OBJECTIVES

- Discuss the importance of early detection of insulin resistance
- Review how to appropriately diagnose IR, IGT, Pre-DM, Type2
  - Clinical exam
  - Laboratory measures
    - Staging
- Focus on the importance of individualizing treatment
  - Diet, lifestyle, nutraceuticals, gut microbiota



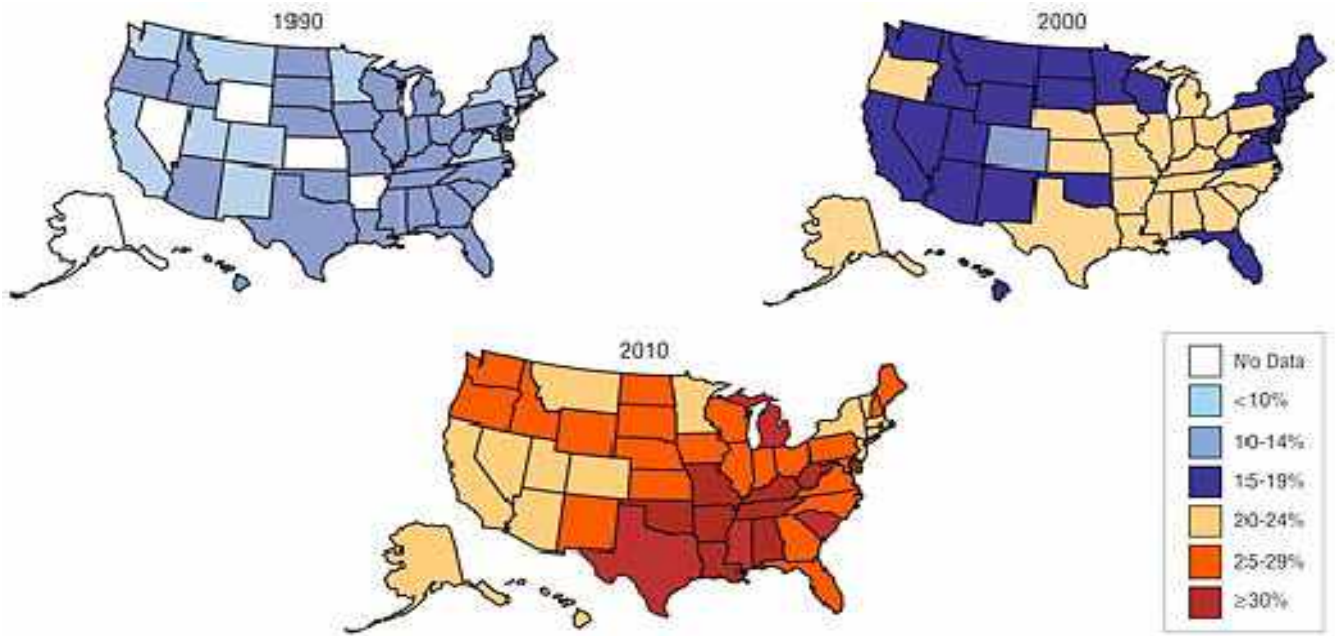
CARDIOVASCULAR DISEASE AND DIABETES ARE LINKED TO EACH OTHER THROUGH OBESITY, INSULIN RESISTANCE AND INFLAMMATION.



OBESITY TRENDS* AMONG U.S. ADULTS

BRFSS, 1990, 1999, 2010

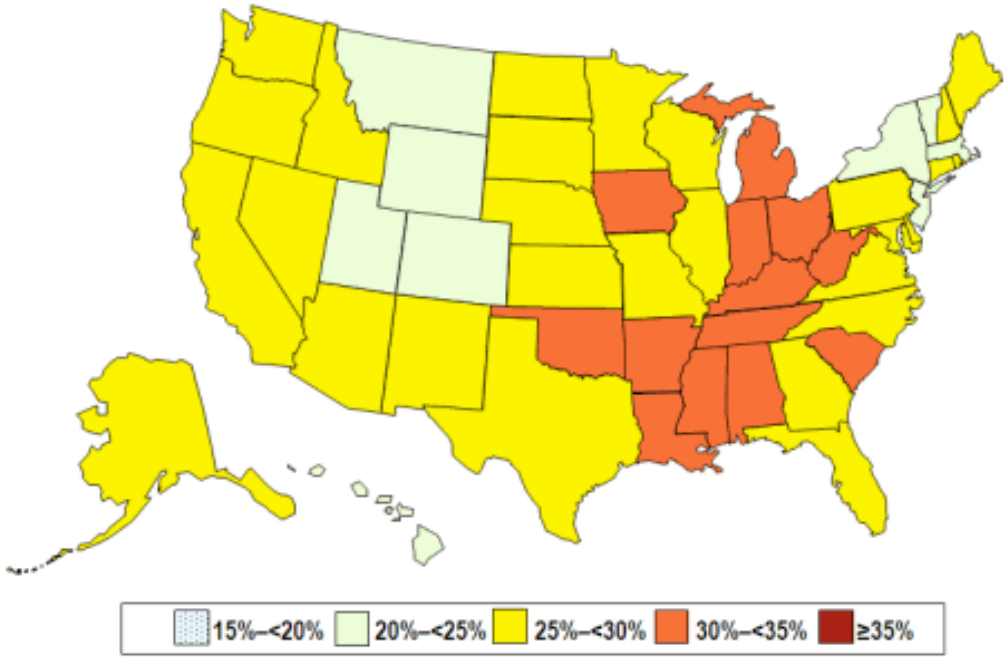
(*BMI ≥ 30, OR ABOUT 30 LBS. OVERWEIGHT FOR 5'4" PERSON)



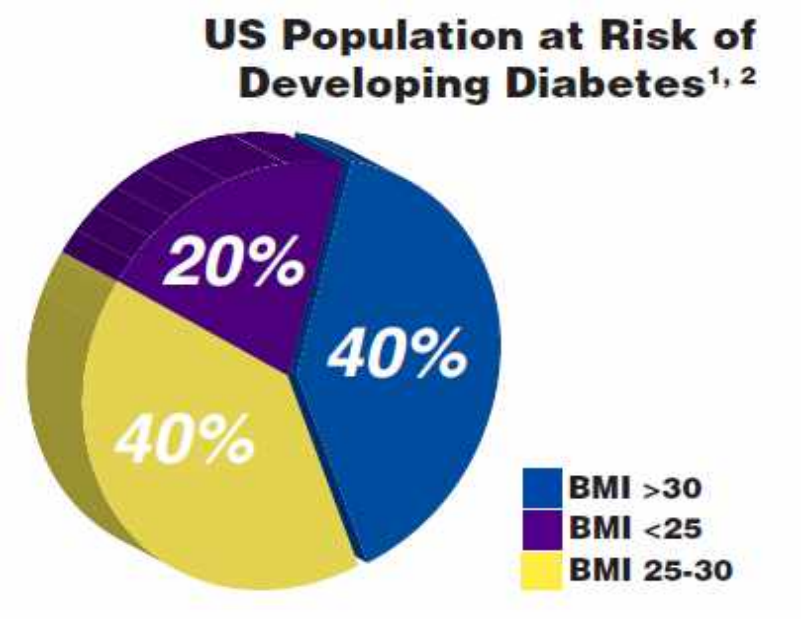
Filomena Trindade, MD, MPH

Prevalence* of Self-Reported Obesity Among U.S. Adults
BRFSS, 2012

*Prevalence reflects BRFSS methodological changes in 2011, and these estimates should not be compared to those before 2011.



CDC: Only **40%** of the risk of developing diabetes occurs in people who are obese!



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

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%**

RATES OF CARDIOMETABOLIC SYNDROME

Metabolic Syndrome = Constellation of lipid and non-lipid risk factors of metabolic origin

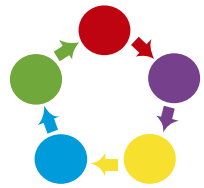
1988: Gerald Reaven coined the term "**Syndrome X**"

2004: National Cholesterol Education Program (NCEP) update (ATP III): Any 3 of 5 traits are required for the definition.

Focus has since shifted to **insulin resistance** as the dominant and independent predictor of age-related diseases.

Metabolic Syndrome

- Increased waist circumference (40 inches for males; 35 inches for females)
- Low HDL-cholesterol (<40 mg/dL for males; <50 mg/dL for females)
- High Triglycerides (>150 mg/dL)
- High Fasting GLUCOSE (>100 mg/dL)
- Hypertension (BP >130/85)



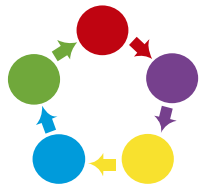
Continuum of Insulin Resistance

Wellness **Illness**

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

Health *No Symptoms* *Symptoms/Pathology*

WHERE DO YOU SEE MANIFESTATIONS OF INSULIN RESISTANCE OR THE METABOLIC SYNDROME?



INSULIN RESISTANCE

↓

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

↓

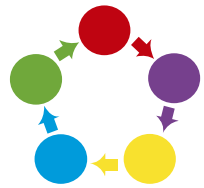
Impaired Glucose Tolerance
(Uncompensated Hyperinsulinemia)

↓

Pre-Diabetes

↓

Diabetes



How and where does insulin resistance start?

And…

WHAT HAPPENS IN THE PERSON WITH DYSFUNCTIONAL INSULIN SIGNALING?

Adipocyte Dysregulation

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

Endocrine Reviews 23(2):201–229

Disordered Fat Storage and Mobilization in the Pathogenesis of Insulin Resistance and Type 2 Diabetes

GARY F. LEWIS, ANDRÉ CARPENTIER, KHOSROW ADELI, AND ADRIA GIACCA

Department of Medicine, Division of Endocrinology (G.F.L., A.C., A.G.), Department of Physiology (A.G.), and Department of Laboratory Medicine and Pathobiology (K.A.), University of Toronto, Toronto, Canada M5G 2C4

The primary genetic, environmental, and metabolic factors responsible for causing insulin resistance and pancreatic β-cell paired pancreatic β-cell function. The precise biochemical mechanisms whereby fatty acids and cytosolic triglycerides

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.

Endocrine Reviews, 2002

OTHER THEORIES

- Barbara Corkey:
  - *"Insulin resistance starts in the Beta cell with hyperinsulinemia causing insulin resistance. The initial cause is damage to the Beta cell."*

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?

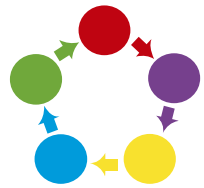
Striking correlations between the toxin polybrominated diphenyl ethers, air conditioning, antidepressant prescriptions, and average home temperature and the prevalence of obesity have been shown by Allison and colleagues (1). The worldwide expansion of metabolic diseases across all age-groups decreases 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.

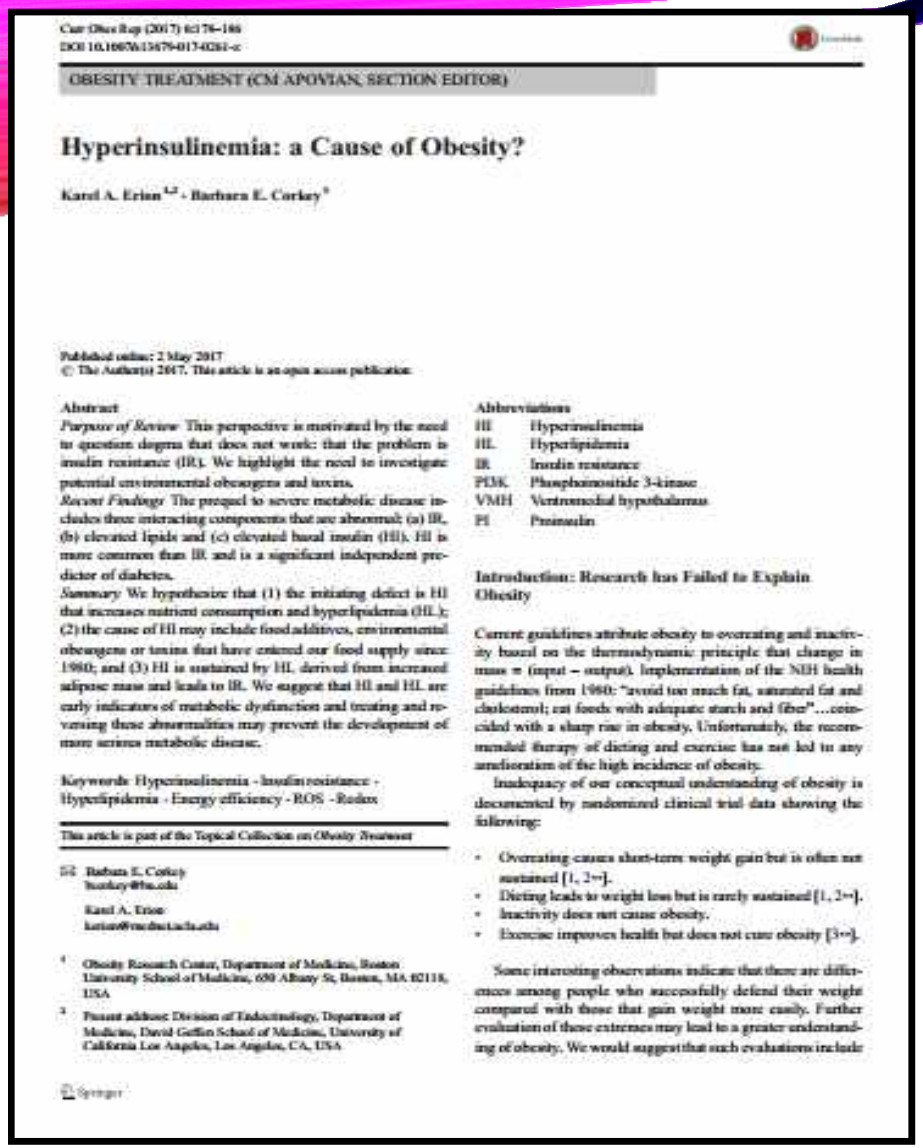
The proposed new model (Fig. 1) is based on the hy-



Beta-cell Toxicity

Insulin resistance is caused by hyperinsulinemia, a consequence of increased beta-cell secretion due to toxicity. Dr. Corkey has identified in her lab that mono-oleoylglycerol, iron, and saccharin may all be common dietary ingredients that are capable of producing this hyperinsulinemia.

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.



Curr Obes Rep (2017) 6:176–186
DOI 10.1007/s13679-017-0262-y

OBESITY TREATMENT (CM APOVIAN, SECTION EDITOR)

Hyperinsulinemia: a Cause of Obesity?

Karel A. Erion[1,2] · Barbara E. Corkey[1]

Published online: 2 May 2017

Abstract

Purpose of Review This perspective is motivated by the need to question dogma that does not work: that the problem is insulin resistance (IR). We highlight the need to investigate potential environmental obesogens and toxins.

Recent Findings The prequel to severe metabolic disease includes three interacting components that are abnormal: (a) IR, (b) elevated lipids and (c) elevated basal insulin (HI). HI is more common than IR and is a significant independent predictor of diabetes.

Summary We hypothesize that (1) the initiating defect is HI that increases nutrient consumption and hyperlipidemia (HL); (2) the cause of HI may include food additives, environmental obesogens or toxins that have entered our food supply since 1980; and (3) HI is sustained by HL derived from increased adipose mass and leads to IR. We suggest that HI and HL are early indicators of metabolic dysfunction and treating and reversing these abnormalities may prevent the development of more serious metabolic disease.

Keywords Hyperinsulinemia · Insulin resistance · Hyperlipidemia · Energy efficiency · ROS · Redox

This article is part of the Topical Collection on *Obesity Treatment*

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Abbreviations

HI	Hyperinsulinemia
HL	Hyperlipidemia
IR	Insulin resistance
PI3K	Phosphoinositide 3-kinase
VMH	Ventromedial hypothalamus
PI	Proinsulin

Introduction: Research has Failed to Explain Obesity

Current guidelines attribute obesity to overeating and inactivity based on the thermodynamic principle that change in mass = (input − output). Implementation of the NIH health guidelines from 1980: "avoid too much fat, saturated fat and cholesterol; eat foods with adequate starch and fiber"…coincided with a sharp rise in obesity. Unfortunately, the recommended therapy of dieting and exercise has not led to any amelioration of the high incidence of obesity.

Inadequacy of our conceptual understanding of obesity is documented by randomized clinical trial data showing the following:

- Overeating causes short-term weight gain but is often not sustained [1, 2••].
- Dieting leads to weight loss but is rarely sustained [1, 2••].
- Inactivity does not cause obesity.
- Exercise improves health but does not cure obesity [3••].

Some interesting observations indicate that there are differences among people who successfully defend their weight compared with those that gain weight more easily. Further evaluation of these extremes may lead to a greater understanding of obesity. We would suggest that such evaluations include

Springer

" We suggest that HI and HL are early indicators of metabolic dysfunction and treating and reversing these abnormalities may prevent the development of more serious metabolic disease"

Diabetes Care Volume 39, February 2016 179

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

Diabetes Care 2016;39:179–186 | DOI: 10.2337/dc15-1585

PERSPECTIVES IN CARE

The current classification system presents challenges to the diagnosis and treatment of patients with diabetes mellitus (DM), in part due to its conflicting and confounding definitions of type 1 DM, type 2 DM, and latent autoimmune diabetes of adults (LADA). The current schema also lacks a foundation that readily incorporates advances in our understanding of the disease and its treatment. For appropriate and coherent therapy, we propose an alternate classification system. The β-cell–centric classification of DM is a new approach that obviates the inherent and unintended confusions of the current system. The β-cell–centric model presupposes that all DM originates from a final common denominator—the abnormal pancreatic β-cell. It recognizes that interactions between genetically predisposed β-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. Individually or in concert, and often self-perpetuating, these factors contribute to β-cell stress, dysfunction, or loss through at least 11 distinct pathways. Available, yet underutilized, treatments provide rational choices for personalized therapies that target the individual 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 essential function of a classification system is as a navigation tool that helps direct research, evaluate outcomes, establish guidelines for best practices for prevention and care, and educate on all of the above. Diabetes mellitus (DM) subtypes as currently categorized, however, do not fit into our contemporary understanding of the phenotypes of diabetes (1–6). The inherent challenges of the current system, together with the limited knowledge that existed at the time of the crafting of the current system, yielded definitions for type 1 DM, type 2 DM, and latent autoimmune diabetes in adults (LADA) that are not distinct and are ambiguous and imprecise.

Discovery of the role played by autoimmunity in the pathogenesis of type 1 DM created the assumption that type 1 DM and type 2 DM possess unique etiologies, disease courses, and, consequently, treatment approaches. There exists, however, overlap among even the most "typical" patient cases. Patients presenting with otherwise

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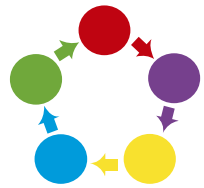
Corresponding author: Stanley S. Schwartz, stschwar@gmail.com.

Received 22 July 2015 and accepted 3 November 2015.

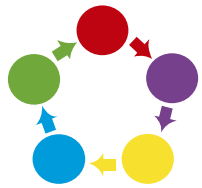
This article issues an urgent call for the review of the current DM classification system toward "the consensus on a new, more useful system"



WHAT ARE THE CAUSES OF INSULIN RESISTANCE?

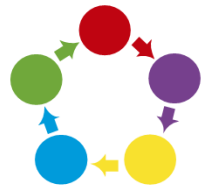
AND

HOW DO WE APPROACH THE PT WITH INSULIN RESISTANCE?



HOW DID THIS PERSON DEVELOP INSULIN RESISTANCE?

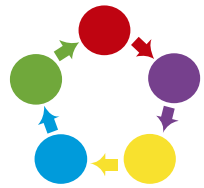
- Consider the Following:
  - Food allergies and/or sensitivities
  - Dysbiosis, leaky gut and gut microbiota
  - Toxins (POP's, heavy metals, pesticides, endogenous)
  - EMF/Dirty Electricity
  - Food additives or excesses
  - Digestive Insufficiencies
  - Oxidative Stress
  - Mitochondrial dysfunction
  - Obesity
  - Stress or adrenal fatigue/dysfunction
  - Lack of sleep
  - Hormone imbalances
  - Infections (bacterial/fungal/viral/parasitic and occult-dental)
  - Nutrient deficiencies/excesses
  - Rx Drugs (statins, PPI's,…)
  - Genetic predispositions/snp's
  - More than one cause?



GET THE HISTORY!

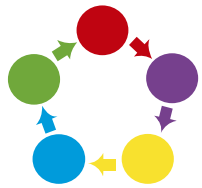
THAT STORY IS TYPICALLY TOLD AS…

- Chief Complaint (CC)
- History of Present Illness (HPI)
- Past Medical History (PMH)
- Family History (FH)
- Dietary History
- Supplement and Medication History
- Lifestyle, Social, and Exercise History
- Physical Exam Findings
- Laboratory Evaluation



CHRONIC CONDITIONS LINKED TO THE PATHOPHYSIOLOGY OF INSULIN RESISTANCE AND HYPERINSULINEMIA

- Cardiovascular disease
- Type 2 diabetes
- Hypertension
- Polycystic ovary syndrome (PCOS)
- Cancer (breast, colon, other)
- Nonalcoholic fatty liver disease (NAFLD) and non-alcoholic steato-hepatitis (NASH)
- Elevated Liver Function (AST/ALT) &/or GGT
- Obstructive sleep apnea
- Inflammation
- Thyroid Problems
- Cushings or Addison's Disease



J Reprod Infertil. 2013 Oct;14(4):197-201.

Assessment of C-reactive Protein and C3 as Inflammatory Markers of Insulin Resistance in Women with Polycystic Ovary Syndrome: A Case-Control Study.

Dehdashtihaghighat S[1], Mehdizadehkashi A[1], Arbabi A[2], Pishgahroudsari M[3], Chaichian S[3].

Author information

Abstract

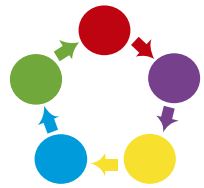
BACKGROUND: Polycystic ovary syndrome (PCOS), a co
menstrual dysfunction, hirsutism and frequent miscarriages.
disorder with increase in inflammatory markers and risk of t
markers, including C-reactive protein and C3 (Complement

METHODS: A case-control study including forty-two wome
forty-two healthy controls, matched for body mass index (BM
and C3 were assessed as possible determinants of the hor
sample t-test was used to compare the means of the groups
glucose) and for CRP, Fasting Insulin and 2 hr Plasma Insul
correlation were used for analyzing the data. The p<0.05 wa

RESULTS: Levels of plasma CRP (p=0.039), 2 hr pp (p=0.045), Fasting Insulin (p=0.002), 2 hr Plasma Insulin (p=0.002) and HOMA index (p=0.002) were significantly higher in PCOS patients. But C3 was not significantly higher in cases (p=0.885). There was no significant correlation between C3 and CRP with HOMA index.

CONCLUSION: CRP increased significantly in patients with PCOS and was associated with insulin resistance, the most probable cause of PCOS. However, such an association was not found in C3.

CRP increased significantly in patients with PCOS and was associated with insulin resistance, the most probable cause of PCOS.



Diabetes Care. 2013 Oct 7. [Epub ahead of print]

Association of Obstructive Sleep Apnea and Glucose Metabolism in Subjects With or Without Obesity.

Kim NH, Cho NH, Yun CH, Lee SK, Yoon DW, Cho HJ, Ahn JH, Seo JA, Kim SG, Choi KM, Baik SH, Choi DS, Shin C.

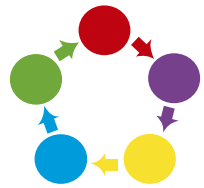
Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Ansan, Korea.

Abstract

OBJECTIVEThe purpose of this study was to investigate whether the impact of obstructive sleep apnea (OSA) on glucose metabolism was different according to the presence or absence of obesity.RESEARCH DESIGN AND METHODSA total of 1,344 subjects >40 years old from the Korean Genome and Epidemiology Study were included. OSA was detected by home portable slee monitoring. Plasma glucose, HbA_{1c}, and insulin resistance were compared according to OSA and obesity status. The associations between OSA and impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG + IGT, and diabetes were evaluated in subjects with and without obesity after adjusting for several confounding variables. The effect of visceral obesity on this association was evaluated in 820 subjects who underwent abdominal computed tomography scanning.RESULTSIn subjects without obesity, fasting glucose, 2-h gluco
controlling for age, sex, a
IFG + IGT and diabetes a
IFG + IGT and diabetes, r
obesity, none of the abno
nonobese individuals is s
diabetes and cardiovascu

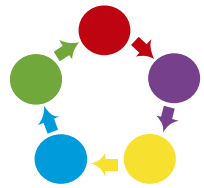
PMID: 24101695 [PubMed -

The presence of OSA in nonobese individuals is significantly associated with impaired glucose metabolism, which can be responsible for future risk for diabetes and cardiovascular disease.



Stoll BA. Upper abdominal obesity, insulin resistance and breast cancer risk. Int J Obes Relat Metab Disord, 2002. 26(6): p. 747-53.

- The higher breast cancer risk associated with greater abdominal visceral obesity may be related to aberrant insulin signaling leading to insulin resistance, hyperinsulinemia and increased concentrations of endogenous estrogen and androgen.
- Overall adiposity in women adversely affects breast cancer risk mainly by greater exposure of mammary epithelial tissue to endogenous estrogen.



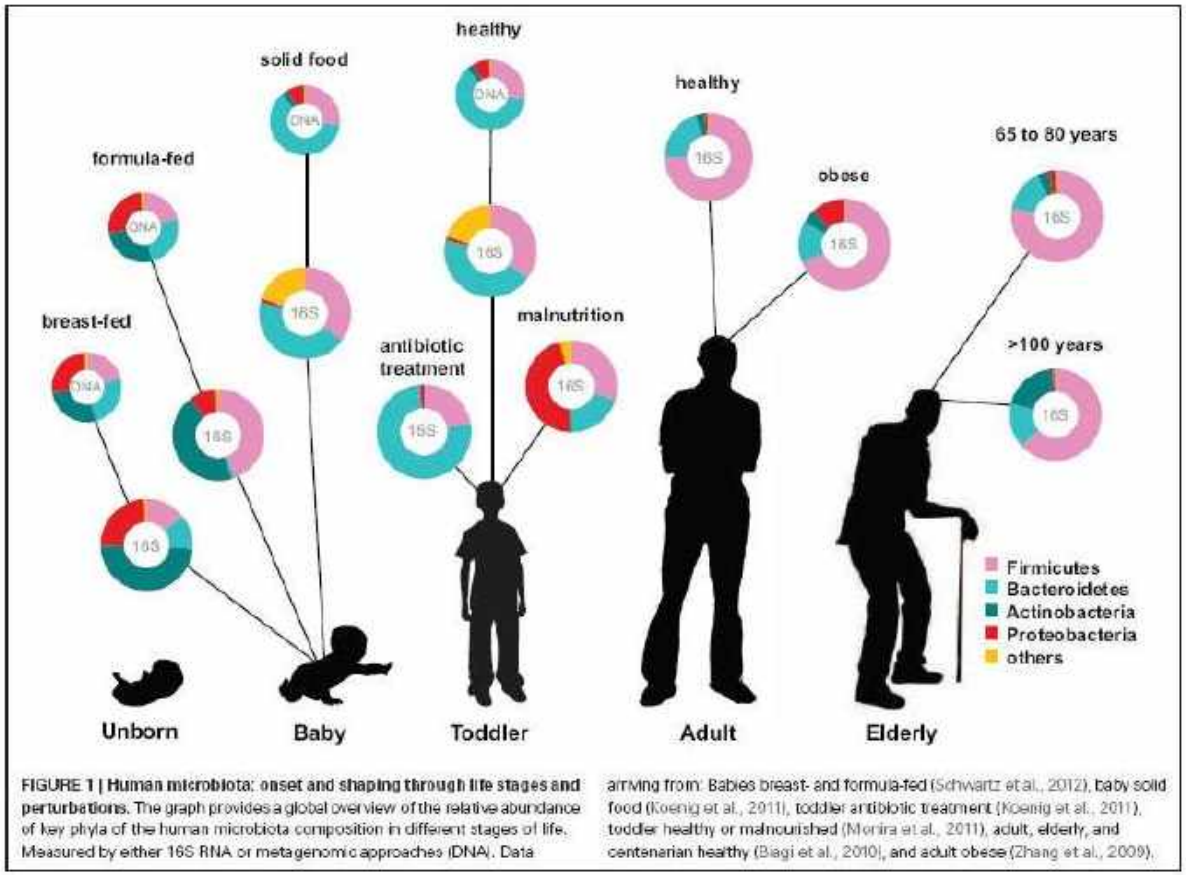
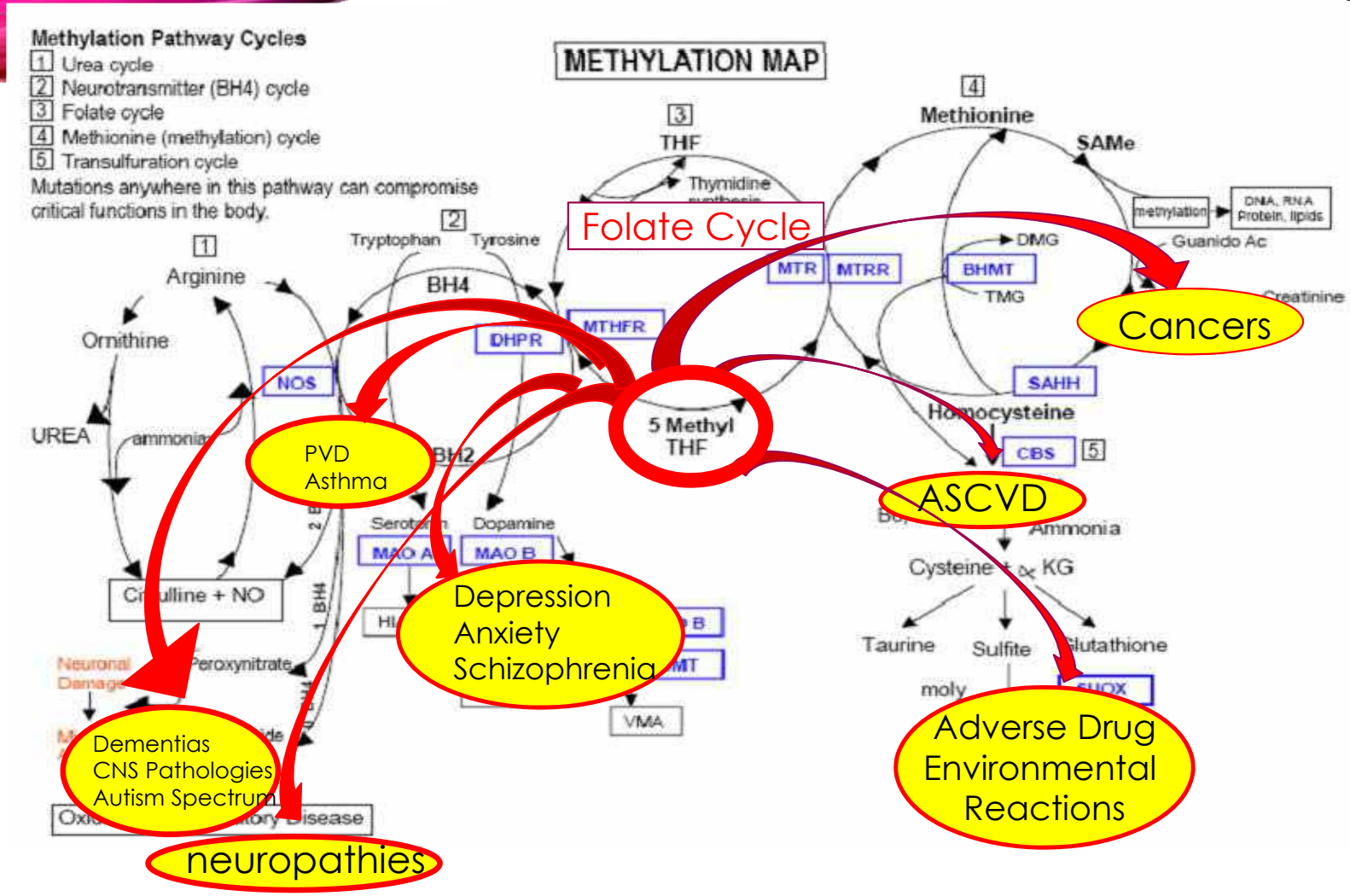


FIGURE 1 | Human microbiota: onset and shaping through life stages and perturbations. The graph provides a global overview of the relative abundance of key phyla of the human microbiota composition in different stages of life. Measured by either 16S RNA or metagenomic approaches (DNA). Data arriving 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).

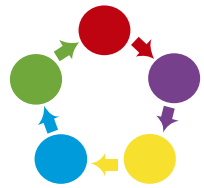
Noora Ottman et al. The function of our microbiota: who is out there and what do they do? Frontiers in Cellular and Infection Microbiology. Aug 2012, (2). 104

B-Vitamin Status and Methylation



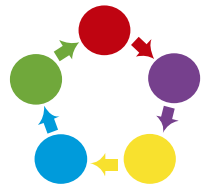
HISTORY OF DIGESTION/GUT FUNCTION

- Flatulence
  - Timing with meals
- GERD
- Food particles on stool
- Constipation
- Diarrhea
- Abdominal Pain
- Dyspepsia



YUN JW, CHO YK, PARK JH, KIM HJ, PARK DI, SOHN CI, JEON WK, KIM BI ABNORMAL GLUCOSE TOLERANCE IN YOUNG MALE PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE. LIVER INT. 2009 APR;29(4):525-9.

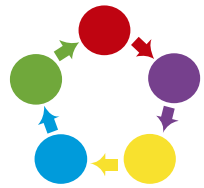
- Non-alcoholic fatty liver disease (NAFLD), the commonest liver problem in the Western world can be seen in patients with insulin resistance, metabolic syndrome and pre-diabetes.



NAFLD/NASH

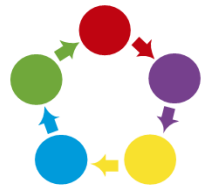
- NAFLD is the most common cause of elevated LFT's without clinical symptoms. Insulin Resistance is the cause of NAFLD.

- 1/3 of NAFLD cases progress to NASH and 20-25% of NASH cases go on to cirrhosis.



HOW DID THIS PERSON DEVELOP INSULIN RESISTANCE?

- Consider the Following:
  - Food allergies and/or sensitivities
  - Dysbiosis, leaky gut and gut microbiota
  - Toxins (POP's, heavy metals, pesticides, endogenous)
  - EMF/Dirty Electricity
  - Food additives or excesses
  - Digestive Insufficiencies
  - Oxidative Stress
  - Mitochondrial dysfunction
  - Obesity
  - Stress or adrenal fatigue/dysfunction
  - Lack of sleep
  - Hormone imbalances
  - Infections (bacterial/fungal/viral/parasitic and occult-dental)
  - Nutrient deficiencies/excesses
  - Rx Drugs (statins, PPI's,…)
  - Genetic predispositions/snp's
  - More than one cause?



Exp Clin Endocrinol Diabetes. 2008 Apr;116(4):241-5. Epub 2007 Dec 10.

IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles.

Wilders-Truschnig M[1], Mangge H, Lieners C, Gruber H, Mayer C, März W.

Author information

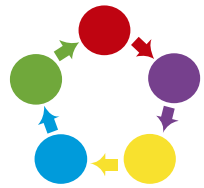
Abstract

OBJECTIVE: Systemic low grade inflammation may contribute to the development of obesity, insulin resistance, diabetes mellitus and atherosclerotic vascular disease. Food intolerance reflected by immunoglobulin G (IgG) antibodies may predispose to low grade inflammation and atherogenesis. We examined the relationship between IgG antibodies specific for food components, low grade inflammation and early atherosclerotic lesions in obese and normal weight juveniles.

RESEARCH METHODS AND PROCEDURES: We determined IgG antibodies directed against food antigens, C-reactive protein (CRP) and the thickness of the intima media layer (IMT) of the carotid arteries in 30 obese children and in 30 normal weight children.

RESULTS: Obese juveniles showed a highly significant increase in IMT (p=0.0001), elevated CRP values (p=0.0001) and anti-food IgG antibody concentrations (p=0.0001) compared to normal weight juveniles. Anti-food IgG showed tight correlations with CRP (p=0.001/r=0.546) and IMT (p=0.0001/r=0.513) and sustained highly significant in a multiple regression model.

DISCUSSION: We show here, that obese children have significantly higher IgG antibody values directed against food antigens than normal weight children. Anti- food IgG antibodies are tightly associated with low grade systemic inflammation and with the IMT of the common carotid arteries. These findings raise the possibility, that anti-food IgG is pathogenetically involved in the development of obesity and atherosclerosis.

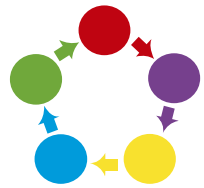


Six Months of Gluten-Free Diet Do Not Influence Autoantibody Titers, but Improve Insulin Secretion in Subjects at High Risk for Type 1 Diabetes

MATTEO-ROCCO PASTORE, ELENA BAZZIGALUPPI, CRISTINA BELLONI, CLAUDIA ARCOVIO, EZIO BONIFACIO, AND EMANUELE BOSI

Internal Medicine, Diabetes and Endocrinology Unit, San Raffaele Vita-Salute University Hospital and Scientific Institute, 20132 Milan, Italy

Removal of gluten from the diet can attenuate the intensity of autoimmunity and reduces the incidence of diabetes in the nonobese diabetic mouse. In this study, we tested whether a gluten-free diet could reduce autoimmunity in human preclinical type 1 diabetes. A trial consisting of 6 months of a gluten-free diet followed by another 6 months of normal gluten-containing diet was performed in 17 first-degree relatives with at least 2 antibodies among islet cell antibodies, glutamic acid decarboxylase autoantibodies, protein tyrosine islet antigen-2 autoantibodies, and insulin autoantibodies. Treatment effect was measured as autoantibody titers and acute insulin response to iv glucose tolerance test. Two subjects dropped out for lack of compliance to diet restrictions. Of the remaining 15 subjects, 3 developed diabetes. Autoantibody titers did not show significant changes after 6 months of gluten-free diet and again after return to normal diet. Acute insulin response to iv glucose tolerance test significantly increased in 12 of 14 subjects after the first 6 months of gluten deprivation ($P = 0.04$) and decreased in 10 of 13 subjects during the following 6-month period of normal diet ($P = 0.07$). Insulin sensitivity (homeostasis model assessment-insulin resistance) nonsignificantly improved after the gluten-free diet and subsequently decreased ($P < 0.005$) after 6 months of normal diet. These findings indicate that 6 months of gluten deprivation do not influence humoral autoimmunity, but may have a beneficial effect on preservation of β-cell function in subjects at risk for type 1 diabetes. (*J Clin Endocrinol Metab* 88: 162–165, 2003)



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

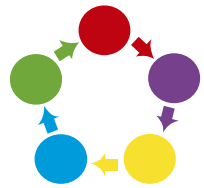
Artificial sweeteners induce glucose intolerance by altering the gut microbiota.

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.



OPEN ACCESS Freely available online

PLOS ONE

Low-Dose Aspartame Consumption Differentially Affects Gut Microbiota-Host Metabolic Interactions in the Diet-Induced Obese Rat

Marie S. A. Palmnäs[1,2*], Theresa E. Cowan[3], Marc R. Bomhof[3], Juliet Su[2], Raylene A. Reimer[1,3], Hans J. Vogel[1,2], Dustin S. Hittel[1,3], Jane Shearer[1,3]

1 Department of Biochemistry and Molecular Biology, University of Calgary, Calgary, Alberta, Canada, 2 Department of Biological Sciences, University of Calgary, Calgary, Alberta, Canada, 3 Faculty of Kinesiology, University of Calgary, Calgary, Alberta, Canada

Abstract

Aspartame consumption is implicated in the development of obesity and metabolic disease despite the intention of limiting caloric intake. The mechanisms responsible for this association remain unclear, but may involve circulating metabolites and the gut microbiota. Aims were to examine the impact of chronic low-dose aspartame consumption on anthropometric, metabolic and microbial parameters in a diet-induced obese model. Male Sprague-Dawley rats were randomized into a standard chow diet (CH, 12% kcal fat) or high fat (HF, 60% kcal fat) and further into *ad libitum* water control (W) or low-dose aspartame (A, 5–7 mg/kg/d in drinking water) treatments for 8 week (n = 10–12 animals/treatment). Animals on aspartame consumed fewer calories, gained less weight and had a more favorable body composition when challenged with HF compared to animals consuming water. Despite this, aspartame elevated fasting glucose levels and an insulin tolerance test showed aspartame to impair insulin-stimulated glucose disposal in both CH and HF, independently of body composition. Fecal analysis of gut bacterial composition showed aspartame to increase total bacteria, the abundance of *Enterobacteriaceae* and *Clostridium leptum*. An interaction between HF and aspartame was also observed for *Roseburia* spp wherein HF-A was higher than HF-W ($P<0.05$). Within HF, aspartame attenuated the typical HF-induced increase in the Firmicutes:Bacteroidetes ratio. Serum metabolomics analysis revealed aspartame to be rapidly metabolized and to be associated with elevations in the short chain fatty acid propionate, a bacterial end product and highly gluconeogenic substrate, potentially explaining its negative affects on insulin tolerance. How aspartame influences gut microbial composition and the implications of these changes on the development of metabolic disease require further investigation.

Citation: Palmnäs MSA, Cowan TE, Bomhof MR, Su J, Reimer RA, et al. (2014) Low-Dose Aspartame Consumption Differentially Affects Gut Microbiota-Host Metabolic Interactions in the Diet-Induced Obese Rat. PLoS ONE 9(10): e109841. doi:10.1371/journal.pone.0109841

Editor: Michael Müller, University of East Anglia, United Kingdom

Received: June 20, 2014; Accepted: August 28, 2014; Published: October 14, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Funding: Research was funded by a National Science and Engineering Council of Canada Discovery Grant. H. J. V. currently holds the Lance Armstrong Chair for Molecular Cancer Research. J. S. is an Alberta Innovates Health Solutions Scholar. 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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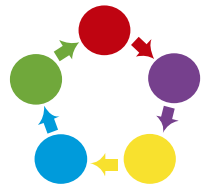
Introduction

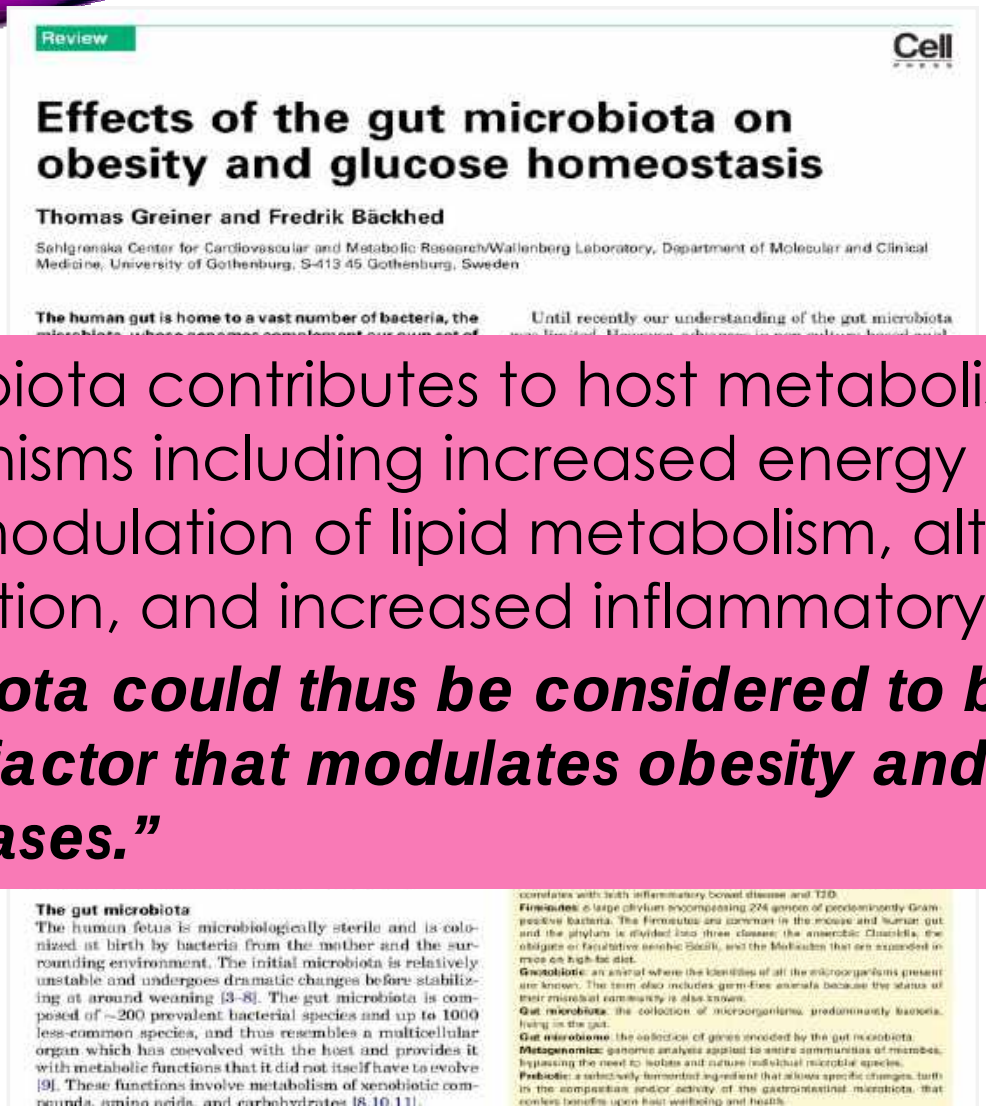
Regular consumption of artificially sweetened soft drinks is associated with disorders of the metabolic syndrome, including abdominal obesity, insulin resistance and/or impaired glucose tolerance, dyslipidemia and high blood pressure [1–3]. In particular, daily diet soda consumption (primarily sweetened with N-a-L-aspartyl-L-phenylalanine methyl ester, aspartame; APM), is reported to increase the relative risk of type 2 diabetes and the metabolic syndrome by 67% and 36% respectively [3]. Given this data, and the presence of APM in over 6000 food products, there is a need to understand the potential role of APM sweetened products in the development and maintenance of metabolic disease [4].

Emerging evidence on the gut microbiome suggests that metabolic diseases, such as type 2 diabetes, are associated with an altered gut microbiota profile [5,6]. The gut microbiome plays an important role in metabolism and caloric extraction from dietary sources. It is highly complex and one of the most diverse ecosystems, with over 50 phyla identified [7,8]. Alterations in the proportions of the two phyla that make up ~90% of the human gut microbiome, Firmicutes and Bacteroidetes, have been linked to obesity, type 2 diabetes and systemic inflammation [8–10] with the majority of studies reporting increases in the abundance of Firmicutes and reductions in Bacteroidetes compared to lean individuals [5–7,11]. Compositional and functional changes in the microbiome are also manifested as alterations of metabolite concentrations in the blood. Microbial metabolites appearing in serum consist of metabolic intermediates, organic acids and bacterial fermentation end products including the short chain fatty acids (SCFA) [12–14].

Aims of the present study were to examine the interaction of chronic low-dose APM on anthropometric, metabolic, metabolomic and gut microbiota profiles. As observational data in humans cannot show causality, we examined an animal model

Serum metabolomics analysis revealed aspartame to be rapidly metabolized and to be associated with elevations in the short chain fatty acid propionate, a bacterial end product and highly gluconeogenic substrate, potentially explaining its negative affects on insulin tolerance.





Review

Cell

Effects of the gut microbiota on obesity and glucose homeostasis

Thomas Greiner and Fredrik Bäckhed

Sahlgrenska Center for Cardiovascular and Metabolic Research/Wallenberg Laboratory, Department of Molecular and Clinical Medicine, University of Gothenburg, S-413 45 Gothenburg, Sweden

The human gut is home to a vast number of bacteria, the

Until recently our understanding of the gut microbiota

The gut microbiota

The human fetus is microbiologically sterile and is colonized at birth by bacteria from the mother and the surrounding environment. The initial microbiota is relatively unstable and undergoes dramatic changes before stabilizing at around weaning [3–8]. The gut microbiota is composed of ~200 prevalent bacterial species and up to 1000 less-common species, and thus resembles a multicellular organ which has coevolved with the host and provides it with metabolic functions that it did not itself have to evolve [9]. These functions involve metabolism of xenobiotic compounds, amino acids, and carbohydrates [8,10,11].

correlates with both inflammatory bowel disease and T2D.

Firmicutes: a large phylum encompassing 274 genera of predominantly Gram-positive bacteria. The Firmicutes are common in the mouse and human gut and the phylum is divided into three classes: the anaerobic Clostridia, the obligate or facultative aerobic Bacilli, and the Mollicutes that are expanded in mice on high-fat diet.

Gnotobiotic: an animal where the identities of all the microorganisms present are known. The term also includes germ-free animals because the status of their microbial community is also known.

Gut microbiota: the collection of microorganisms, predominantly bacteria, living in the gut.

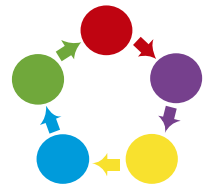
Gut microbiome: the collection of genes encoded by the gut microbiota.

Metagenomics: genome analysis applied to entire communities of microbes, bypassing the need to isolate and culture individual microbial species.

Prebiotic: a selectively fermented ingredient that allows specific changes, both in the composition and/or activity of the gastrointestinal microbiota, that confers benefits upon host wellbeing and health.

"The gut microbiota contributes to host metabolism by several mechanisms including increased energy harvest from the diet, modulation of lipid metabolism, altered endocrine function, and increased inflammatory tone.

The gut microbiota could thus be considered to be an environmental factor that modulates obesity and other metabolic diseases."



MECHANISMS IN ENDOCRINOLOGY

Gut microbiota in patients with type 2 diabetes mellitus

Kristine H Allin, Trine Nielsen and Oluf Pedersen

The Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 1, DK-2100 Copenhagen Ø, Denmark

Correspondence should be addressed to O Pedersen
Email: oluf@sund.ku.dk

Abstract

Perturbations of the composition and function of the gut microbiota have been associated with metabolic disorders including obesity, insulin resistance and type 2 diabetes. Studies on mice have demonstrated several underlying mechanisms including host signalling through bacterial lipopolysaccharides derived from the outer membranes of Gram-negative bacteria, bacterial fermentation of dietary fibres to short-chain fatty acids and bacterial modulation of bile acids. On top of this, an increased permeability of the intestinal epithelium may lead to increased absorption of macromolecules from the intestinal content resulting in systemic immune responses, low-grade inflammation and altered signalling pathways influencing lipid and glucose metabolism. While mechanistic studies on mice collectively support a causal role of the gut microbiota in metabolic diseases, the majority of studies in humans are correlative of nature and thus hinder causal inferences. Importantly, several factors known to influence the risk of type 2 diabetes, e.g. diet and age, have also been linked to alterations in the gut microbiota complicating the interpretation of correlative studies. However, based upon the available evidence, it is hypothesised that the gut microbiota may mediate or modulate the influence of lifestyle factors triggering development of type 2 diabetes. Thus, the aim of this review is to critically discuss the potential role of the gut microbiota in the pathophysiology and pathogenesis of type 2 diabetes.

European Journal of Endocrinology (2015) 172, R167–R177

Introduction

In addition to well-established risk factors for type 2 diabetes, including genetic predisposition, poor physical activity, foetal programming and obesity (1), an altered configuration of the microbial community in our gut – the microbiota – has emerged as a new candidate that may be linked to type 2 diabetes. Trillions of micro-organisms inhabit the distal gut, where they together weigh about 1.5 kg and may be regarded as a microbial organ that carries out key functions that the human host is incapable to perform by itself. The gut microbiota includes members from all three domains of life (Bacteria, Archaea and Eukarya) as well as their viruses, but is dominated by anaerobic bacteria. More than 90% of the ~1000 prevalent bacterial species (2) can be grouped into the two

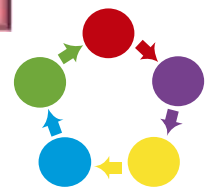
Invited Author's profile

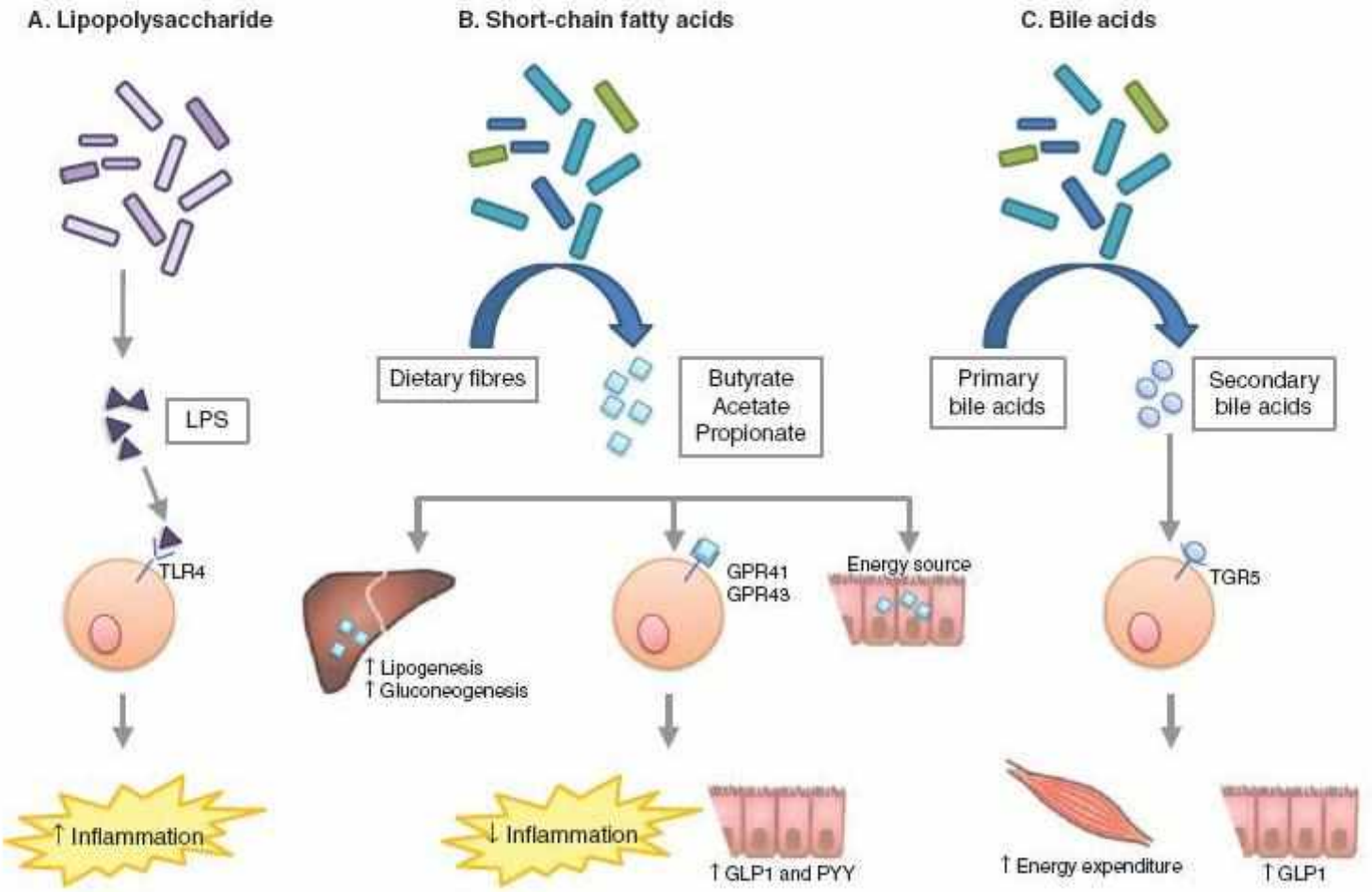
Oluf Pedersen is Professor of Molecular Metabolism at the University of Copenhagen (UCPH). He is also director at the Novo Nordisk Foundation Center for Basic Metabolic Research at UCPH. Prof Pedersen and his team are focused on discovering genomic variation that predisposes for common and rare cardio-metabolic disorders. Another major research effort is centred at studies of the role of the gut microbiota in metabolic health. Herein, the research team is doing quantitative metagenomics to characterise the human gut microbiome at levels of microbial genes, various taxa and derived functional potentials.

www.eje-online.org
DOI: 10.1530/EJE-14-0874

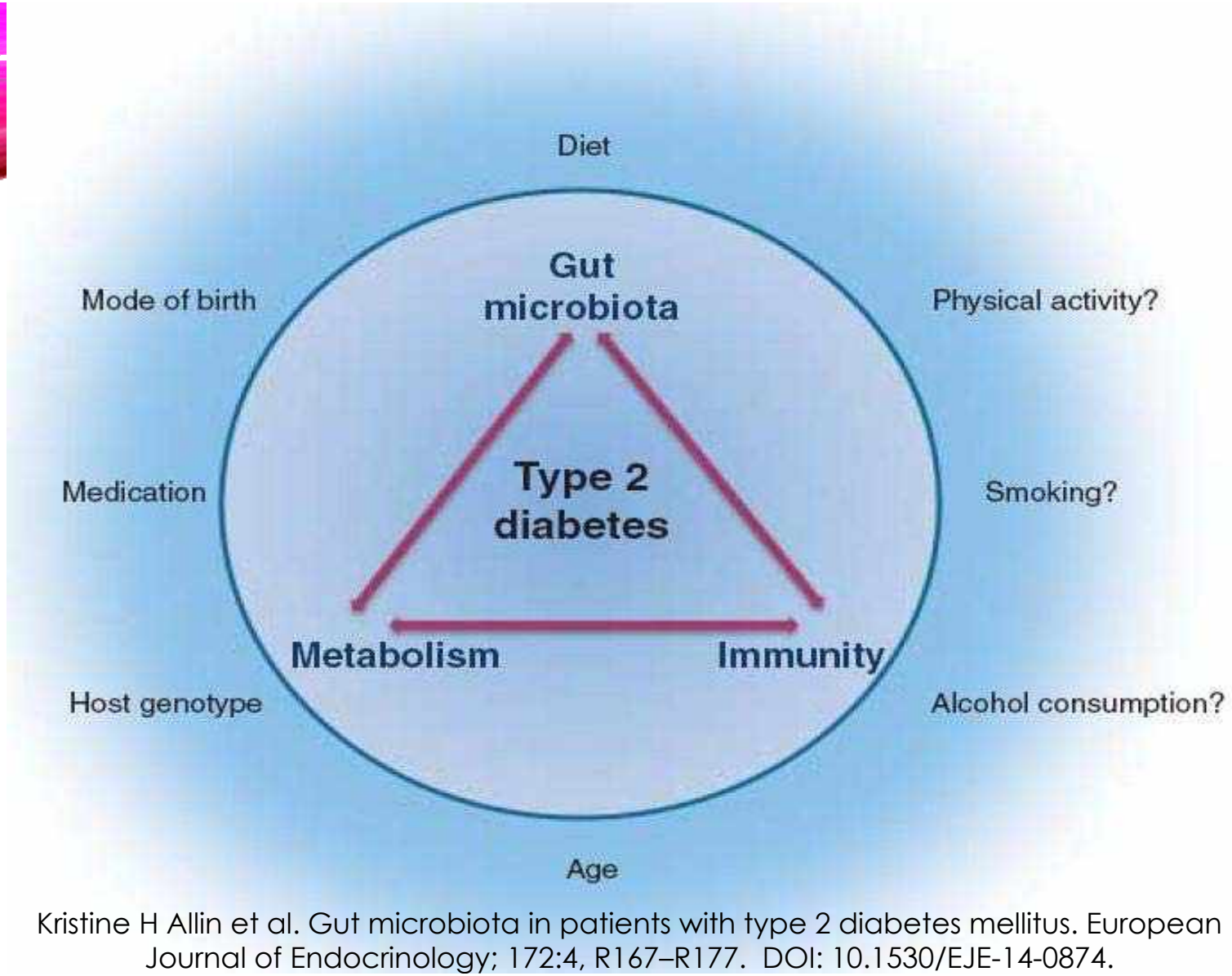
Published by Bioscientifica Ltd.

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





Kristine H Allin et al. Gut microbiota in patients with type 2 diabetes mellitus. European Journal of Endocrinology; 172:4, R167–R177.



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Review | K H Allin and others | Gut microbiota in T2DM | 172:4 | R167–R177

MECHANISMS IN ENDOCRINOLOGY

Gut microbiota in patients with type 2 diabetes mellitus

Kristine H Allin, Trine Nielsen and **Oluf Pedersen**

The Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, Faculty of Health

Correspondence should be addressed to O Pedersen
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"The collective evidence as of today suggests that the gut microbiota may in fact act as an important mediator of a number of environmental factors triggering common diseases including type 2 diabetes."

"One may envision that, in the future, the effect of the 'minimal microbiota' administered as slow-release encapsulated microbial cultures may be tested in randomised clinical trials together with a healthy diet also rich in natural prebiotics."

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

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

Received 6 October 2010; revised 8 November 2010; accepted 12 November

Summary

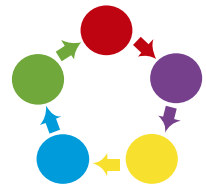
Diabetes mellitus is a chronic disease requiring lifelong medical attention. With hundreds of millions suffering worldwide, and a rapidly rising incidence, diabetes mellitus poses a great burden on healthcare systems. Recent studies investigating the underlying mechanisms involved in disease development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

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.

(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 type 2 diabetes mellitus has dramatically increased, resulting from changes in diet, reduced physical activities and exposure to certain environmental factors described in the 'hygiene' and 'overload' hypotheses (2). Certainly, as type 1 and type 2 diabetes are multifactorial diseases, genetic factors consisting of multiple susceptibility genes as well as environmental influences contribute to disease development. In a number of countries, type 2 diabetes mellitus has become the most prevalent type of diabetes in children (3). The dramatic rise in prevalence will have impact on the

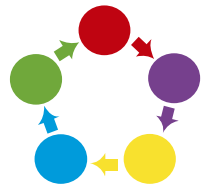
disease, stroke and diabetes (1).

Diabetes affects the gut: there is ample evidence that diabetes mellitus affects gastrointestinal morphology and function. Conversely, *the gut affects diabetes*: several recent publications provide evidence that an altered bowel function contributes to the pathogenesis of diabetes mellitus. In this respect, the intestinal barrier is particularly relevant with focus on intestinal permeability (IP), immune response and intestinal microbiota. Intestinal barrier function is compromised in various gastrointestinal disorders such as inflammatory bowel disease, celiac disease, non-alcoholic steatohepatitis/non-alcoholic fatty liver disease (NASH/NAFLD) and irritable bowel disease, but also in autoimmune and systemic diseases (4). This review explores the



GUT MICROBIOTA AND INCREASED PERMEABILITY OF INTESTINAL EPITHELIUM

- Increased gut permeability-leading to
  - Increased absorption of macromolecules from the intestinal content resulting in systemic immune responses
  - Low grade inflammation
  - Altered signaling pathways influencing lipid and glucose metabolism



Reducing Childhood Obesity by Eliminating 100% Fruit Juice

Janet M. Wojcicki, PhD, MPH, and Melvin B. Heyman, MD, MPH

The Healthy Hunger-Free Kids Act of 2010 presents an opportunity to change the nutritional quality of foods served in low-income child-care centers, including Head Start centers.

Excessive fruit juice consumption is associated with increased risk for obesity. Moreover, there is recent scientific evidence that sucrose consumption without the corresponding fiber, as is commonly present in fruit juice, is associated with the metabolic syndrome, liver injury, and obesity.

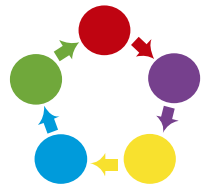
Given the increasing risk of obesity among preschool children, we recommend that the US Department of Agriculture's Child and Adult Food Care Program, which manages the meal patterns in childcare centers such as Head Start, promote the elimination of fruit juice in favor of whole fruit for children. (*Am J Public Health*. 2012; 102:1630–1633. doi:10.2105/

CHILDHOOD OBESITY HAS reached epidemic proportions in the United States. By age four, 18.4% of all children are obese, with a body mass index (BMI; defined as weight in kilograms divided by height in meters squared) in the 95th percentile or greater for age and gender. There is an even greater prevalence among Hispanic (22.0%), American Indian or Alaska Native (31.2%), and non-Hispanic Black children (20.8%) than among non-Hispanic White children.[1] Among older children, the greatest increase in the prevalence of obesity has been in those in low-education, -income, and -employment households that have sustained increases from 22% to 33% from 2003 to 2008.[2] Per capita daily caloric intake increases in beverages, particularly sugar-sweetened beverages and 100% fruit juices, parallel the surge in childhood obesity. This necessitates a more aggressive approach, for example, to limit high caloric beverages such as 100% fruit juice, particularly among young children, who are first developing eating behaviors and practices.

A unique opportunity to reshape the eating and drinking habits of high-risk US children presents itself in the forms of the Child Nutrition and WIC Reauthorization Act and the Healthy, Hunger-Free Kids Act.[6] The Healthy, Hunger-Free Kids Act is designed to target the nutritional health of high-risk, low-income children younger than five years, including those participating in the Child and Adult Food Care Program (CAFCP), which includes Head Start and other low-income daycare centers. The US Department of Agriculture (USDA) is mandated to develop, as early as fall 2013, updated meal patterns also parallel the act's mandate that only low-fat milk options be served to children older than two years, that water be made readily available and accessible,[7] and that CAFCP programs adhere to the limits placed on 100% fruit juice by professional organizations and institutes in the past 10 years.

PRESCHOOL CHILDREN'S INCREASED FRUIT JUICE CONSUMPTION

US children have increasing per capita daily caloric contribution from sweetened beverages and 100% fruit juice.[3] Toddlers and young children have the highest consumption of fruit juice of all age groups in the United States.[8] Fruit juices and flavored drinks are the second and third largest contributors to energy intake among toddlers.[9] Total consump-



Przegl Lek. 2012;69(4):157-62.

[Carbohydrate sweeteners and obesity].

[Article in Polish]

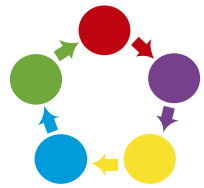
Wystrychowski G[1], Zukowska-Szczechowska E, Obuchowicz E, Grzeszczak W, Wystrychowski A.

Author information

Abstract

The U.S. prevalence of obesity increases since the mid-70s of the 20th century. Around that time high-fructose corn syrup (HFCS)--mixture of fructose and glucose was introduced as a sweetener replacing sucrose in the food production. HFCS containing 55% fructose and 42-45% glucose (HFCS55) has dominated the American soft drink industry and HFCS has recently become commonly used in Poland. The coincidence of HFCS introduction and obesity epidemic raised widely publicized suspicions of a causal relationship between the two. As a possible mechanism, a higher content of fructose in the HFCS55, as compared with sucrose was suggested -fructose is known to increase serum uric acid level, induce hepatic lipogenesis and not stimulate postprandial hyperinsulinemia, a main activator of leptin release. Few comparative studies of HFCS and sucrose have largely failed to reveal any different impacts on the metabolic parameters, yet they were mainly short-term. It has been recently shown that obesity is linked with changes in the intenstinal flora. Among the causes of allegedly different effects of sucrose and HFCS on metabolism, their influence on the gut microbiome has not been examined. Some bacterial types do not hydrolyze sucrose which may determine different compositions of gut flora with the use of both sweeteners. Studies involving quantitative analysis of bacterial DNA in the stool, both in animals and in humans, shall shed light on the issue that has recently so much absorbed the U.S. public opinion.

PMID: 23029710 [PubMed - indexed for MEDLINE]



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Hindawi

Review Article

Mitochondrial Dysfunction in Metabolic Syndrome and Asthma

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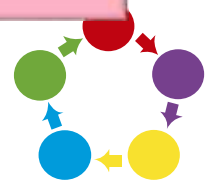
Academic Editor: Anurag

"…mitochondrial dysfunction is the common factor for most of the risk factors of metabolic syndrome, such as central obesity, dyslipidemia, hypertension, insulin resistance, and type 2 diabetes…"

Though severe or refractory asthma merely affects less than 10% of asthma population, it consumes significant health resources and contributes significant morbidity and mortality. Severe asthma does not fell in the routine definition of asthma and requires alternative treatment strategies. It has been observed that asthma severity increases with higher body mass index. The obese-asthmatics, in general, have the features of metabolic syndrome and are progressively causing a significant burden for both developed and developing countries thanks to the westernization of the world. As most of the features of metabolic syndrome



Review

All *EHP* content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1205502.

Evaluation of the Association between Persistent Organic Pollutants (POPs) and Diabetes in Epidemiological Studies: A National Toxicology Program Workshop Review

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Background: Diabetes is a major threat to public health in the United States and worldwide. Understanding the role of environmental chemicals in the development or progression of diabetes is an emerging issue in environmental health.

Objective: We assessed the epidemiologic literature for evidence of associations between persistent organic pollutants (POPs) and type 2 diabetes.

Methods: Using a PubMed search and reference lists from relevant studies or review articles, we identified 72 epidemiological studies that investigated associations of persistent organic pollutants (POPs) with diabetes. We evaluated these studies for consistency, strengths and weaknesses of study design (including power and statistical methods), clinical diagnosis, exposure assessment, study population characteristics, and identification of data gaps and areas for future research.

Conclusions: Heterogeneity of the studies precluded conducting a meta-analysis, but the overall evidence is sufficient for a positive association of some organochlorine POPs with type 2 diabetes. Collectively, these data are not sufficient to establish causality. Initial data mining revealed that the strongest positive correlation of diabetes with POPs occurred with organochlorine compounds, such as *trans*-nonachlor, dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs), and dioxins and dioxin-like chemicals. There is less indication of an association between other nonorganochlorine POPs, such as perfluoroalkyl acids and brominated compounds, and type 2 diabetes. Experimental data are needed to confirm the causality of these POPs, which will shed new light on the pathogenesis of diabetes. This new information should be considered by governmental bodies involved in the regulation of environmental contaminants.

Key words: chemically induced, diabetes, environment, epidemiology, glucose, hormone, insulin, metabolic syndrome, obesity, persistent organic pollutants, pollution, toxicology.

Environ Health Perspect 121:774–783 (2013). http://dx.doi.org/10.1289/ehp.1205502 [Online 7 May 2013]

Diabetes Association 2011; Knowler et al. 2002). Recently, T2D is being diagnosed in individuals earlier in life, including adolescents (NIDDK 2011). Given the number of people impacted by the disease, an estimated 346 million people worldwide (WHO 2011), and the long-term consequences of diabetes in terms of morbidity, mortality, and economic costs, there is considerable interest in understanding the contribution of "nontraditional" risk factors, such as environmental chemicals, to the diabetes epidemic. Environmental exposures that have been linked to diabetes in at least some study populations include persistent organic pollutants (POPs), arsenic, bisphenol A, phthlatates, organotins, nonpersistent pesticides (Thayer et al. 2012), and air pollution (Coogan et al. 2012; Hathout et al. 2006; Krämer et al. 2010; O'Neill et al. 2007; Pearson et al. 2010).

Over the past several years, research addressing the role of environmental chemicals

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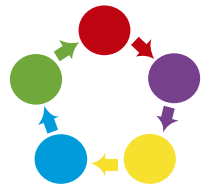


in T2D has rapidly expanded. The February 2011 Diabetes Strategic Plan (NIDDK 2011) acknowledged the growing science base in this area and cited the need to understand more about the role of environmental exposures as part of future research and prevention strategies. To help develop such a research strategy, the National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS) organized a state-of-the-science workshop in January 2011 titled "Role of Environmental Chemicals in the Development of Diabetes and Obesity" (NTP 2011). The objective of this workshop was to examine the literature for evidence of associations between certain chemicals and obesity or diabetes. Epidemiological studies of associations between diabetes and POPs, particularly the halogenated POPs, were considered at the workshop, along with studies of diabetes in association with arsenic, maternal smoking during pregnancy, bisphenol A, phthalates, organotins, and non-persistent pesticides (Thayer et al. 2012). A wide variety of chemicals were included in the POPs category, including organochlorines [2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), Agent Orange, other non-TCDD polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), and dichlorodiphenyldichloroethane (DDD)]; brominated compounds [polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs)]; and perfluorinated compounds [perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate, and perfluorononanoic acid].

For the present review we evaluated the literature in terms of consistency, strengths and weaknesses (including power and statistical methods) of the clinical diagnosis, exposure assessment, and study population characteristics in order to identify data gaps and areas for future evaluation and research in the area of POPs exposure and diabetes outcomes.

Methods

Literature search. We developed a PubMed (http://www.ncbi.nlm.nih.gov/pubmed) Medical Subject Headings (MeSH)-based and keyword search–based strategy to identify epidemiological studies of POPs exposure (organochlorine, organofluorine, and organobromine compounds) and health outcomes related to T1D, T2D, and childhood obesity [for detailed information on the literature search strategy, see Supplemental Material, pp. 2–3 (http://dx.doi.org/10.1289/ehp.1205502)]. We conducted an initial search on 24 August 2009 and subsequently updated the search through 15 December 2010. Studies of POPs and T2D or diabetes-related outcomes (e.g., metabolic syndrome) in both adults and children were eligible for review. We excluded studies from consideration if they were occupational studies, used death certificates to identify T2D, or did not present original data. Because of time constraints, we formally assessed only studies with T2D as the outcome, excluding studies with metabolic syndrome as the outcome. Our search identified 2,752 publications (after removal of duplicates), 72 of which presented original data on diabetes-related studies (see Supplemental Material, Figure S1). We excluded 28 studies from consideration because the health outcome was not T2D or because the method used to measure exposure or classify T2D was not adequate (see Supplemental Table S1). We considered blood or target tissue levels the most informative exposure measures; however, this information was not always available (e.g., studies of Vietnam veterans). Studies on Vietnam veterans were excluded if they were not specific enough to imply exposure to Agent Orange or TCDD; for example, studies comparing veterans who were in Vietnam with those who were not in Vietnam were excluded because they did not specify exposed versus unexposed veterans. We did not consider occupational studies because exposure may be more targeted depending on the occupation, nor did we consider a study by Anderson-Mahoney et al. (2008) because the population studied comprised plaintiffs involved in a lawsuit filed due to unusually high PFOA levels in drinking water. In addition, we chose to limit the introduction of potential biases that are unique to these studies, such as the healthy worker effect. We also excluded studies that used death certificates to identify diabetes cases because the prevalence of diabetes is underestimated from mortality data. For example, in a U.S.-based study that characterized the sensitivity and specificity of death certificates for diabetes (Cheng et al. 2008), diabetes was listed as a direct or contributing cause of death on only 6.2% of the death certificates for adults who were known to have diabetes.

We identified an additional 17 articles by reviewing the reference lists in the primary literature and review articles, for a total of 43 studies.

Data extraction. NTP Office of Health Assessment and Translation staff extracted the main findings from the included studies [see Supplemental Material, Table S2 (http://dx.doi.org/10.1289/ehp.1205502)]. The identification of the main findings was based on the following strategy:

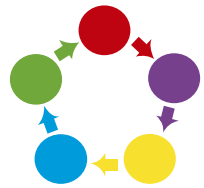
- When a study did not report a statistically significant association (i.e., $p > 0.05$) between POPs exposure and T2D at any exposure level, we extracted the main finding from the highest exposure group compared with the referent group (e.g., fourth quartile vs. first quartile).
- When a study reported a statistically significant association (i.e., $p < 0.05$) between POPs exposure and T2D and that association displayed a monotonic dose response, we extracted the main finding based on the lowest exposure group with a statistically significant association (e.g., third quartile vs. first quartile).
- When associations were nonmonotonic in nature, we identified the main findings on a case-by-case basis and considered any statistical trend analyses that might have been conducted, consistency of the overall pattern across exposure groups, and/or the biological significance of the nonmonotonic finding.

POPs represent a toxicologically diverse range of chemicals, all of which are persistent in the body (i.e., have a long half-life) and the environment. Chemicals are broadly divided into categories based on the halogen group (e.g., chlorinated, fluorinated, brominated). Chemicals in the chlorinated group were further divided into common chemical class designations (i.e., dioxins, PCBs, DDT/DDE/DDD). In assessing the PCB studies, we evaluated both total PCBs and PCB153 together because PCB153 is a major contributor to total PCB exposure and is used as an indicator PCB. PCB153 is often used as a surrogate measure for total PCBs because it is less expensive to measure (Cote et al. 2006; Meeker and Hauser 2010). Assessing patterns of association for individual PCBs across studies is particularly challenging because the class contains 209 structures that are not easy to categorize on the basis of structural similarity and/or biological activity. Even the categorization of "dioxin-like" or "nondioxin-like" is not sufficient because both categories of PCBs are linked to diabetes (Giesy and Kannan 1998; Lee et al. 2006, 2010, 2011a). In general, the findings for individual PCB congeners other than PCB153 are less suggestive for an overall association [see Supplemental Material, Figure S2 (http://dx.doi.org/10.1289/ehp.1205502)] (Codru et al. 2007; Everett et al. 2007; Lee et al. 2010; Patel et al. 2010; Turyk et al. 2009a).

Study quality. We categorized studies into groups on the basis of study design and nature of the exposure: *a*) cohort studies with a prospective or nested case–control design, *b*) cross-sectional studies, *c*) case–control studies, *d*) occupational studies, *e*) ecological studies, *f*) studies of maternal exposure, and *g*) studies of Vietnam veterans.

We included a study for consideration if it identified T2D as the outcome and the exposure measure was deemed adequate. Study quality was evaluated by panel members during workshop deliberations. Aspects of study

…the overall evidence is sufficient for a positive association of some …POPs with type 2 diabetes.



Obes Rev. 2013 Sep 2. doi: 10.1111/obr.12086. [Epub ahead of print]

Persistent organic pollutants meet adipose tissue hypoxia: does cross-talk contribute to inflammation during obesity?

Myre M, Imbeault P.

Behavioral and Metabolic Research Unit, School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada.

Abstract

Lipophilic persistent organic pollutants (POPs) accumulate in lipid-rich tissues such as human adipose tissue. This is particularly problematic in individuals with excess adiposity, a physiological state that may be additionally characterized by local adipose tissue hypoxia. Hypoxic patches occur when oxygen diffusion is insufficient to reach all hypertrophic adipocytes. POPs and hypoxia independently contribute to the development of adipose tissue-specific and systemic inflammation often associated with obesity. Inflammation is induced by increased proinflammatory mediators such as tumour necrosis factor-alpha, interleukin-6, and monocyte chemotactic protein-1, as well as reduced adiponectin release, an anti-inflammatory and insulin-sensitizing adipokine. The aryl hydrocarbon receptor (AhR) mediates the cellular response to some pollutants, while hypoxia responses occur through the oxygen-sensitive tra
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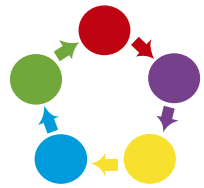
through the AhR and HIF-1 signalling pathways remains to be tested.

"POPs and hypoxia independently contribute to the development of adipose tissue-specific and systemic inflammation often associated with obesity".



Environ Res. 2015 Jan 23;137C:419-423. doi: 10.1016/j.envres.2015.01.010. [Epub ahead of print]

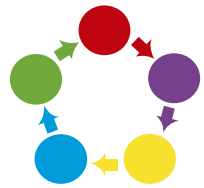
Urinary phthalate metabolites are associated with insulin resistance in obese subjects.

Dirinck E[1], Dirtu AC[2], Geens T[2], Covaci A[2], Van Gaal L[3], Jorens PG[4].

Author information

Abstract

Phthalates are potentially involved in the development of type 2 diabetes mellitus. In a cohort of 123 obese subjects, 10 phthalate metabolites were analyzed. An oral glucose tolerance test was performed and various estimates of insulin resistance and beta-cell function were calculated. After adjustment for age, physical activity level, smoking behavior, medication use and body mass index, several phthalate metabolites were linked to markers of glucose tolerance and insulin resistance.



Environ Health Perspect. 2013 Aug;121(8):906-11. doi: 10.1289/ehp.1206113. Epub 2013 May 13.

Diabetes, metabolic syndrome, and obesity in relation to serum dioxin concentrations: the Seveso women's health study.

Warner M, Mocarelli P, Brambilla P, Wesselink A, Samuels S, Signorini S, Eskenazi B.

Center for Environmental Research and Children's Health, School of Public Health, University of California, Berkeley, Berkeley, CA 94720, USA. mwarner@berkeley.edu

Abstract

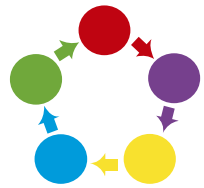
BACKGROUND: In animal studies, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters glucose transport and increases serum lipid levels and blood pressure. Epidemiologic evidence suggests an association between TCDD and metabolic disease.

OBJECTIVES: On 10 July 1976, a chemical explosion in Seveso, Italy, resulted in the highest known residential exposure to TCDD. Using data from the Seveso Women's Health Study (SWHS), a cohort study of the health of the women, we examined the relation of serum TCDD to diabetes, metabolic syndrome, and obesity > 30 years later.

METHODS: In 1996, we enrolled 981 women who were newborn to 40 years of age in 1976 and resided in the most contaminated areas. Individual TCDD concentration was measured in archived serum that had been collected soon after the explosion. In 2008, 833 women participated in a follow-up study. Diabetes was classified based on self-report or fasting serum glucose and glycated hemoglobin levels. Metabolic syndrome was defined by International Diabetes Federation criteria. Obesity was defined as body mass index ≥ 30 kg/m2.

RESULTS: A 10-fold increase in serum TCDD (log10TCDD) was not associated with diabetes (adjusted hazard ratio = 0.76; 95% CI: 0.45, 1.28) or obesity [adjusted odds ratio (OR) = 0.80; 95% CI: 0.58, 1.10]. Log10TCDD was associated with metabolic syndrome, but only among women who were ≤ 12 years of age at the time of the explosion (adjusted OR = 2.03; 95% CI: 1.25, 3.29; pinteraction = 0.01).

CONCLUSIONS: We found an increased prevalence of metabolic syndrome associated with TCDD, but only among women who were the youngest at the time of the explosion. Continued follow-up of the SWHS cohort will be informative.



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.

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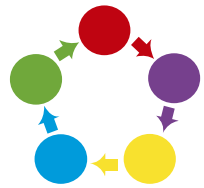
a Northern Medical Program, University of Northern British Columbia , Prince George , British Columbia , Canada.

Abstract

Evidence from recent epidemiological studies has emerged implicating exposure to environmental toxicants as a novel risk factor for the development of type 2 diabetes (T2D) and the metabolic syndrome in the general population. Humans and other organisms in high trophic levels of the food chain consume persistent organic pollutants (POP) through their diet. Few experimental studies demonstrating cause and effect are available and evidence for a direct association between accumulation of POP and T2D is preliminary; however, the possibility exists that lipophilic chemicals that accumulate in fatty tissue may disrupt cellular function and 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 repres

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



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**

Eur Rev Med Pharmacol Sci. 2015 Jan;19(1):123-128.

Effect of environmental air pollution on type 2 diabetes mellitus.

Meo SA[1], Memon AN, Sheikh SA, Al Rouq F, Mahmood Usmani A, Hassan A, Arian SA.

Author information

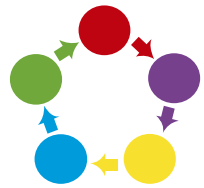
Abstract

OBJECTIVE: Air pollution is a novel risk factor for insulin resistance and occurrence of type 2 diabetes mellitus (T2DM), but the evidence is limited and diverse. Therefore, the aim of this study was to assess the effect of environmental air pollution on incidence of type 2 diabetes mellitus.

METHODS: In this study, we identified 102 published studies through a systematic data base search including ISI-Web of Science, EMBASE and PubMed. We searched the related literature by using the key terms including diabetes mellitus, air pollution, occupational and environmental pollution, gaseous, NO2, particulate matter pollutants PM2.5, and PM10. Studies in which diabetes mellitus, insulin resistance, air pollution, occupational and environmental pollution was discussed were included in the study. No confines on publication status, study design or language of publication were considered. Descriptive and quantitative information were extracted from the selected literature. Finally we included 21 publications and remaining studies were excluded.

RESULTS: Air pollution is a leading cause of insulin resistance and incidence of type 2 diabetes mellitus. The association between air pollution and diabetes is stronger for traffic associated pollutants, gaseous, nitrogen dioxide, tobacco smoke and particulate matter.

CONCLUSIONS: Exposure to air pollutants is significantly associated with increased risk of type 2 diabetes mellitus. It is suggested that, environmental protection officials must take high priority steps to minimize the air pollution, hence to decrease the incidence of type 2 diabetes mellitus.



Yonsei Med J. 2015 Jul;56(4):944-50. doi: 10.3349/ymj.2015.56.4.944.

Blood Mercury and Insulin Resistance in Nondiabetic Koreans (KNHANES 2008-2010).

Kim KN[1], Park SJ[1], Choi B[2], Joo NS[3].

Author information

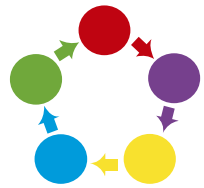
Abstract

PURPOSE: Blood mercury levels are associated with inflammation, and chronic low-grade inflammation is a cause of insulin resistance. This study aimed to investigate the association between serum mercury and insulin resistance.

MATERIALS AND METHODS: Subjects from the 2008-2010 Korean National Health and Nutrition Examination Survey were selected (n=29235) and the relevant data of 5388 subjects (2643 males and 2745 females) were analyzed cross-sectionally. Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was compared according to blood mercury quartiles, and the odds ratio (OR) of having the highest quartile of HOMA-IR according to blood mercury quartiles was calculated.

RESULTS: Blood mercury levels in men and women were 29.4 nmol/L and 20.5 nmol/L, respectively, and fasting blood sugar (FBS), insulin, and HOMA-IR were significantly correlated with blood mercury levels. The correlation was stronger in men than in women. In men, FBS and HOMA-IR showed step-wise increases as the quartiles of blood mercury increased; only HOMA-IR differed significantly in the third and fourth blood mercury quartiles, compared to the first quartile. In women, however, both FBS and HOMA-IR differed significantly in the third and fourth blood mercury quartiles, compared to the first quartile. Among men, the OR of being in the highest HOMA-IR quartile was greatest for the highest blood mercury quartile (OR=1.720, 95% CI; 1.172-2.526), compared with the lowest quartile.

CONCLUSION: In this large population-based study, blood mercury levels were weakly correlated with HOMA-IR and may be a risk factor for insulin resistance in nondiabetic Koreans.



HEAVY METALS AND INSULIN RESISTANCE

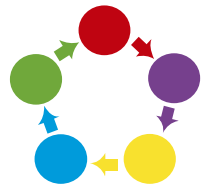
Low-level arsenic exposure reported to be associated with insulin resistance.

JAMA 2008; 300: 814-22

STATINS AND DM

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).

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



Am J Physiol Gastrointest Liver Physiol. 2014 Nov 15;307(10):G951-7. doi: 10.1152/ajpgi.00268.2014. Epub 2014 Sep 25.

Systems biology analysis of omeprazole therapy in cirrhosis demonstrates significant shifts in gut microbiota composition and function.

Bajaj JS[1], Cox IJ[2], Betrapally NS[3], Heuman DM[4], Schubert ML[4], Ratneswaran M[5], Hylemon PB[6], White MB[4], Daita K[4], Noble NA[4], Sikaroodi M[3], Williams R[2], Crossey MM[5], Taylor-Robinson SD[5], Gillevet PM[3].

Author information

Abstract

Proton pump inhibitors (PPI) have been associated with infectious complications in cirrhosis, but their impact on distal gut microbiota composition and function is unclear. We aimed to evaluate changes in stool microbiota composition and function in patients with cirrhosis and healthy controls after omeprazole therapy. Both 15 compensated cirrhotic patients and 15 age-matched controls underwent serum gastrin measurement, stool microbiota profiling with multitagged pyrosequencing, and urinary metabolic profiling with NMR spectroscopy to assess microbial cometabolites before/after a 14-day course of 40 mg/day omeprazole under constant diet conditions. Results before (pre) and after PPI were compared in both groups, compare
diet or MELD (m
significantly incr
(pre 29.9 ± 14.5
controls and cirr
normally abunda
vs. 9%) and was
hippurate in cirrh
vs. preomeprazo
analysis, signific
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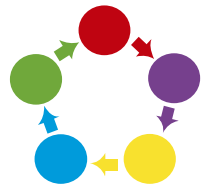
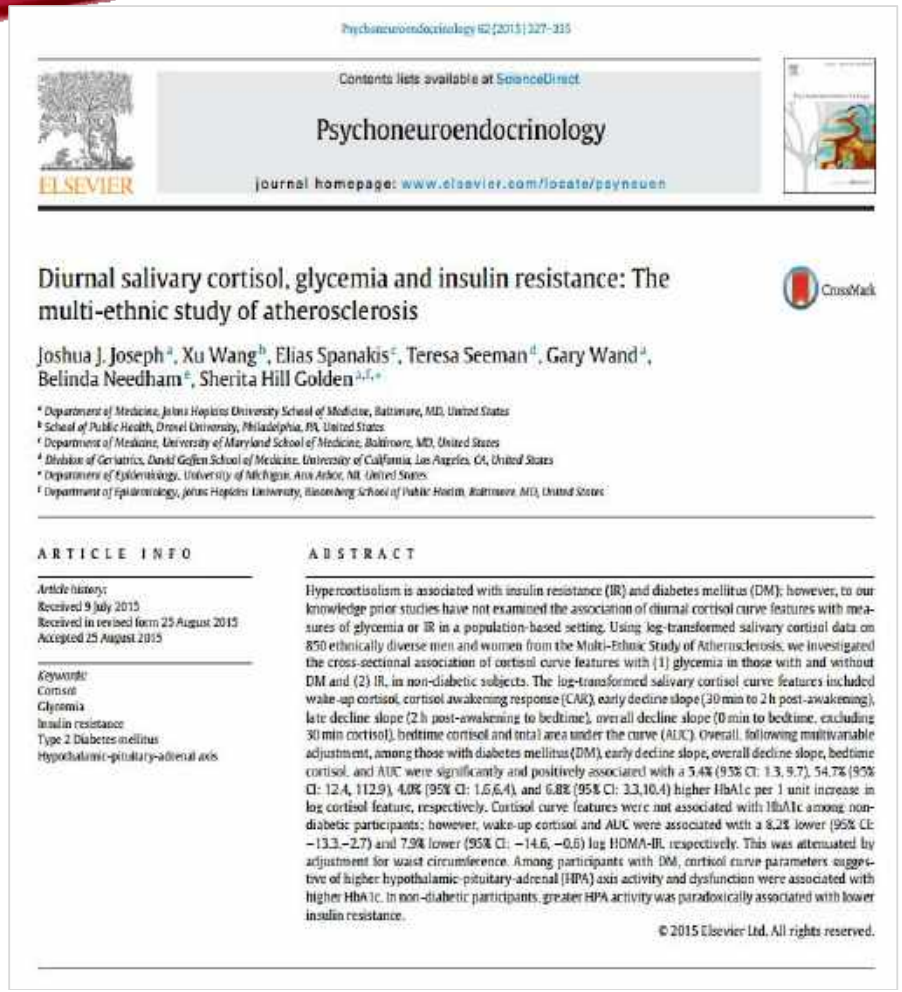
a microbiota shi
set the stage for bacterial overgrowth.

Omeprazole is associated with a microbiota shift and functional change in the distal gut in patients with compensated cirrhosis that could set the stage for bacterial overgrowth.



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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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. 2015 DEC;62:327-35.

Genes (Basel). 2017 Apr 20;8(4). pii: E125. doi: 10.3390/genes8040125.

Inherited Variation in Vitamin D Genes and Type 1 Diabetes Predisposition.

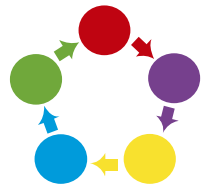
Penna-Martinez M[1], Badenhoop K[2].

⊕ Author information

Abstract

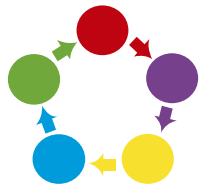
The etiology and pathophysiology of type 1 diabetes remain largely elusive with no established concepts for a causal therapy. Efforts to clarify genetic susceptibility and screening for environmental factors have identified the vitamin D system as a contributory pathway that is potentially correctable. This review aims at compiling all genetic studies addressing the vitamin D system in type 1 diabetes. Herein, association studies with case control cohorts are presented as well as family investigations with transmission tests, meta-analyses and intervention trials. Additionally, rare examples of inborn errors of vitamin D metabolism manifesting with type 1 diabetes and their immune status are discussed. We find a majority of association studies confirming a predisposing role for vitamin D receptor (VDR) polymorphisms and those of the vitamin D metabolism, particularly the CYP27B1 gene encoding the main enzyme for vitamin D activation. Associations, however, are tenuous in relation to the ethnic background of the studied populations. Intervention trials identify the specific requirements of adequate vitamin D doses to achieve vi[illegible] to achieve target effects due to pharma[illegible]

"Efforts to clarify genetic susceptibility and screening for environmental factors have identified the vitamin D system as a contributory pathway that is potentially correctable"

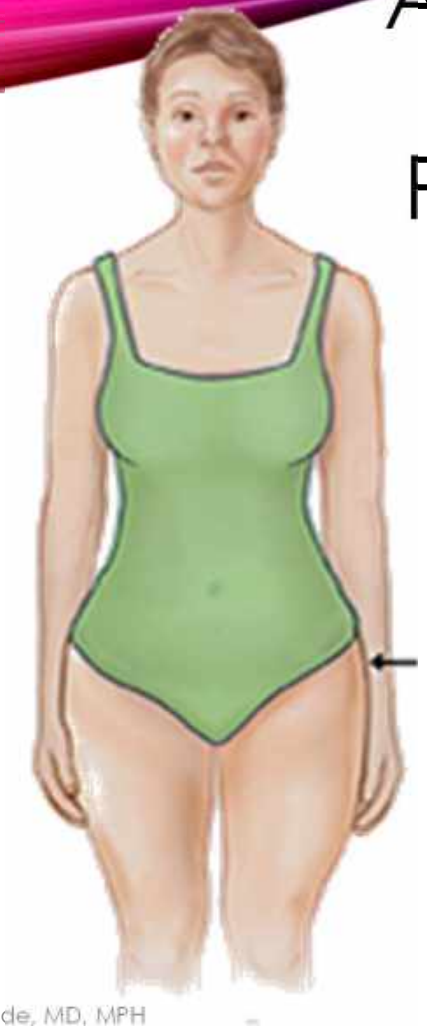


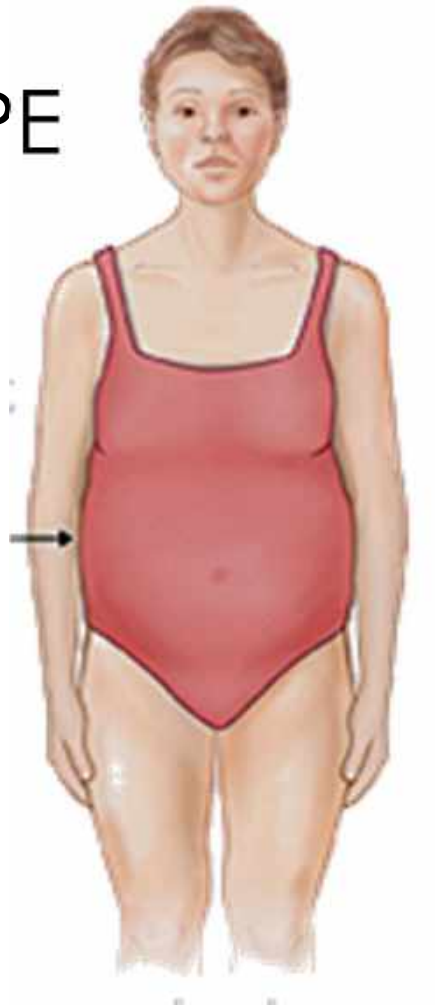
PHYSICAL EXAM FINDINGS

- Body Shape
- Acanthosis Nigricans
- Skin Tags
  - melasma
- Hirsutism-women
- Hair loss-men
- Waist circumference
- Abdominal Exam
- Nails
- Hair
- Muscle bulk

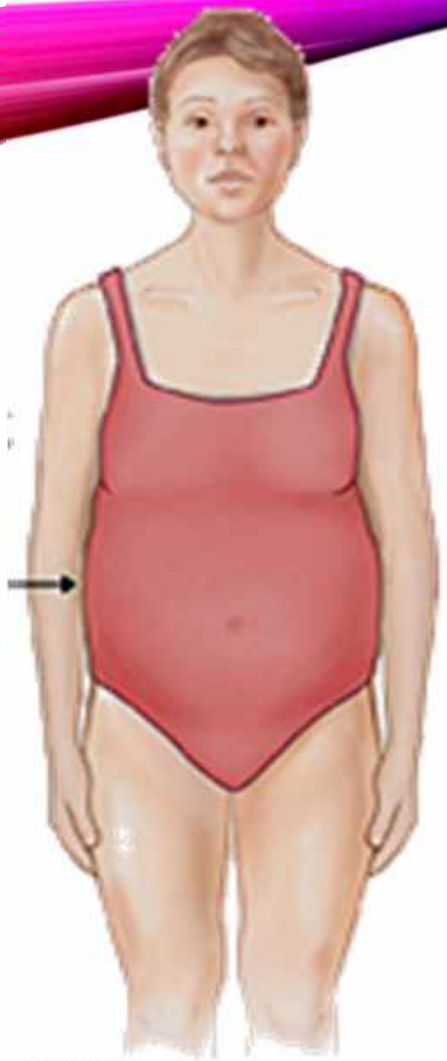


APPLE BODY TYPE
VS
PEAR BODY TYPE





ANDROID BODY TYPE
COMMON BIOMARKER PATTERNS TO RECOGNIZE

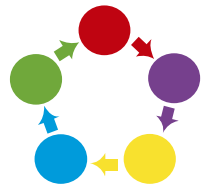


Increased Inflammation Through Adipocytokine Communication

Insulin Resistance/Hyperinsulinemia and Reduced Adiponectin

"The peri-menopause is associated with a more rapid increase in fat mass and redistribution of fat to the abdomen, resulting in a transition from a gynoid to an android pattern of fat distribution and an increase in total body fat."

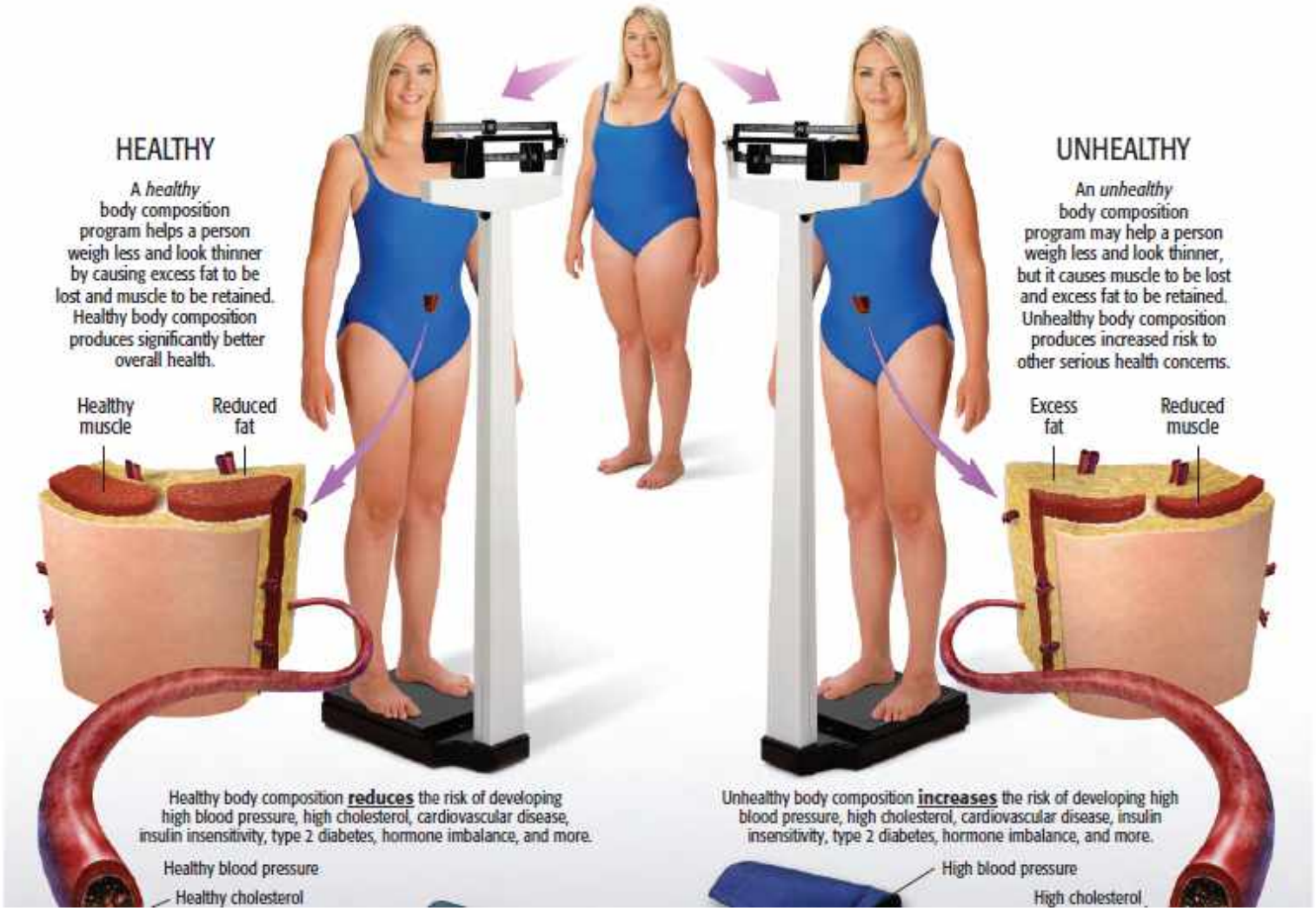
POEHLMAN E , T OTH M J, G ARDNER A . CHANGES IN ENERGY BALANCE AND BODY COMPOSITION AT MENOPAUSE: A CONTROLLED LONGITUDINAL STUDY . *ANN INTERN MED* 1995 ; 123 : 673 – 8.



HIGH INSULIN

- Overweight
- Inflammation
  - Arthritis, skin rash, urge incontinence
- Metabolic Syndrome
  - High blood pressure, obesity, high cholesterol
- Any of the high adrenaline or high cortisol symptoms

BODY COMPOSITION & HEALTH



HIGH CORTISOL

- Depressed +/- anxiety
- Weight around midsection
- Frequent infections
- Elevated cholesterol
- Any of the high adrenaline symptoms

HIGH ADRENALINE

- Losing weight
- Anxious
- Hot flashes if midlife
- Cold
  - Compensatory hypothyroidism
- Muscle wasting if not exercising to build muscles

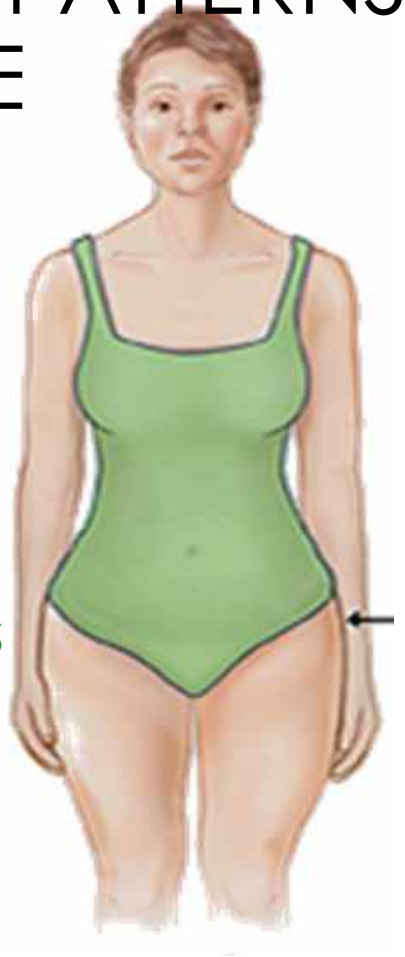
GYNOID BODY TYPE:
COMMON BIOMARKER PATTERNS TO RECOGNIZE

Increased Risk for HPATG Dysfunction

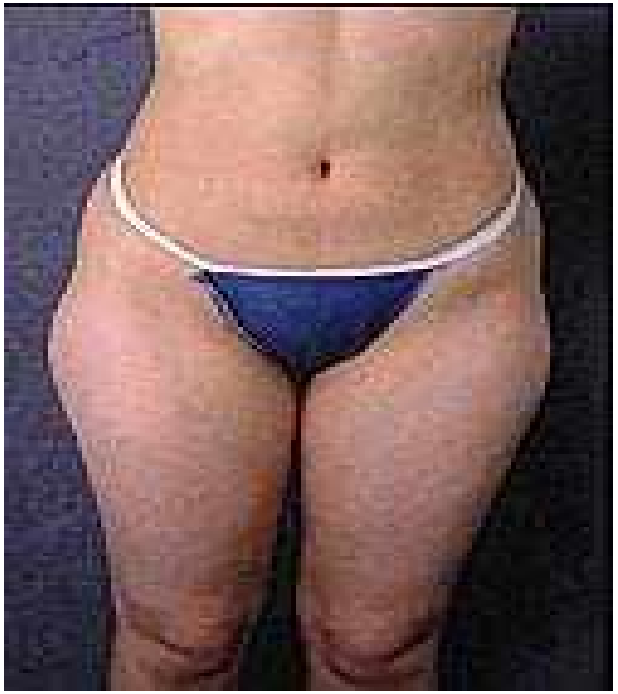
Infecto-obesity Risks

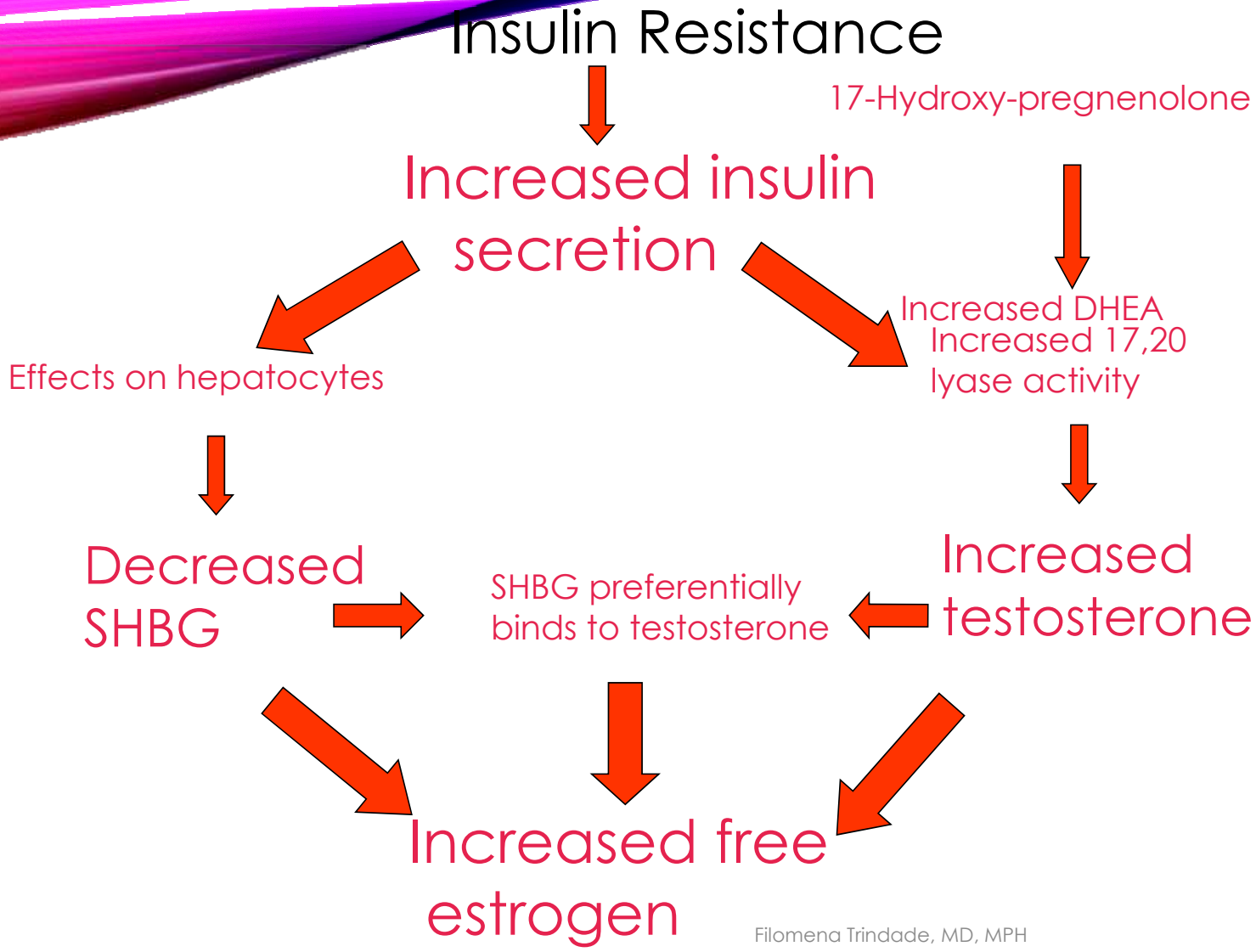
Detoxification Abnormalities

Gastrointestinal Concerns and Allergies



HIGH ESTROGEN BODY TYPE




Insulin Resistance
17-Hydroxy-pregnenolone
Increased insulin secretion
Increased DHEA
Increased 17,20 lyase activity
Effects on hepatocytes
Decreased SHBG
SHBG preferentially binds to testosterone
Increased testosterone
Increased free estrogen

Aust Fam Physician. 2013 Aug;42(8):524-7.

The metabolic syndrome.

Harris MF.

MBBS, FRACGP, MD, is Professor and Director, Centre for Primary Health Care and Equity, University of New South Wales and the Centre for Research Excellence in Obesity Management and Prevention in Primary Health Care.

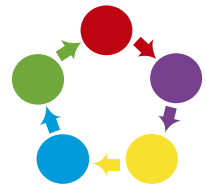
Abstract

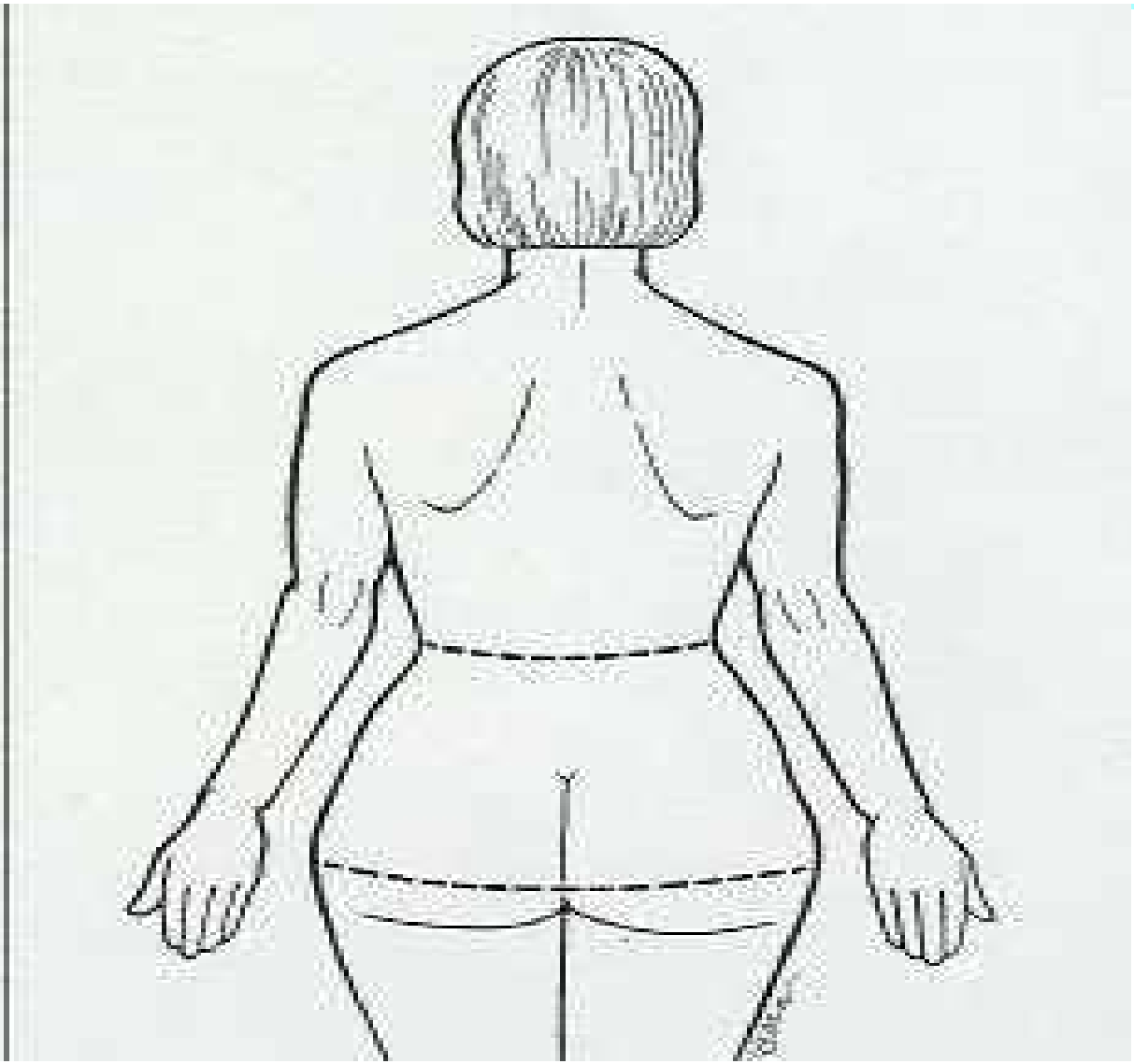
BACKGROUND: The metabolic syndrome (MetSy) is increasingly common in Australia. It is associated with the rise in obesity and lifestyle risk behaviours. It is also controversial - its value in predicting cardiovascular disease and diabetes risk and in guiding therapy has been challenged.

OBJECTIVE: This article aims to provide advice on the diagnosis of the MetSy and the principles for

MetSy assessment requires measurement of waist circumference - a simple but seldom performed procedure in general practice. The most essential components for the prevention and management of the MetSy are measures to change diet and physical activity in order to achieve and sustain weight loss.

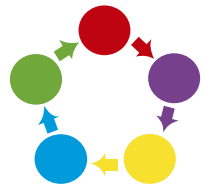
sustain weight loss.



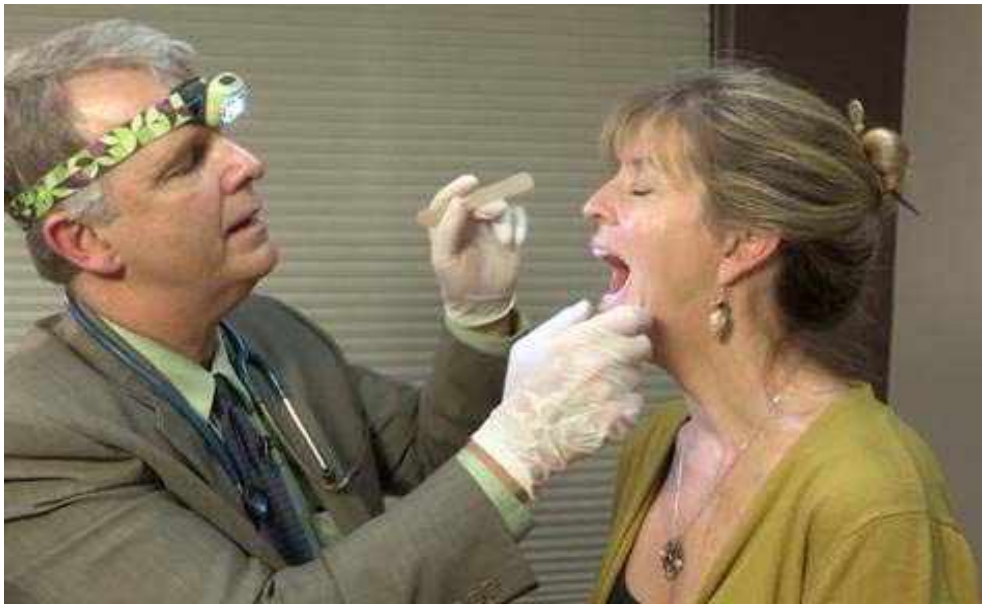


WAIST TO HIP RATIO

- Ratio greater than:
  - 1.0 in men
  - 0.8 in women
- Considered obese
- And "apple shaped"



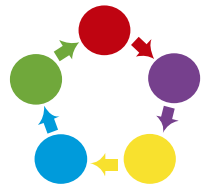
INSULIN RESISTANCE, DM AND NUTRITIONAL PHYSICAL EXAM FINDINGS



Eyes to See and Expectation to Find

CONCENTRATE ON TISSUE WITH RAPID TURNOVER OR METABOLIC VULNERABILITY

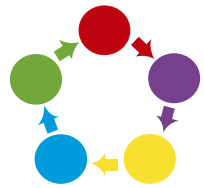
1. Mucosa and Skin
2. Nails and Hair
3. Senses and Nerve Function



TONGUE

COLOR, COVERINGS, BUDS, SIZE, MOVEMENT

• **Glossitis (Red Tongue)**	Protein Under-nutrition, Iron, Riboflavin, niacin, B6, folate, B12
• **Decreased taste/smell, burning tongue**	Zinc, Vitamin C
• **Tongue fissuring**	Niacin, gut triggered immune issues
• **Tongue - taste bud atrophy**	Iron, Riboflavin, niacin, B12
• **Leukoplakia**	Vitamin A, B2, niacin, B6, Folate, B12
• **Hairy black tongue**	Not Specific; associated with smoking, sulfur, granule positive bacteria, antibiotics

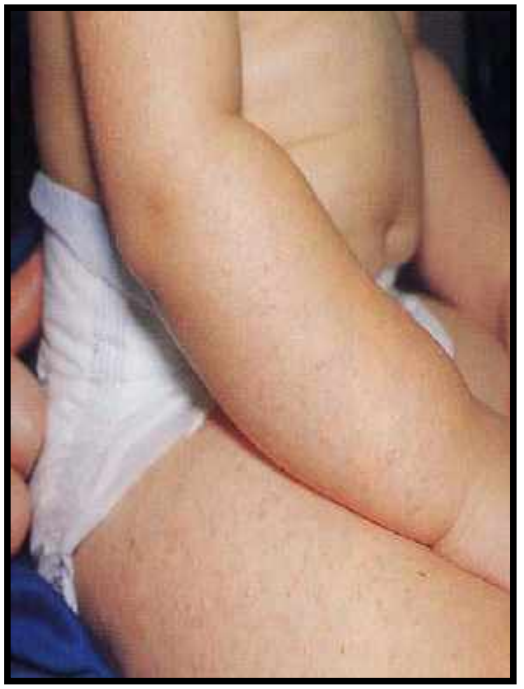


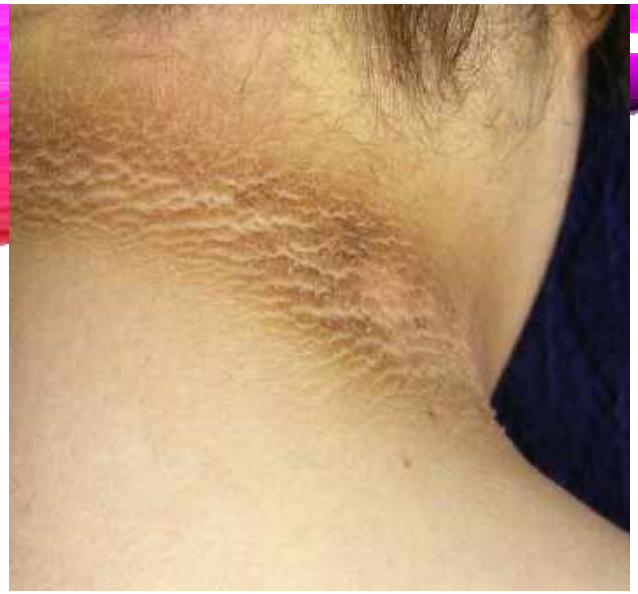
TOUCH THE SKIN ON THE ARM

Character:

- Temperature
- Texture
- Color
- Hydration
- Lesions
- Hair Distribution

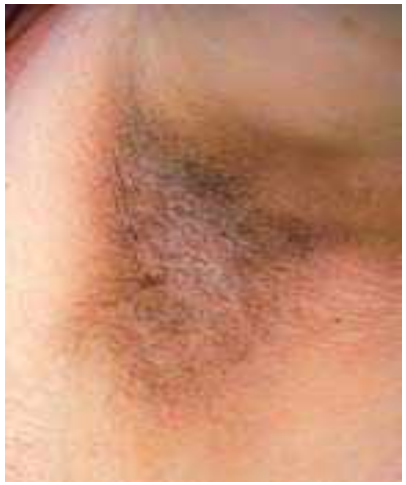
Hyperkeratosis pilari

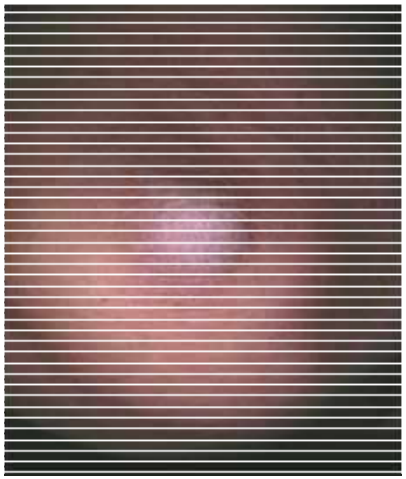


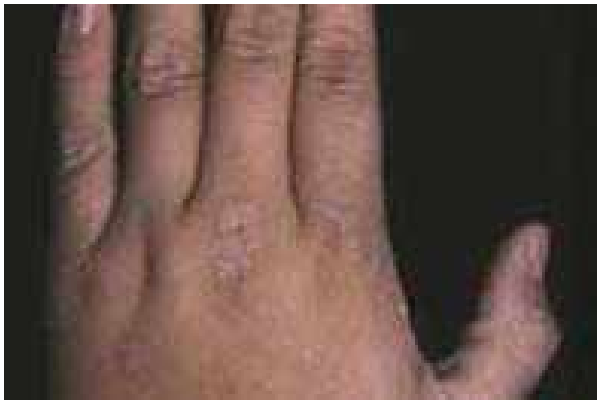


ACANTHOSIS NIGRICANS

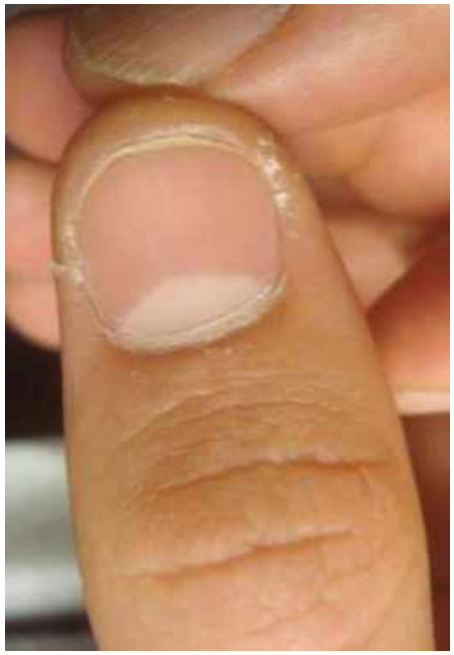
- Smooth, velvet-like, hyperkeratotic plaques in intertriginous areas (e.g., groin, axillae, neck)
- Generally caused by hyperinsulinemia

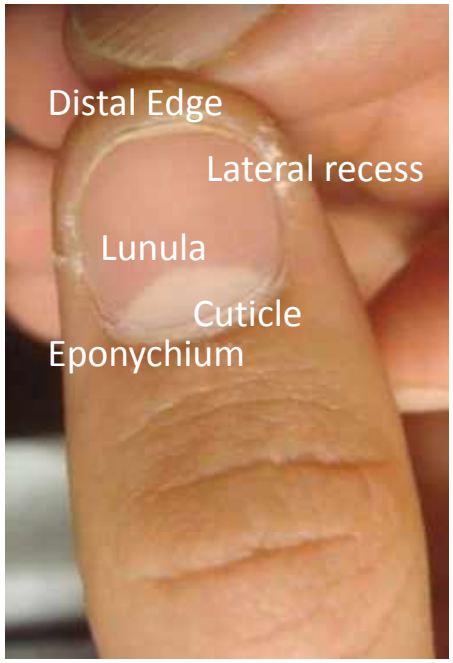






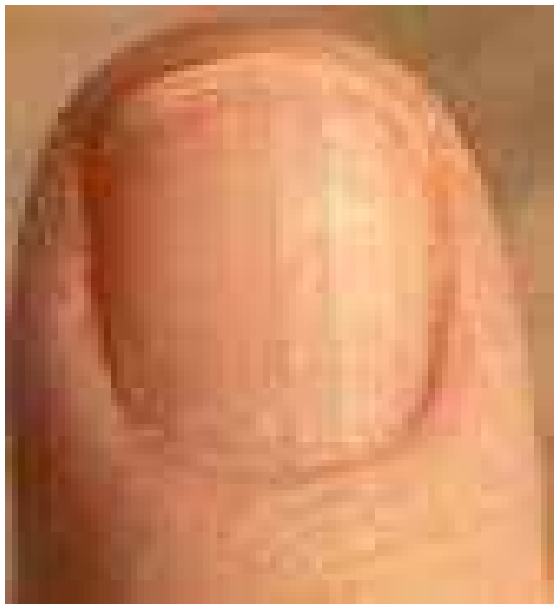
LOOK AT THE NAILS





- Shape
- Color
- Pattern of Color
- Texture and strength
- Growth Pattern
- Surrounding Tissue

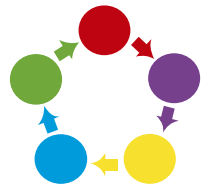
VERTICAL RIDGES ON NAILS



SUMMARY: PE SIGNS

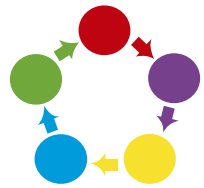
- **Acanthosis nigricans**
  - Insulin Resistance
- **White spots on nails**
  - Zinc
- **Hyperkeratosis Pilaris**
  - Omega 3 deficiency

- **Tongue fissuring**
  - Up-regulated GALT
- **Taste bud atrophy**
  - B2, B12, iron, niacin
- **New Onset Abdominal Girth**
  - Cortisol steal



INSULIN'S EFFECTS

- Effects CBO, lipid, Metabolism
- Insulin effects thyroid function…and thyroid function effects insulin production
- Insulin effects endothelial function
- Other hormones….



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DOI: 10.5603/EP.2017.0026
Tom/Volume 68; Numer/Number 3/2017
ISSN 0423–104X

Insulin resistance in endocrine disorders — treatment options

Anita Rogowicz-Frontczak, Anna Majchrzak, Dorota Zozulińska-Ziółkiewicz

Department of Internal Medicine and Diabetology, Poznan University of Medical Science, Poland

Abstract

Changes in sensitivity to insulin occur in the course of a number of endocrine disorders. Most of the hormones through their antagonistic action to insulin lead to increased hepatic glucose output and its decreased utilisation in peripheral tissues. Carbohydrate disorders observed in endocrine diseases result from the phenomenon of insulin resistance, and in some cases also a reduction in insulin secretion is present. Abnormalities of glucose metabolism are observed in acromegaly, but also in growth hormone deficiency, hypercortisolism in the course of Cushing's syndrome, hyper- or hypothyroidism, primary hyperparathyroidism, aldosteronism, pheochromocytoma, congenital hypertrophy of the adrenal glands, polycystic ovarian syndrome, hypoprolactin, or other hormonally active neuroendocrine tumours. They are of a secondary nature in relation to impaired hormonal balance. Hyperglycaemia is therefore often reversible, and the most effective method of treatment of impaired insulin sensitivity is successful therapy of specific endocrinopathies. Insulin sensitisers, also with a good effect, are used. Most experiences to date can be attributed to metformin therapy. Attempts have been made at treatment with other agents that are also effective in reducing insulin resistance or incretins or glitazones.

In the presented paper, the authors reviewed endocrine diseases in which there is a clinically significant change in insulin sensitivity. Moreover, methods of therapy of concomitant disturbed glucose metabolism were presented. (Endokrynol Pol 2017; 68 (3): 324–332)

Key words: insulin resistance; endocrinopathies; diabetes mellitus

Introduction

Most hormones, through their antagonistic action to insulin, lead to increased hepatic glucose production and reduced utilisation at the peripheral tissues. If they are secreted in excess, or are unbalanced in relation to the level of insulin, they can lead to various degrees of disorders of glucose metabolism. Dysregulations in hormonal metabolism usually lead to compensatory hyperinsulinaemia in response to increasing insulin resistance. Some hormones, by acting on pancreatic β cells, stimulate or reduce the secretion of insulin. Hormones of potential diabetogenic effect include: growth hormone (GH), glucocorticosteroids (GS), thyroxine, catecholamines, aldosterone, parathyroid hormone, glucagon, and somatostatin. Changes in the sensitivity of cells to insulin action occur in the course of the majority of endocrine disorders. For this reason, patients with endocrinopathies should also be evaluated for carbohydrate metabolism disorders [1].

Insulin resistance and methods of treatment

Insulin resistance is defined as a disorder of glucose homeostasis involving reduced sensitivity of muscles, adipose tissue, liver, and other tissues to the action of insulin, despite its normal or elevated level in the blood. Insulin resistance may be accompanied by various disorders, such as: impaired glucose tolerance, diabetes, hypercholesterolaemia, hypertriglyceridaemia, obesity, and hypertension. Insulin acts through specific receptors present on the surface of most cells in the body. The highest presence of these receptors was found on fat cells, hepatocytes, and cells of striated muscles. Insulin resistance may be also due to the presence of hormones antagonistic to insulin (e.g. cortisol, glucagon, thyroid hormones) [2].

In the course of hormonal imbalance the best therapeutic effects in improving the sensitivity of tissues to insulin action are achieved with their effective treatment. However, complete recovery of certain endocrine diseases is not always possible. The normalisation of glucose metabolism in the course of endocrinopathy depends on many factors, such as: age, duration and severity of hormonal or metabolic disorders, and genetic predisposition [3]. Therefore, to obtain a reduction of insulin resistance, lifestyle changes and pharmacological treatment should be introduced.

When impaired insulin sensitivity is a consequence of obesity, lifestyle changes aimed at reducing body weight through diet and exercise lead to a reduction of insulin resistance.

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Are vasomotor symptoms an independent risk factor for metabolic syndrome?

Maturitas. 2017 Mar;97:61-65. doi: 10.1016/j.maturitas.2016.12.010. Epub 2017 Jan 10.

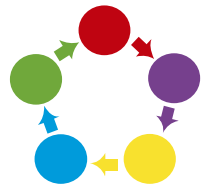
Vasomotor symptoms and metabolic syndrome.

Tuomikoski P[1], Savolainen-Peltonen H[2].

⊕ Author information

Abstract

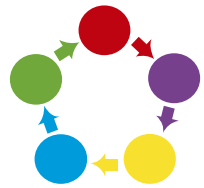
A vast majority of menopausal women suffer from vasomotor symptoms, such as hot flushes and night sweats, the mean duration of which may be up to 7-10 years. In addition to a decreased quality of life, vasomotor symptoms may have an impact on overall health. Vasomotor symptoms are associated with overactivity of the sympathetic nervous system, and sympathetic overdrive in turn is associated with metabolic syndrome, which is a known risk factor for cardiovascular disease. Menopausal hot flushes have a complex relationship to different features of the metabolic syndrome and not all data point towards an association between vasomotor symptoms and metabolic syndrome. Thus, it is still unclear whether vasomotor symptoms are an independent risk factor for metabolic syndrome. Research in this area is constantly evolving and we present here the most recent data on the possible association between menopausal vasomotor symptoms and the metabolic syndrome.



IMPORTANCE OF LABORATORY EVALUATION

- Not all overweight individuals are insulin-resistant.
- Not all normal-weight individuals are insulin-sensitive.
- Not all insulin-resistant individuals develop diabetes.

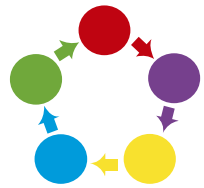
- How can we identify those at risk?



- Compared with a glucose level of 4.2 mmol/l (75 mg/dl), a fasting and 2-h glucose level of 6.1 mmol/dl (110 mg/dl) and 7.8 mmol/l (140 mg/dl) was associated with a relative cardiovascular event risk of 1.33 and 1.58 respectively.

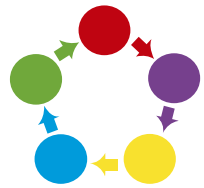
- CONCLUSIONS: The progressive relationship between glucose levels and cardiovascular risk extends below the diabetic threshold.

Coutinho M, et al. The relationship between glucose and incident cardiovascular events. A meta regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care, 1999. 22(2): p. 233-40.*



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

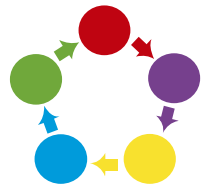
Khaw KT, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ, 2001. 322(7277): p. 15-8.



HOMA-IR

- Homeostatic Model Assessment-Insulin Resistance

- Calculation based on plasma levels of:
  * Fasting glucose and Insulin
  * Used to assess insulin sensitivity



Published online: August 1, 2013

Insulin Resistance and not BMI is the Major Determinant of Early Vascular Impairment in Patients with Morbid Obesity

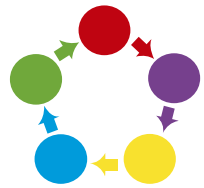
Graziana Lupattelli[1], Stefano De Vuono[1], Marcello Boni[2], Rony Helou[1], Massimo Raffaele Mannarino[1], Anna Rita Roscini[1], Abdalkader Alaeddin[1], Matteo Pirro and Gaetano Vaudo[1]

[1]Internal Medicine, Angiology and Atherosclerosis, Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy
[2]Surgery Department, San Giovanni Battista Hospital, Foligno, Italy

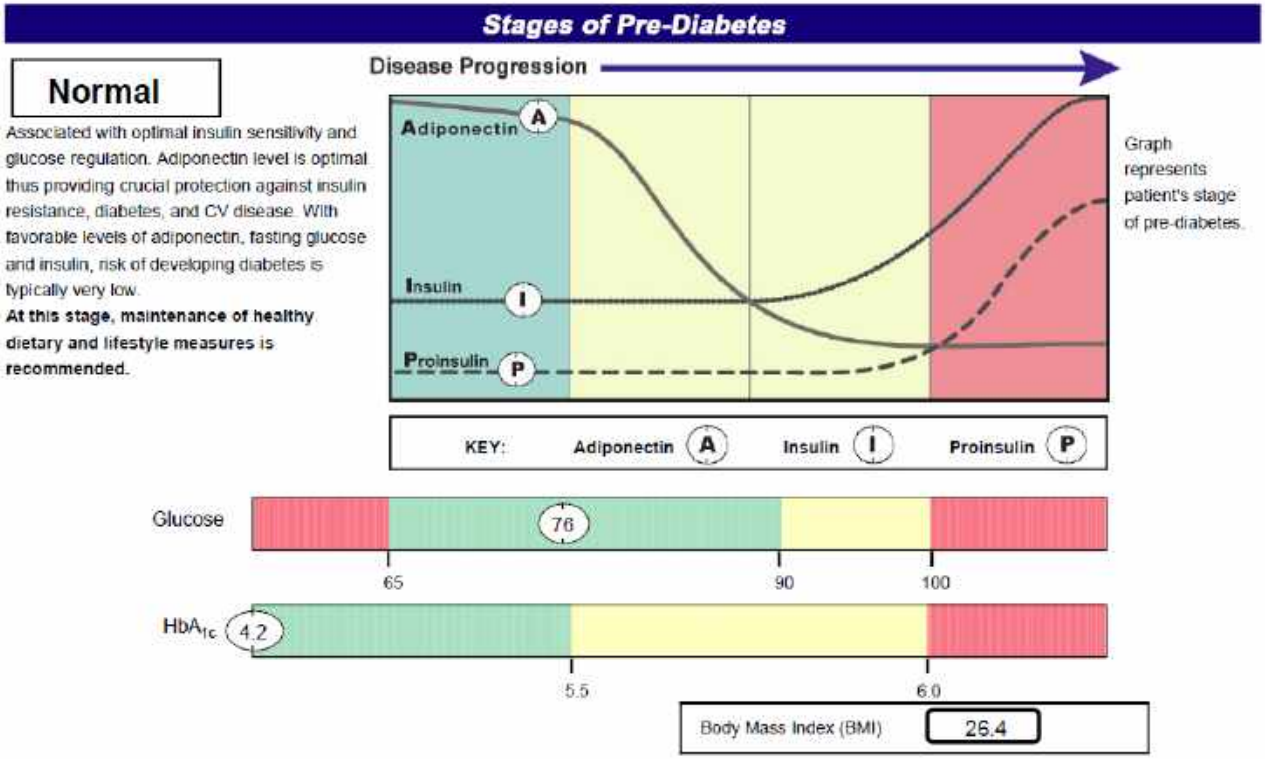
Aim: Several factors contribute to the development of atherogenesis in patients with obesity. The aim of our study was to evaluate the different roles of insulin resistance, strictly correlated to visceral adiposity, and the body mass index (BMI), an estimate of overall adiposity, on early vascular impairment in patients with morbid obesity.

Methods: We enrolled 65 morbidly obese subjects (BMI 44.6±7 kg/m²) who were free of previous cardiovascular events and 28 nonobese subjects (control group) in a cross-sectional study. The pres-

"In the present study, among the morbidly obese subjects, early vascular impairment was predicted by the HOMA-IR, which is strictly related to visceral fat…..
the HOMA-IR, not BMI, may be more suitable for identifying individuals with higher cardiovascular risks".



OPTIMAL FUNCTION



Intervention = Maintenance of healthy diet & lifestyle

STAGE 1 – DECLINING ADIPONECTIN

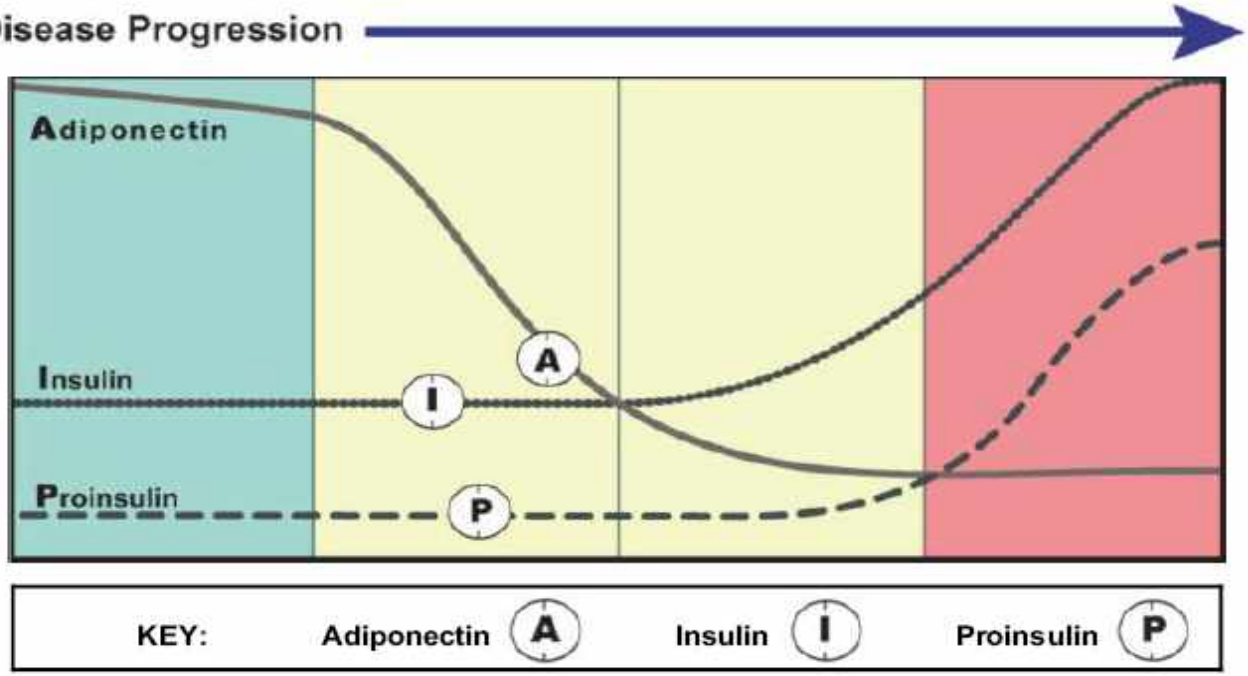
Stage 1 – Early Insulin Resistance

Stage 1 – Early Insulin Resistance

Stage 1

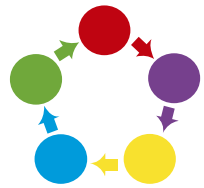
Stage 1 of of metabolic dysglycemia represents early insulin resistance, with adequate pancreatic beta-cell compensation to maintain normal glucose. Insulin level may be normal or high. Adiponectin, which provides protection against insulin resistance, diabetes and cardiovascular disease declines. Dyslipidemia may or may not be present, including elevated triglycerides and LDL-C, and/or low HDL-C.

At this stage, dietary and lifestyle measures are usually adequate for improving insulin sensitivity and preventing progression to Stage 2.



LOW ADIPONECTIN IS ASSOCIATED WITH…

- Insulin resistance
- Glucose intolerance
- Dyslipidemia
- Increased risk of vascular injury and atherosclerosis
- Increased risk of diabetes mellitus
- Inflammation

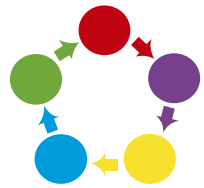


Stage 1: Early Insulin Resistance

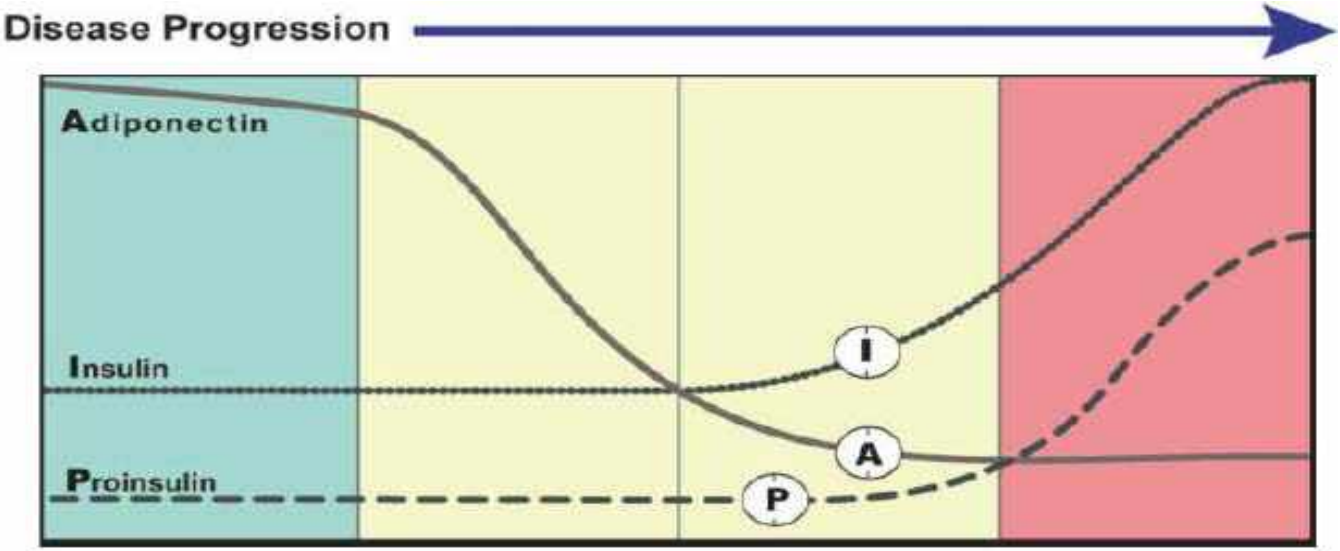
- Pattern recognition:
  - LOW Adiponectin
  - Normal or slightly high HOMA-IR
  - 'Normal' Glucose, HbA1C, Insulin, and Proinsulin
    - *"Normal" fasting blood sugar = < 100 mg/dL*
    - ***Blood sugar >87 mg/dL = progressive increase of type 2 DM!***
    - *Blood sugar < 81 mg/dL = low risk of DM*

NEJM 2005;353:1454-62.

- *Treat with diet, lifestyle, supplementation.*



STAGE 2 – ELEVATED FASTING INSULIN



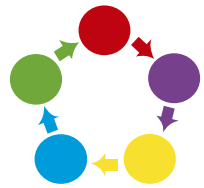
KEY: Adiponectin (A) Insulin (I) Proinsulin (P)

Adiponectin	A	3.4	> 2.7 mcg/mL
Insulin (Fasting)	I	2.8	< 5.4 μIU/mL
Proinsulin	P	12	< 42 pmol/L

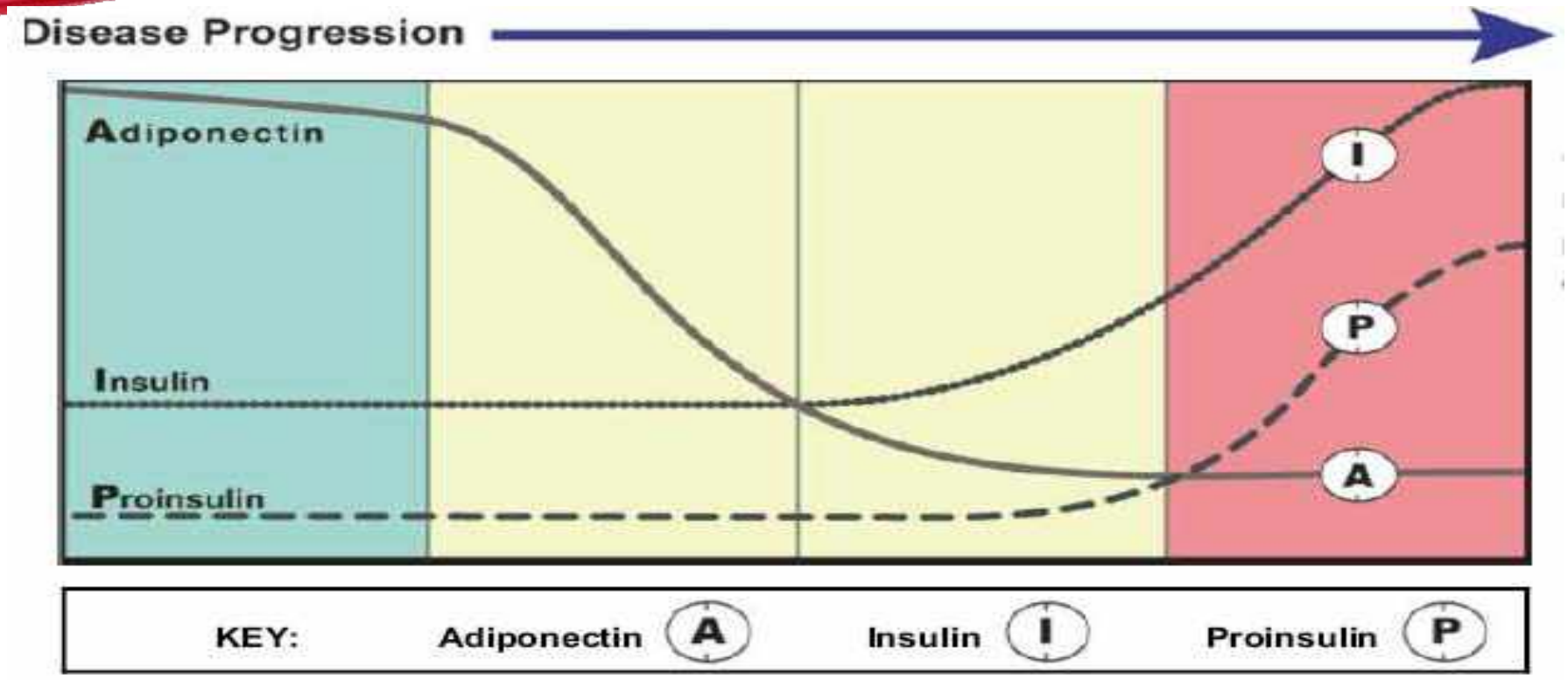
STAGE 2: ELEVATED FASTING INSULIN

- Usually due to a combination of insulin resistance and early beta-cell impairment
- 29.1 million cases of type 2 DM in the U.S., but 86 million cases of 'pre-diabetes'
- Pattern recognition:
  - LOW Adiponectin
  - HIGH or high-normal HOMA-IR
  - HIGH Insulin, but normal Proinsulin
  - Mildly elevated glucose and/or HbA1C

- *Treat with diet, lifestyle, supplementation,* possible *pharmacotherapy.*



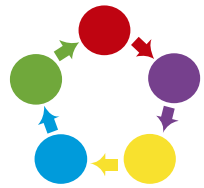
STAGE 3 – ELEVATED PROINSULIN



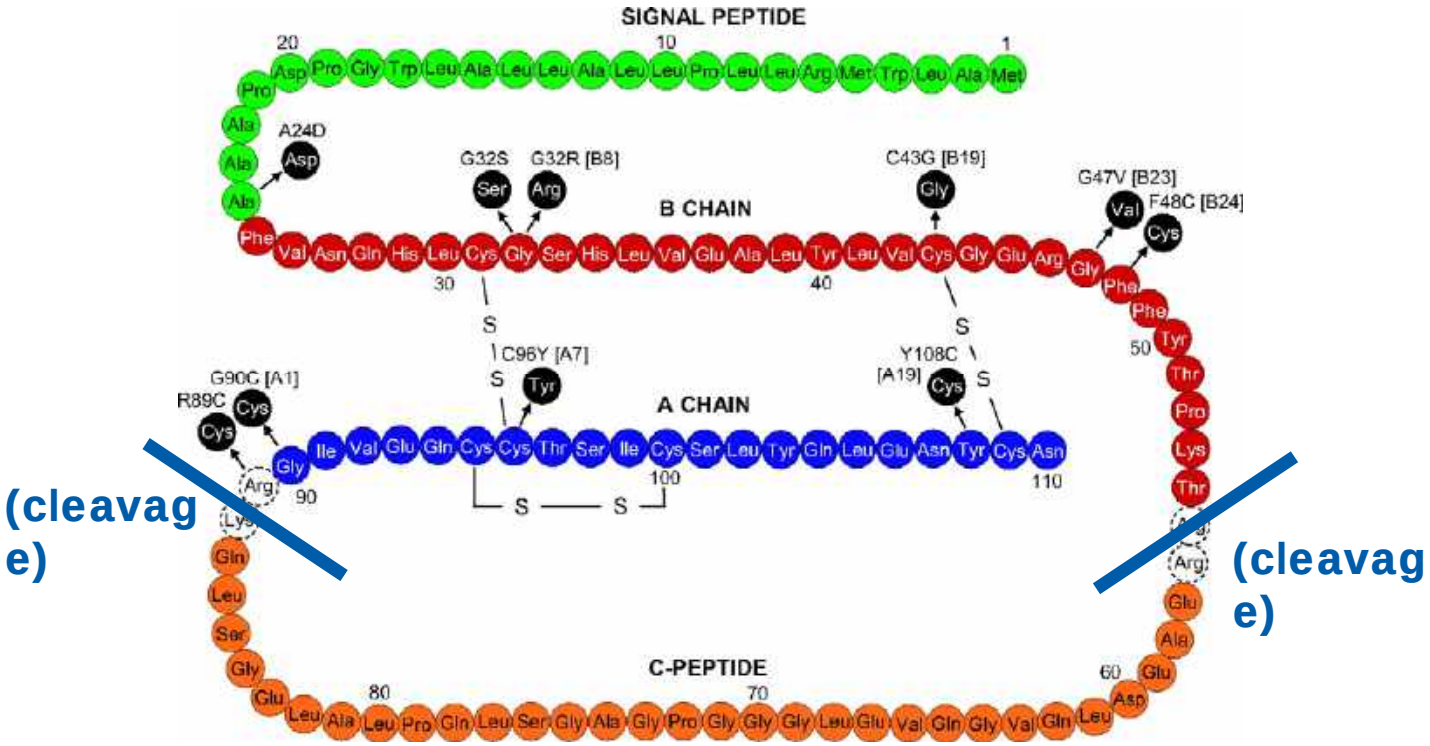
Stage 3: Elevated Pro-Insulin-cont…

- Pattern recognition:
  - LOW Adiponectin
  - HIGH HOMA-IR
  - HIGH Insulin, elevated Proinsulin
  - HIGH Glucose & HbA1C
    - Pre-diabetes
      - Fasting glucose 100-125mg/dL
      - HgbA1c 5.4%-6.4%
    - *May or may not meet ADA definition for Type 2 Diabetes Mellitus*
      - Fasting Glucose > 125 mg/dL
      - HgbA1c ≥ 6.5%

- *Treat with diet, lifestyle, supplementation, and +/_ pharmacotherapy*



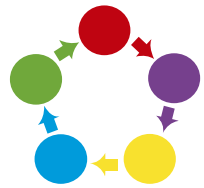
Conversion of Proinsulin to Insulin



C-PEPTIDE

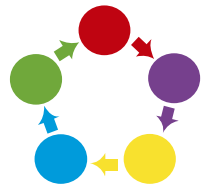
- C-peptide is produced when proinsulin splits apart to form insulin and C-peptide

- Increased levels reflect insulin resistance



INSULIN CONCENTRATION AT 30 MINUTES AFTER GLUCOSE CONSUMPTION HAS BEEN SHOWN TO BE A GOOD MEASURE OF INSULIN SECRETION IN HUMANS.

Ludwig, David, et al; A novel interaction between dietary composition and insulin secretion: effects on weight gain in the Quebec Family Study. AJCN Feb 2008; 87:303-309.



FASTING AND 2 HOUR POSTPRANDIAL INSULIN FOLLOWING A 75 GRAM GLUCOSE LOAD

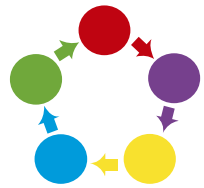
- Fasting
  - <10 µIU/ml normal
  - ≥ 10 µIU/ml resistant
- Postprandial
  - 30 min **<** 57.5 µIU/ml
  - 2 hour postprandial<25 µIU/ml normal
  - 30min ≥ 57.5 resistant
  - 2hr ≥ 25 µIU/ml resistant

Lab values based upon clinical experience and literature review

FASTING AND 2 HOUR POSTPRANDIAL GLUCOSE FOLLOWING A 75 GRAM GLUCOSE LOAD

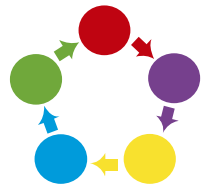
- Fasting
  - 70-99 mg/dl
    - normal
  - 100-125 mg/dl
    - impaired glucose tolerance
  - >125 mg/dl
    - diabetes (i.e. 126 mg/dl or 7mmol/L)
- 2 hour postprandial
  - 70-139 mg/dl
    - normal
  - 140-199 mg/dl
    - impaired glucose tolerance
  - >199 mg/dl
    - diabetes

Lab values based upon American Diabetes Association diagnostic criteria



SUGGESTED INITIAL LABORATORY WORK-UP

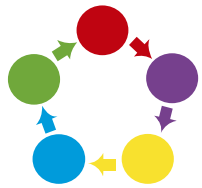
- Adiponectin
- Proinsulin
- HgbA1c
- Fasting Insulin, and 30 min insulin after 75g glucose load, 1 hour and 2hr insulin level
- Fasting glucose, 1 hour and 2 hr glucose after 75g load
- NMR Lipoprotein Profile
- Comprehensive Metabolic Panel
- GGTP
- Uric Acid
- Breath test (hydrogen and methane)
- Comprehensive stool test



URIC ACID AND DM

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

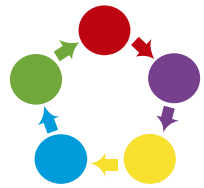
High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies.Lv Q, PLoS One. 2013;8(2):e56864. PMID:23437258



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, Zhang Y, Li F, He J, Ding H, Yan L, Cheng H. *Resistin induces insulin resistance by both AMPK-dependent and AMPK-independent mechanisms in HepG2 cells.* Endocrine. 2009 May 8.



ADDITIONAL LABS-CONTINUED

- Hormone Panels
- Toxic Profiles
- Infections
  - Bacterial
    - Atypical Bacteria
    - Potential Pathogens?
  - Parasitic
  - Fungal
  - Viral
    - Reactivated
- Marker of Oxidative Stress

IL-6, CRP-HS AND PAI-1

- Increased concentrations of interleukin 6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) have been associated with an increased risk of T2DM(1). Elevated plasminogen activator inhibitor type 1 (PAI-1) has also been found to be a predictor of the development of T2DM(2).

1. Wang, X.; Bao, W.; Liu, J.; Ouyang, Y.Y.; Wang, D.; Rong, S.; Xiao, X.; Shan, Z.L.; Zhang, Y.; Yao, P.; et al. Inflammatory markers and risk of type 2 diabetes: A systematic review and meta-analysis. Diabetes Care 2013, 36, 166–175.
2. Nakamura, T.; Adachi, H.; Hirai, Y.; Satoh, A.; Ohuchida, M.; Imaizumi, T. Association of plasminogen activator inhibitor-1 with insulin resistance in japan where obesity is rare. Metabolism 2003, 52, 226–229.

PLoS One. 2014 Jun 5;9(6):e99256. doi: 10.1371/journal.pone.0099256. eCollection 2014.

Standardising the lactulose mannitol test of gut permeability to minimise error and promote comparability.

Sequeira IR[1], Lentle RG[1], Kruger MC[1], Hurst RD[2].

Author information

Abstract

BACKGROUND: Lactulose mannitol ratio tests are clinically useful for as
for assessing mixing in the intestinal lumen. Variations between currently
studies. We determined the optimal sampling period and related this to i

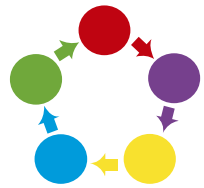
METHODS: Half-hourly lactulose and mannitol urinary excretions were d
administration of either 600 mg aspirin or placebo, in randomised order a
assessed by the SmartPill in 6 subjects from the same population. Half-h
on a basis of compartment transit time. The rate of increase or decrease
regression to assess the optimal period of sampling.

KEY RESULTS: The between subject standard errors for each half-hourl
quantity of each sugar excreted with time was optimal and the difference
the period from 2½-4 h after ingestion. Half-hourly lactulose excretions w
mannitol were unchanged as was the temporal pattern and period of low

CONCLUSION: The results indicate that between subject variation in the
differences in the temporal patterns of excretion would be maximised if t
permeability were restricted to 2½-4 h post dosage. This period corresp
probes is passing from the small to the large intestine.

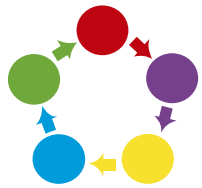
PMID: 24901524 PMCID: PMC4047110 DOI: 10.1371/journal.pone.0099256

The results indicate that between subject variation in the percentage excretion of the two sugars would be minimized and the differences in the temporal patterns of excretion would be maximized if the period of collection of urine used in clinical tests of small intestinal permeability were restricted to 2K-4 h post dosage. This period corresponds to a period when the column of digesta containing the probes is passing from the small to the large intestine..



COMPREHENSIVE STOOL ANALYSIS

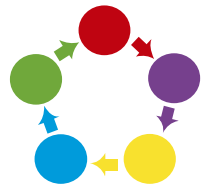
- Diversity
- Microbiology
  - Pathogenic bacteria
  - Fungi
  - Parasites
  - Good bacteria
    - Lactobacillus
    - Bifidobacterium
- SCFA's
  - Proprionate
  - Butyrate
  - Acetate
- Pancreatic Function



ARCHEA AND METHANOGENIC BACTERIA

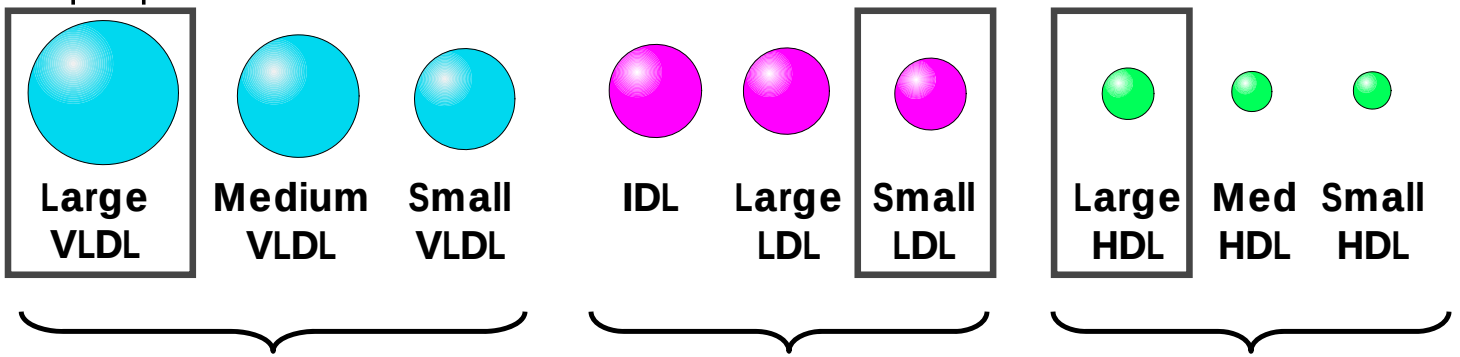
- Methanobrevibacter Smithii-prominent archeon on GIT
- Produces methane from H2, CO2, SCFAs (acetate)
- Methane may influence transit & pH
- Implicated in constipation prevalent IBS, SIBO, obesity and DM-type 2
- Methanogens cause more complete fermentation of CBO's leading to higher production and absorption of SCFA's which can lead to obesity

Pimentel et al. Am J Gastroenterol Supp. 2012, vol 1:28-33



Insulin Resistance – Changes in Lipid Fractions

Lipoprotein Subclass Particle Numbers:



VLDL Particle Number (VLDL-P)

LDL Particle Number (LDL-P)

HDL Particle Number (HDL-P)

VLDL Size

LDL Size

HDL Size

Journal of Clinical Lipidology (2007) 1, 583–592

Journal of Clinical Lipidology

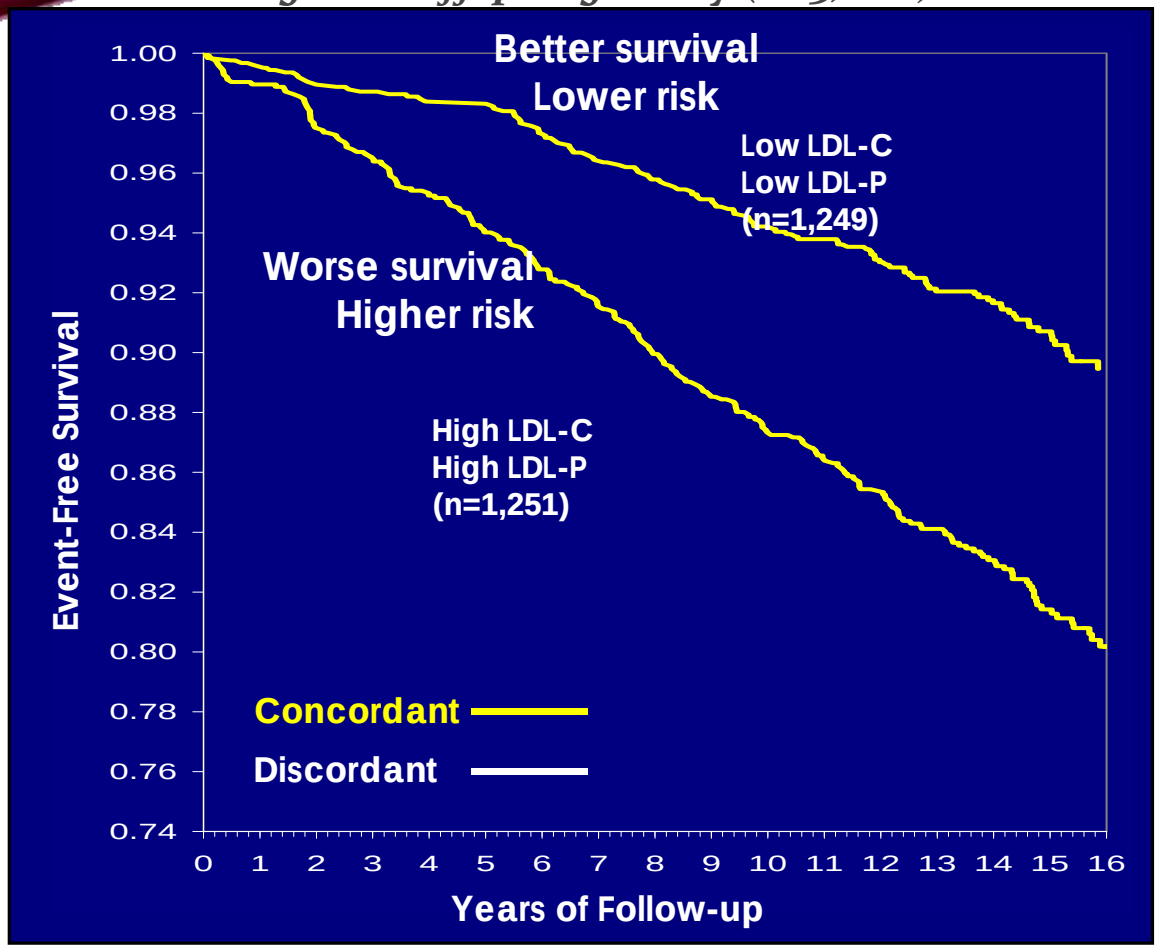
Original Contributions

LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—Implications for LDL management

William C. Cromwell, MD,* James D. Otvos, PhD, Michelle J. Keyes, PhD, Michael J. Pencina, PhD, Lisa Sullivan, PhD, Ramachandran S. Vasan, MD, Peter W. F. Wilson, MD, Ralph B. D'Agostino, PhD

CHD Event Associations of LDL-P versus LDL-C

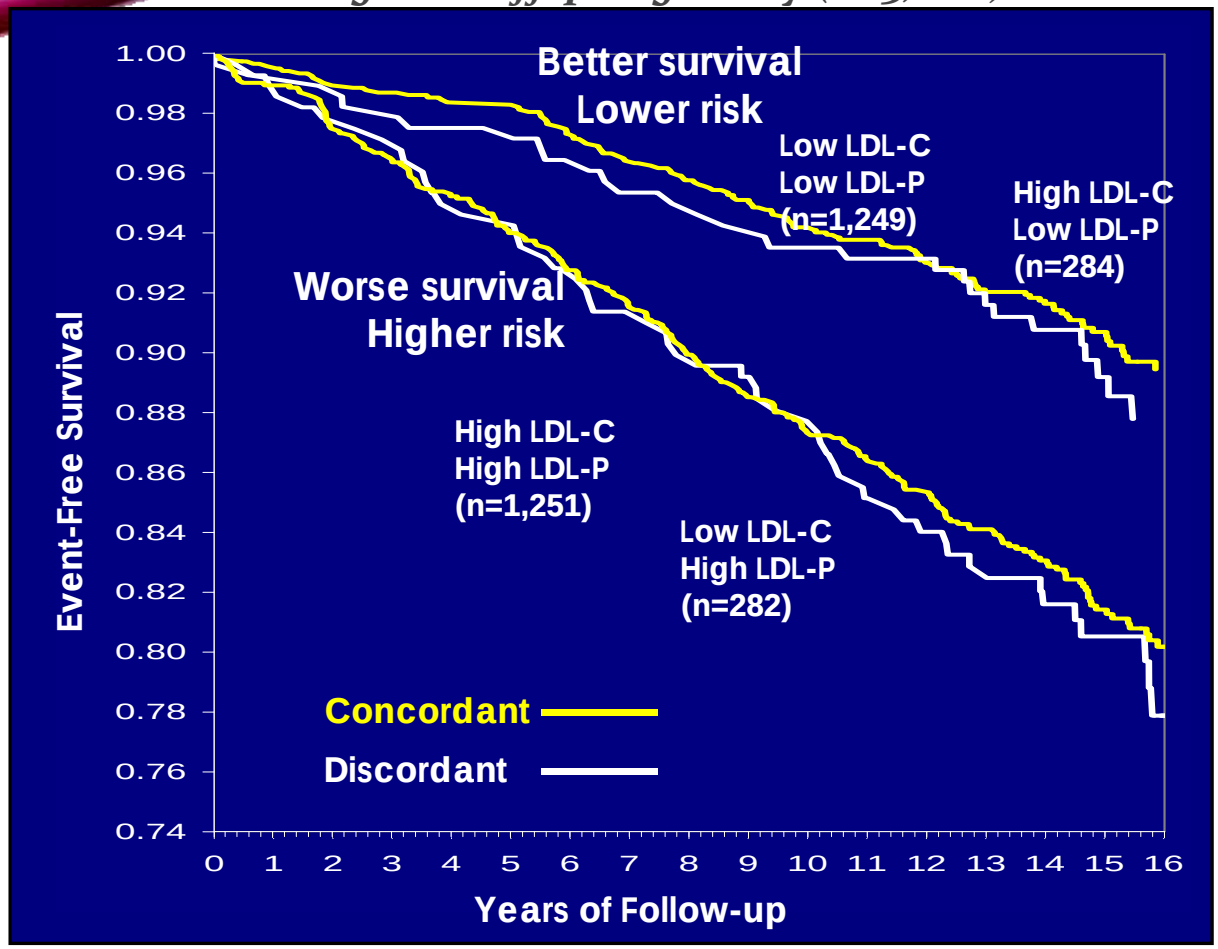
Framingham Offspring Study (n=3,066)



Cromwell WC et al. *J Clin Lipidology* 2007;1(6):583-592.

CHD Event Associations of LDL-P versus LDL-C

Framingham Offspring Study (n=3,066)



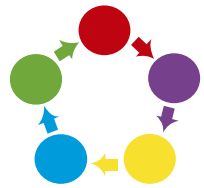
Cromwell WC et al. *J Clin Lipidology* 2007;1(6):583-592.

ADA AND ACC CONSENSUS STATEMENT IN PATIENTS AT RISK

Summary

- A more accurate way to capture the risk posed by LDL may be to measure the number of LDL particles directly using nuclear magnetic resonance (NMR)
- "Many cross-sectional and prospective studies show that LDL particle number is a better discriminator of risk than is LDL cholesterol."
- Measurements of apoB or LDL particle number by NMR more closely quantitate the atherogenic lipoprotein load.

Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822



Circulation. 2014 Feb 4;129(5):553-61. doi: 10.1161/CIRCULATIONAHA.113.005873. Epub 2013 Dec 17.

Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events.

Mora S[1], Buring JE, Ridker PM.

Author information

Abstract

BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) is the traditional measure of risk attributable to LDL. Non-high-density lipoprotein cholesterol (NHDL-C), apolipoprotein B (apoB), and LDL particle number (LDL-P) are alternative measures of LDL-related risk. However, the clinical utility of these measures may only become apparent among individuals for whom levels are inconsistent (discordant) with LDL-C.

METHODS AND RESULTS: LDL-C was measured directly, NHDL-C was calculated, apoB was measured with immunoassay, and LDL-P was measured with nuclear magnetic resonance spectroscopy among 27 533 healthy women (median follow-up 17.2 years; 1070 incident coronary events). Participants were grouped by median LDL-C (121 mg/dL) and each of NHDL-C, apoB, and LDL-P. Discordance was defined as LDL-C greater than or equal to the median and the alternative measure less than the median, or vice versa. Despite high LDL-C correlations with NHDL-C, apoB, and LDL-P (r=0.910, 0.785, and 0.692; all P<0.0001), prevalence of LDL-C discordance as defined by median cut points was 11.6%, 18.9%, and 24.3% for NHDL-C, apoB, and LDL-P, respectively. Among women with LDL-C less than the median, coronary risk was underestimated for women with discordant (greater than or equal to the median) NHDL-C (age-adjusted hazard ratio, 2.92; 95% confidence interval, 2.33-3.67), apoB (2.48, 2.01-3.07), or LDL-P (2.3

me

or L

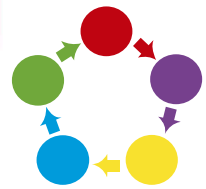
trigl

CO

LDL

CLINICAL TRIAL REGISTRATION URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000479.

For women with discordant LDL-related measures, coronary risk may be underestimated or overestimated when LDL-C alone is used.



TOXINS

Environ Health Perspect. 2016 Oct 7. [Epub ahead of print]

Chronic Exposure to Low Doses of Dioxin Promotes Liver Fibrosis Development in the C57BL6/J Diet-Induced Obesity Mouse Model.

Duval C[1,2], Teixeira-Clerc F[3,4], Leblanc AF[1,2], Touch S[5,6], Emond C[7], Guerre-Millo M[5,6], Lotersztajn S[3,4,8], Barouki R[1,2,9], Aggerbeck M[1,2], Coumoul X[1,2,10].

Author information

Abstract

BACKGROUND: Exposure to persistent organic pollutants (POPs) has been associated with the progression of chronic liver diseases, yet the contribution of POPs to the development of fibrosis in non-alcoholic fatty liver disease (NAFLD), a condition closely linked to obesity, remains poorly documented.

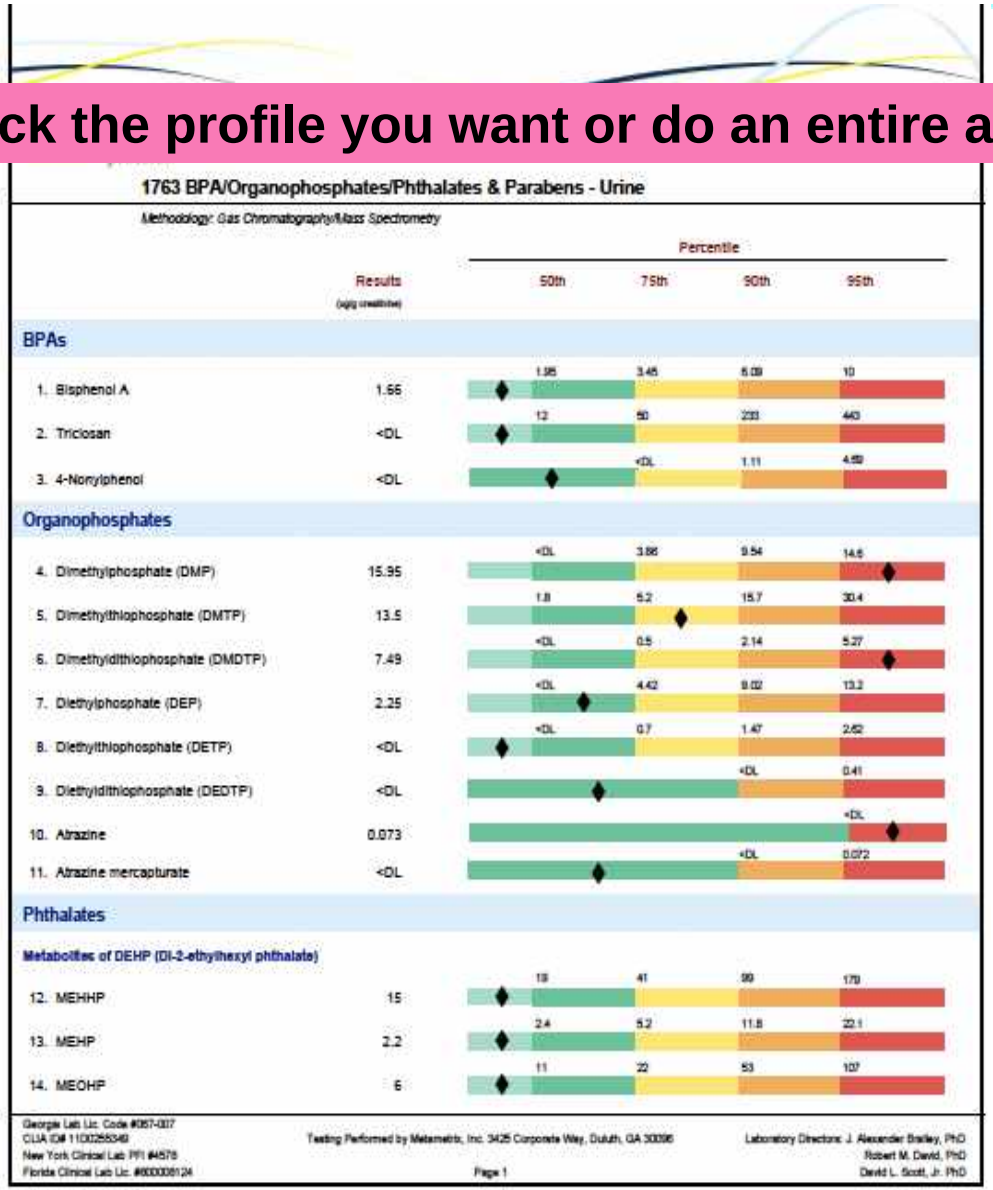
OBJECTIVES: We investigated the effects of subchronic exposure to low-doses of the POP 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), an aryl hydrocarbon receptor ligand, on NAFLD progression in diet-induced obese C57BL/6J mice.

METHODS: Male C57BL/6J mice were fed either a 10% low fat (LFD) or a 45% high fat (HFD) purified diet during 14 weeks and TCDD-exposure groups were injected once a week with 5 µg/kg TCDD or the vehicle for the last 6 weeks of the diet.

RESULTS: Liver histology and triglyceride levels showed that exposure of HFD fed mice to TCDD worsened hepatic steatosis, as compared to either HFD alone or LFD plus TCDD and the mRNA levels of key genes of hepatic lipid metabolism were strongly altered in co-treated mice. Further, increased liver collagen staining and serum transaminase levels showed that TCDD induced liver fibrosis in the HFD fed mice. TCDD in LFD fed mice increased the expression of several inflammation and fibrosis marker genes with no additional effect from a HFD.

CONCLUSIONS: Exposure to TCDD amplifies the impairment of liver functions observed in mice fed an enriched fat diet as compared to a low fat diet. The results provide new evidence that environmental pollutants promote the development of liver fibrosis in obesity-related NAFLD C57BL/6J in mice.

Pick the profile you want or do an entire array:



1763 BPA/Organophosphates/Phthalates & Parabens - Urine

Methodology: Gas Chromatography/Mass Spectrometry

	Results (ug/g creatinine)	Percentile 50th	75th	90th	95th
BPAs					
1. Bisphenol A	1.66	1.95	3.45	6.09	10
2. Triclosan	<DL	12	50	233	443
3. 4-Nonylphenol	<DL	<DL	1.11	4.69	
Organophosphates					
4. Dimethylphosphate (DMP)	15.95	<DL	3.86	9.54	14.6
5. Dimethylthiophosphate (DMTP)	13.5	1.8	5.2	15.7	30.4
6. Dimethyldithiophosphate (DMDTP)	7.49	<DL	0.5	2.14	5.27
7. Diethylphosphate (DEP)	2.25	<DL	4.42	9.02	13.2
8. Diethylthiophosphate (DETP)	<DL	<DL	0.7	1.47	2.62
9. Diethyldithiophosphate (DEDTP)	<DL			<DL	0.41
10. Atrazine	0.073				<DL
11. Atrazine mercapturate	<DL			<DL	0.072
Phthalates					
Metabolites of DEHP (DI-2-ethylhexyl phthalate)					
12. MEHHP	15	19	41	99	179
13. MEHP	2.2	2.4	5.2	11.8	22.1
14. MEOHP	6	11	22	53	107

Georgia Lab Lic. Code #067-007
CLIA ID# 11D0265349
New York Clinical Lab PFI #4578
Florida Clinical Lab Lic. #800008124

Testing Performed by Metametrix, Inc. 3425 Corporate Way, Duluth, GA 30096

Page 1

Laboratory Directors: J. Alexander Bralley, PhD
Robert M. David, PhD
David L. Scott, Jr. PhD

0762 Volatile Solvents - Whole Blood

Methodology: Gas Chromatography/Mass Spectrometry

	Results (ng/mL)	Percentile 50th	75th	90th	95th
1. Benzene	<DL	<DL	0.06	0.17	0.26
2. Ethylbenzene	<DL	<DL	0.05	0.08	0.11
3. Styrene	<DL	<DL	0.05	0.09	0.12
4. Toluene	<DL	<DL	0.43	0.68	
5. m,p-Xylene	<DL	0.13	0.2	0.28	0.34
6. o-Xylene	<DL	<DL	0.51	0.72	0.9

Percentile values are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, CDC, 2009.

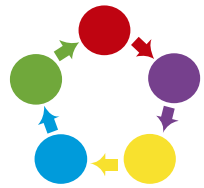
7. Hexane	211	183	209	254	278
8. 2-Methylpentane	45	52	63	75	88
9. 3-Methylpentane	93	100	116	142	164
10. Iso-octane	5.7	7.6	8.6	9.8	10.2

No national reference ranges are established for hexane, 2- and 3- methylpentane and iso-octane. Percentile ranges are based on patient samples analyzed at Metametrix.

<DL = less than detection limit

These levels provide a reference range to determine whether an individual has been exposed to higher levels of toxicants than found in the general population.

For interpretive information, visit www.metametrix.com/vs and select the Interpretive Guide from the downloads tab.



0763 Organophosphates Profile - Urine

Methodology: Gas Chromatography/Mass Spectrometry

	Results ug/g creatinine	Percentile 50th	75th	90th	95th
1. Dimethylthiophosphate (DMTP)	10	1.8	5.2	15.7	30.4
2. Dimethyldithiophosphate (DMDTP)	5.26	<DL	0.5	2.14	5.27
3. Diethylthiophosphate (DETP)	<DL	<DL	0.7	1.47	2.82
4. Diethyldithiophosphate (DEDTP)	<DL			<DL	0.41
5. Atrazine	0.32				<DL
6. Atrazine mercapturate	0.143			<DL	0.072

Creatinine = 66 mg/dL

Percentile values for organophosphates are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, CDC, 2009. No national reference ranges are established for atrazine or atrazine mercapturate; percentile ranges are based on patient samples analyzed at Genova Diagnostics.

These levels provide a reference range to determine whether an individual has been exposed to higher levels of toxicants than found in the general population.

<DL = less than detection limit

For interpretive information, visit www.metametrix.com/gp and select the Interpretive Guide from the downloads tab.

POTENTIALLY TOXIC METALS

METALS	RESULT µg/g creat	REFERENCE RANGE	WITHIN REFERENCE RANGE	ELEVATED	VERY ELEVATED
Aluminum	3.8	< 25			
Antimony	< dl	< 0.3			
Arsenic	19	< 108			
Barium	2	< 7			
Beryllium	< dl	< 0.5			
Bismuth	< dl	< 10			
Cadmium	0.4	< 0.8			
Cesium	4.3	< 9			
Gadolinium	< dl	< 0.3			
Lead	0.4	< 2			
Mercury	0.8	< 3			
Nickel	4.7	< 10			
Palladium	< dl	< 0.3			
Platinum	< dl	< 1			
Tellurium	0.2	< 0.3			
Thallium	0.2	< 0.5			
Thorium	< dl	< 0.03			
Tin	0.2	< 9			
Titanium	N/A	< 15			
Tungsten	< dl	< 0.4			
Uranium	< dl	< 0.03			

URINE CREATININE

	RESULT mg/dL	REFERENCE RANGE	2SD LOW	1SD LOW	MEAN	1SD HIGH	2SD HIGH
Creatinine	65.4	45- 225					

SPECIMEN DATA

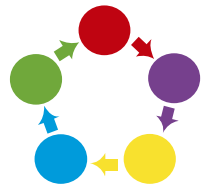
Comments:
Date Collected:
Date Received: 12/9/2010
Date Completed: 12/12/2010
Method: ICP-MS

pH upon receipt: Acceptable
<dl: less than detection limit
Provoking Agent: DMSA

Collection Period: timed: 6 hours
Volume: 1600 ml
Provocation:

INFECTIONS

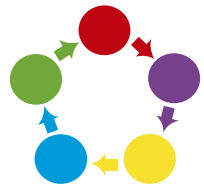
- Viral
  - Reactivated
- Bacterial
  - Atypical Bacteria
- Fungal
- Parasitic
- Endodontic Infections



TREATMENT

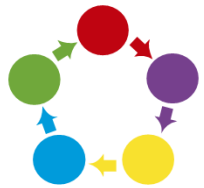
REMOVE THE TRIGGERS AND MEDIATORS

- Diet/Nutrition Protocol
  - Sugar
  - Trans and saturated fats
  - Polyunsaturated omega 6 oils (except GLA)
  - Toxins
  - Low fiber
- Food allergies/Sensitivities?
    - Elimination Diet
      - (Gluten, Dairy, Soy, Corn, Nightshade family)
- Dysbiosis/Altered Gut Microbiota/Leaky Gut
    - 4R
- Toxins in environment/home?
- Hormone Imbalance?
- Stress at work/home? or Toxic Relationships?
- Nutrient Deficiencies?
- Unhealthy Habits?
- Infections? Consider occult--dental



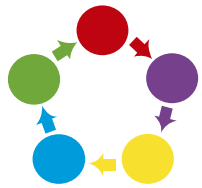
HOW DID THIS PERSON DEVELOP INSULIN RESISTANCE?

- Consider the Following:
  - Food allergies and/or sensitivities
  - Dysbiosis, leaky gut and gut microbiota
  - Toxins (POP's, heavy metals, pesticides, endogenous)
  - EMF/Dirty Electricity
  - Food additives or excesses
  - Digestive Insufficiencies
  - Oxidative Stress
  - Mitochondrial dysfunction
  - Obesity
  - Stress or adrenal fatigue/dysfunction
  - Lack of sleep
  - Hormone imbalances
  - Infections (bacterial/fungal/viral/parasitic and occult-dental)
  - Nutrient deficiencies/excesses
  - Rx Drugs (statins, PPI's,…)
  - Genetic predispositions/snp's
  - More than one cause?



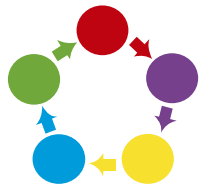
My Approach

- Nutritional Support with wholesome food (fresh, whole, unprocessed, organic, colorful, high fiber, with nuts, seeds and omega 3's) and fermented.
- Digestion
- Elimination Diet
  - personalize
- 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



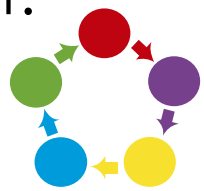
DIETARY MANAGEMENT FOR THE PATIENT WITH INSULIN RESISTANCE

- 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.
  - Agents that modify insulin responsiveness at the cellular level:
    - Spices
    - Herbs
    - Chromium
    - Vitamin D
    - Magnesium
    - Omega-3



GLYCEMIC INDEX AND GLYCEMIC LOAD

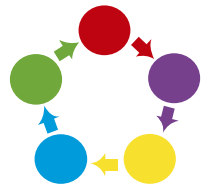
- Foods that have a low GI invariably have a low GL, while foods with an intermediate or high GI can range from a very low to very high GL, depending on usable carbohydrate in a serving.
- Therefore, one can reduce the GL of the diet by limiting foods that have both a high GI and a high carbohydrate content.
- The GL then allows for the assessment of the 'quantity' as well as the 'quality' of the carbohydrate intake in the diet.



INDIVIDUALS WITH HIGH INSULIN RESPONSE TO GLUCOSE ARE MOST SENSITIVE TO EFFECTS OF GLYCEMIC LOAD

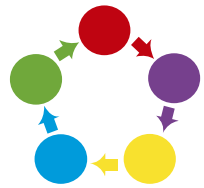
Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA. 2002;287:2414-2423.*

Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. *Pediatrics. 1999;103:E26.*



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.



Format: Abstract Send to

Adv Food Nutr Res. 2013;68:257-71. doi: 10.1016/B978-0-12-394294-4.00014-6.

Kiwifruit, carbohydrate availability, and the glycemic response.

Monro JA[1].

Author information

1 The New Zealand Institute for Plant & Food Research Limited, Palmerston North, New Zealand. john.monro@plantandfood.co.nz

Abstract

An appreciable proportion, about 10%, of the dry weight of kiwifruit consists of primary cell walls. About 80% of dry matter is available carbohydrate consisting of glucose, fructose, and sucrose, and about 10% is digestible protein. The cell wall component, being nonstarch polysaccharide, is undigested in the stomach and small intestine, so the component increases in relative concentration in the gut lumen where its physicochemical properties may be important in modulating carbohydrate digestion and absorption. Released from the constraint of fruit structure, the dietary fiber swells to four times its original volume during in vitro digestion. When the digested remnants are allowed to settle into a packed but uncompressed state, as in the gut, they reduce the rate of glucose diffusion by about 40% and profoundly reduce digesta mixing, especially in the presence of a low background of soluble viscous polysaccharide. An in vitro estimation of the glycemic index (GI) of carbohydrate in kiwifruit, and in vivo estimates show the carbohydrate to be of low GI. On a whole fruit basis because of the high water content of kiwifruit, a 100g kiwifruit would be equivalent to about 5g (1 teaspoon) of glucose in its effect on blood glucose; thus, kiwifruit have low glycemic impact and are suitable for those with diabetes.

PMID: 23394992 DOI: 10.1016/B978-0-12-394294-4.00014-6

[Indexed for MEDLINE]

…kiwifruit have low glycemic impact and are suitable for patients with diabetes.

PLoS One. 2014 Feb 28;9(2):e90352. doi: 10.1371/journal.pone.0090352. eCollection 2014.

Effects of whole grain, fish and bilberries on serum metabolic profile and lipid transfer protein activities: a randomized trial (Sysdimet).

Lankinen M[1], Kolehmainen M[2], Jääskeläinen T[1], Paananen J[1], Joukamo L[1], Kangas AJ[3], Soininen P[4], Poutanen K[5], Mykkänen H[1], Gylling H[6], Orešič M[7], Jauhiainen M[8], Ala-Korpela M[9], Uusitupa M[10], Schwab U[11].

Author information

Abstract

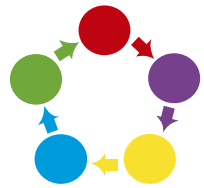
To Achieve Balance Start With Diet & Supplement.

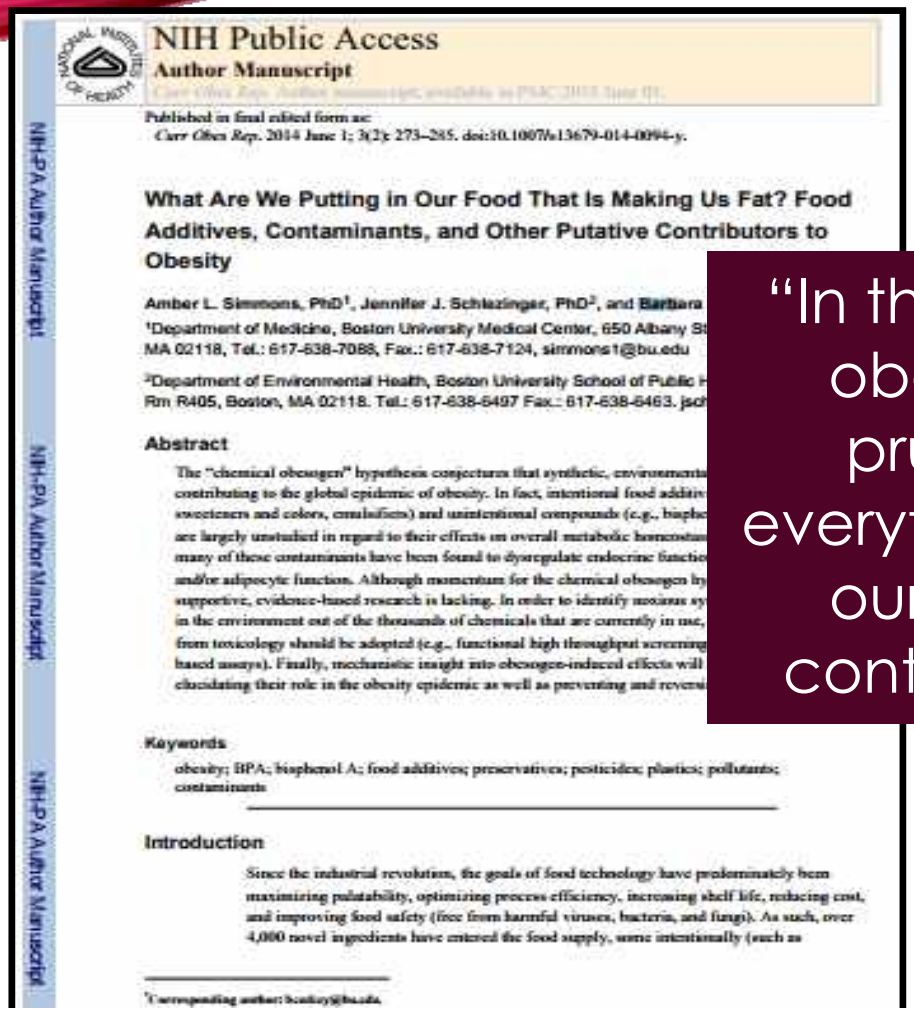
A diet rich in whole grain and low insulin response grain products, fatty fish and berries alter plasma lipid profile and improves glucose metabolism and markers of endothelial function and inflammation .

with increased concentration of large HDL particles, larger average diameter of HDL particles, and increased concentrations of large HDL lipid components, even though total levels of HDL cholesterol remained stable.

CONCLUSIONS: The results suggest that consumption of diet rich in whole grain, bilberries and especially fatty fish causes changes in HDL particles shifting their subclass distribution toward larger particles. These changes may be related to known protective functions of HDL such as reverse cholesterol transport and could partly explain the known protective effects of fish consumption against atherosclerosis.

TRIAL REGISTRATION: The study was registered at ClinicalTrials.gov NCT00573781.





NIH Public Access
Author Manuscript

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

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MA 02118, Tel.: 617-638-7088, Fax.: 617-638-7124, simmons1@bu.edu
[2]Department of Environmental Health, Boston University School of Public H
Rm R405, Boston, MA 02118. Tel.: 617-638-6497 Fax.: 617-638-6463. jsch

Abstract

The "chemical obesogen" hypothesis conjectures that synthetic, environmenta
contributing to the global epidemic of obesity. In fact, intentional food additiv
sweeteners and colors, emulsifiers) and unintentional compounds (e.g., bisphe
are largely unstudied in regard to their effects on overall metabolic homeostas
many of these contaminants have been found to dysregulate endocrine functio
and/or adipocyte function. Although momentum for the chemical obesogen hy
supportive, evidence-based research is lacking. In order to identify noxious sy
in the environment out of the thousands of chemicals that are currently in use,
from toxicology should be adopted (e.g., functional high throughput screening
based assays). Finally, mechanistic insight into obesogen-induced effects will
elucidating their role in the obesity epidemic as well as preventing and reversi

Keywords

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

Introduction

Since the industrial revolution, the goals of food technology have predominately been maximizing palatability, optimizing process efficiency, increasing shelf life, reducing cost, and improving food safety (free from harmful viruses, bacteria, and fungi). As such, over 4,000 novel ingredients have entered the food supply, some intentionally (such as

[1]Corresponding author: bcsday@bu.edu

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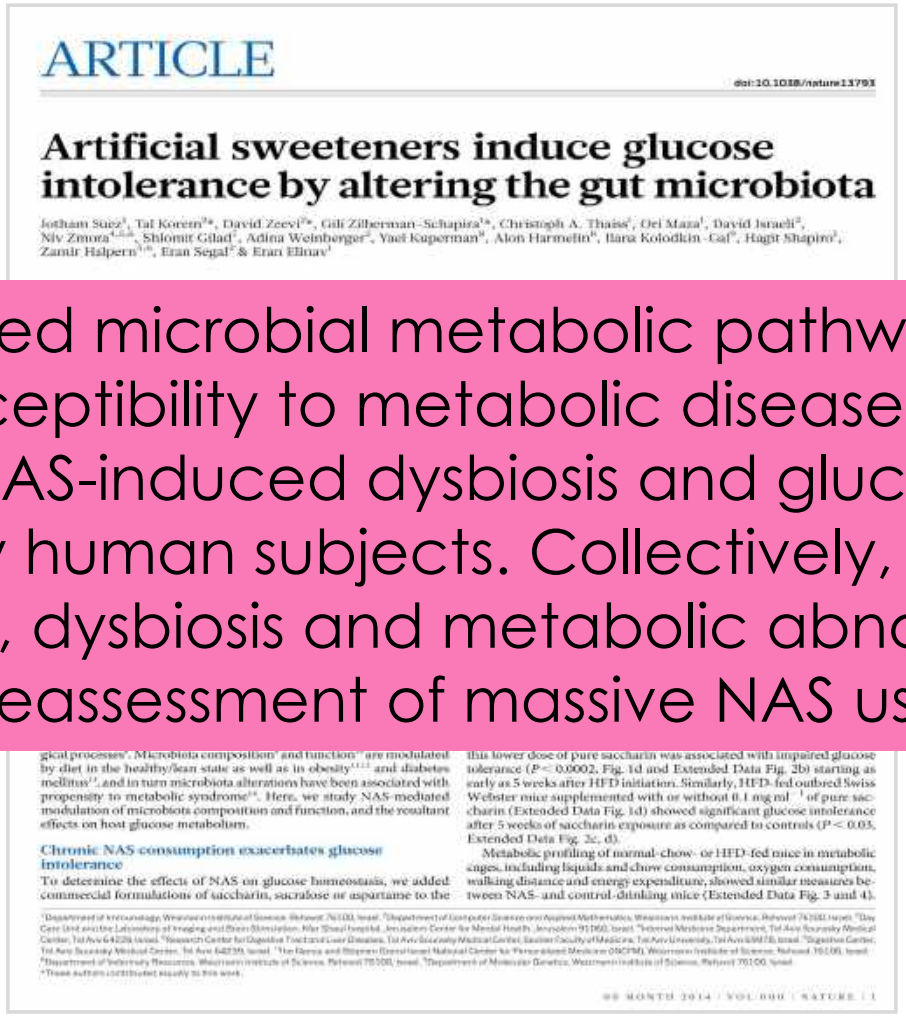
"In the light of the current obesity epidemic, it is prudent to evaluate everything that is added to our food for potential contributions to obesity".



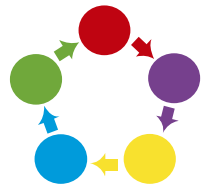
ARTICLE

doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez[1], Tal Korem[2]*, David Zeevi[2]*, Gili Zilberman-Schapira[1]*, Christoph A. Thaiss[2], Oren Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[8], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]

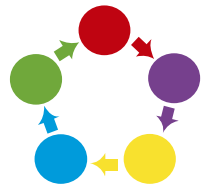
"We identify NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrate similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, our results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage."

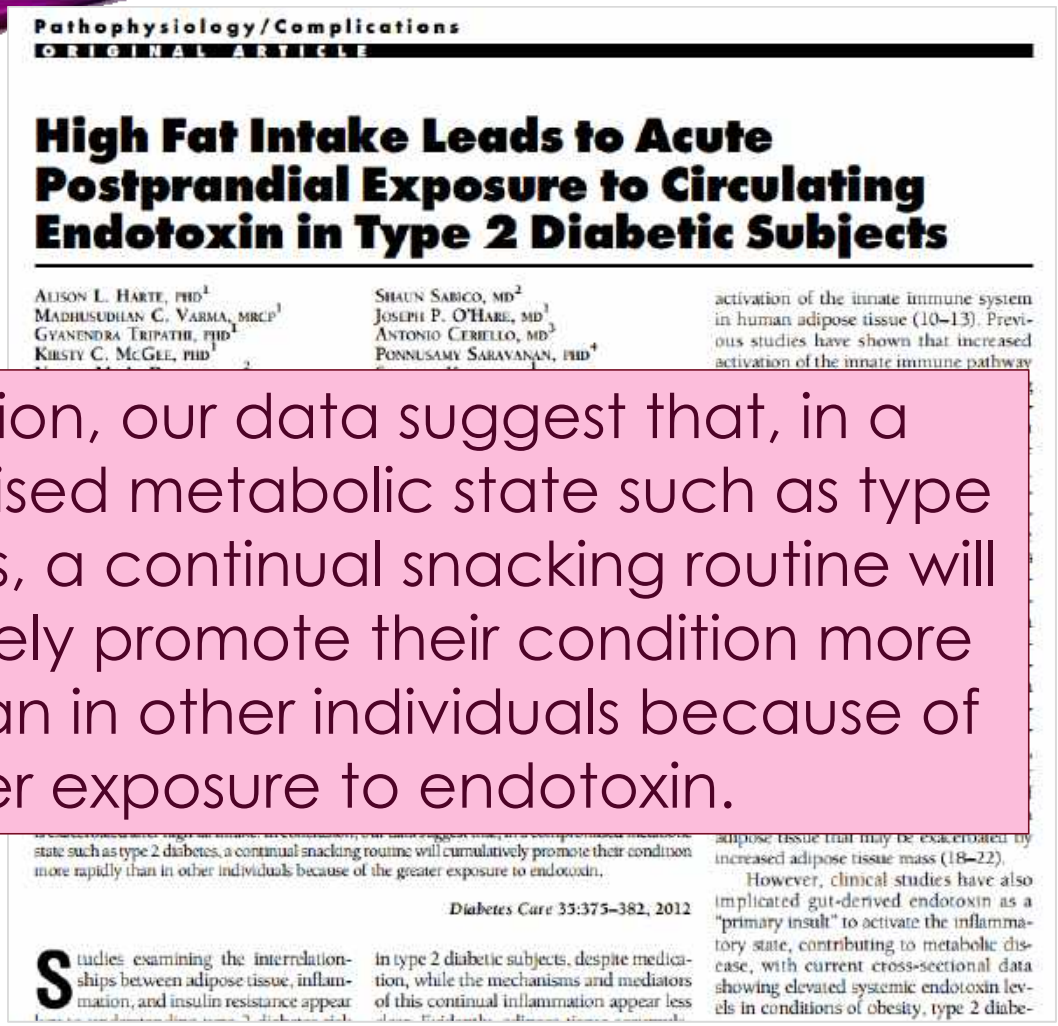


NUTRIENTS AND DIABETES RISK

- Diabetic patients had lower intake of vitamin A, riboflavin and vitamin B12.
- There was significantly lower intake of minerals by diabetic patients.
- Dietary carbohydrate and fat were positively correlated with HOMA-IR and IL-6. Protein and dietary fiber intakes were negatively correlated with HOMA-IR and IL-6.

Association of dietary factors with insulin resistance and inflammatory markers in subjects with diabetes mellitus and coronary artery disease in Indian population. Mahalle N, J diabetes Compications 2014 Jul-Aug;28(4):536-41. PMID:24746438





Pathophysiology/Complications

ORIGINAL ARTICLE

High Fat Intake Leads to Acute Postprandial Exposure to Circulating Endotoxin in Type 2 Diabetic Subjects

ALISON L. HARTE, PHD[1]
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activation of the innate immune system in human adipose tissue (10–13). Previous studies have shown that increased activation of the innate immune pathway

In conclusion, our data suggest that, in a compromised metabolic state such as type 2 diabetes, a continual snacking routine will cumulatively promote their condition more rapidly than in other individuals because of the greater exposure to endotoxin.

adipose tissue that may be exacerbated by increased adipose tissue mass (18–22).

However, clinical studies have also implicated gut-derived endotoxin as a "primary insult" to activate the inflammatory state, contributing to metabolic disease, with current cross-sectional data showing elevated systemic endotoxin levels in conditions of obesity, type 2 diabe-

Diabetes Care 35:375–382, 2012

Studies examining the interrelationships between adipose tissue, inflammation, and insulin resistance appear

in type 2 diabetic subjects, despite medication, while the mechanisms and mediators of this continual inflammation appear less

In this article, calorie restriction, improved β-cell function, improved insulin sensitivity, and alterations in gut physiology, bile acid metabolism, and gut microbiota are reviewed as the potential mechanisms of diabetes remission after Roux-en-Y gastric bypass and sleeve gastrectomy.

Review
Pathophysiology
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dmj
DIABETES & METABOLISM JOURNAL

A Gut Feeling to Cure Diabetes: Potential Mechanisms of Diabetes Remission after Bariatric Surgery

Young Min Cho
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A cure for type 2 diabetes was once a mere dream but has now become a tangible and achievable goal with the unforeseen success of bariatric surgery in the treatment of both obesity and type 2 diabetes. Popular bariatric procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy exhibit high rates of diabetes remission or marked improvement in glycemic control. However, the mechanism of diabetes remission following these procedures is still elusive and appears to be very complex and encompasses multiple anatomical and physiological changes. In this article, calorie restriction, improved β-cell function, improved insulin sensitivity, and alterations in gut physiology, bile acid metabolism, and gut microbiota are reviewed as potential mechanisms of diabetes remission after Roux-en-Y gastric bypass and sleeve gastrectomy.

Keywords: Bariatric surgery; Diabetes mellitus, type 2; Obesity; Roux-en-Y gastric bypass; Sleeve gastrectomy

INTRODUCTION

A potential cure for diabetes has arisen in an unexpected way. As diabetologists, we have tried to determine the pathophysiology of type 2 diabetes so that we can normalize glucose homeostasis without using any oral or injected medications. However, the results of our ceaseless efforts leave us far from a cure. With heart-aching disappointment in mind, we have practiced within a paradigm of "care not cure," which suggests that a cure is impossible to attain but that care is currently the best option. In 1995, Dr. Pories published a paper with a somewhat provocative title, "Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus [1]." At that time, Dr. Pories observed a drastic improvement in blood glucose levels after Roux-en-Y gastric bypass (RYGB) in obese subjects who had diabetes or impaired glucose tolerance. This was the earliest glimpse of a potential diabetes cure by surgical treatment. In a meta-analysis performed in 2004 including approximately 5,000 patients with type 2 diabetes [2], diabetes remission was observed in 76.8% of obese patients with type 2 diabetes who underwent any type of bariatric surgery. However, diabetes remission rates differed according to the type of surgery that patients received (47.9% for gastric banding, 71.6% for vertical banded gastroplasty, 83.7% for RYGB, and 98.9% for biliopancreatic diversion [BPD]) [2], which implies that the mechanism of diabetes remission is complex and encompasses a variety of anatomical, physiological, and molecular changes. In a recent randomized controlled trial with obese type 2 diabetes patients [3], the rate of diabetes remission (defined as a fasting glucose level of <100 mg/dL and an hemoglobin A1c (HbA1c) level of <6.5% with no antidiabetes medications) was 0% with medical therapy alone, 75% with RYGB, and 95% with BPD. In a 1-year randomized controlled trial in obese patients with uncontrolled type 2 diabetes [4], both RYGB and sleeve gastrectomy (SG) achieved improved glycemic control, defined as an HbA1c level of <6.0%, more frequently (42% and 37% of patients, respectively) than medical therapy alone (12% of patients). Therefore, bariatric surgery has evolved into metabolic/diabetes surgery. Furthermore, the benefits of bariatric surgery extend far beyond glycemic control. In the Swedish

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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.

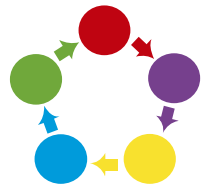
Soares de Oliveira Carvalho AP[1], Kimi Uehara S[2], Nogueria Netto JF[3], Rosa G[4].

Author information

Abstract in **English**, Spanish

Background: The metabolic syndrome is related to the increase in cardiovascular diseases. Polyunsaturated fatty acids from fish oil help in reducing cardiovascular risk factors and are natural bindings of PPAR 2. Objective: To evaluate the impact of hypocaloric diet associated with microencapsulate conducted a ranc presented metab placebo group (n oil containing 0.4 composition, clini t-test was used f considered p < 0 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.

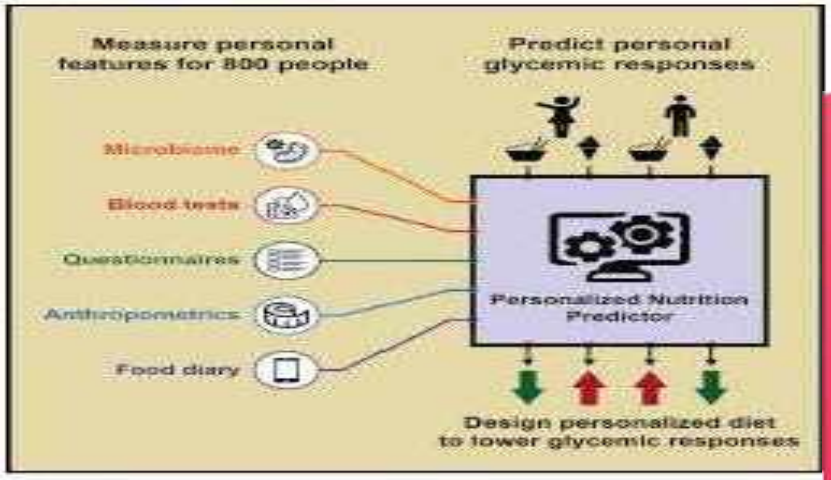
A hypocaloric diet associated with the consumption of microencapsulated fish oil was effective in reducing blood glucose, insulinemia and insulin resistance in women with MS.



Cell

Personalized Nutrition by Prediction of Glycemic Responses

Graphical Abstract



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

Correspondence

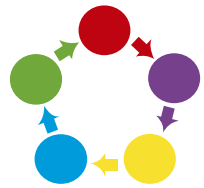
Highlights

- High interpersonal variability in post-meal glucose observed in an 800-person cohort
- 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

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

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

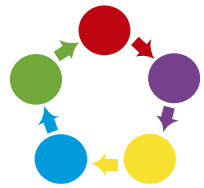
CellPress



SLOW DOWN AND CHEW YOUR FOOD

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

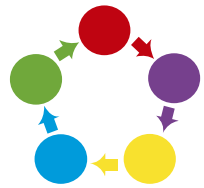
Fast eating and the risk of type 2 diabetes mellitus: a case-control study.Radzevičienė L, Clin Nutr. 2013 Apr;32(2):232-5. PMID:22800734



DRINKING SODA AND DIABETES RISK

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

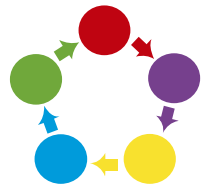
Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPICInterAct. Diabetologia. 2013 Jul;56(7):1520-30. PMID:23620057



EXERCISE

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

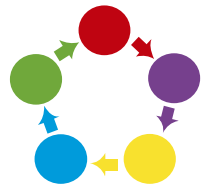
Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. A statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Am J Clin Nutr.*2004;80(2):257-263. Review.



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%.

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

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GLASBERGEN
"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"

J Physiother. 2011;57(3):173-8. doi: 10.1016/S1836-9553(11)70038-8.

Twenty minutes of passive stretching lowers glucose levels in an at-risk population: an experimental study.

Nelson AG[1], Kokkonen J, Arnall DA.

Author information

Abstract

QUESTION: Can passive static stretching lower blood glucose in an at-risk population?

DESIGN: Randomised, within-participant experimental study.

PARTICIPANTS: 22 adults (17 males) either at increased risk of Type 2 diabetes or with Type 2 diabetes.

INTERVENTION: The participants reported to the laboratory 2hr after eating a meal, and drank 355ml of fruit juice (~43g carbohydrate). Thirty minutes later, they underwent either a 40min passive static stretching regimen or a mock passive stretching regimen. Stretching consisted of six lower body and four upper body static passive stretches. For the mock stretches, the same positions were adopted, but no tension was applied to the musculature.

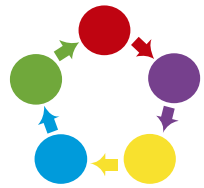
OUTCOME MEASURES: Blood glucose levels for both the stretching and mock stretching were analysed from a finger prick sample using a hand-held glucometer. Values were obtained at baseline (0min), during the regimen (20min), and after the regimen (40min) on both study days.

RESULTS: Compared to mock stretch, stretching resulted in a significantly greater drop in blood glucose at 20min (mean difference 28mg/dL, 95% CI 13 to 43; or 1.57mmol/L, 95% CI 0.72 to 2.39). This effect was also statistically significant at 40min (mean difference 24mg/dL, 95% CI 9 to 39; or 1.35mmol/L, 95% CI 0.50 to 2.17).

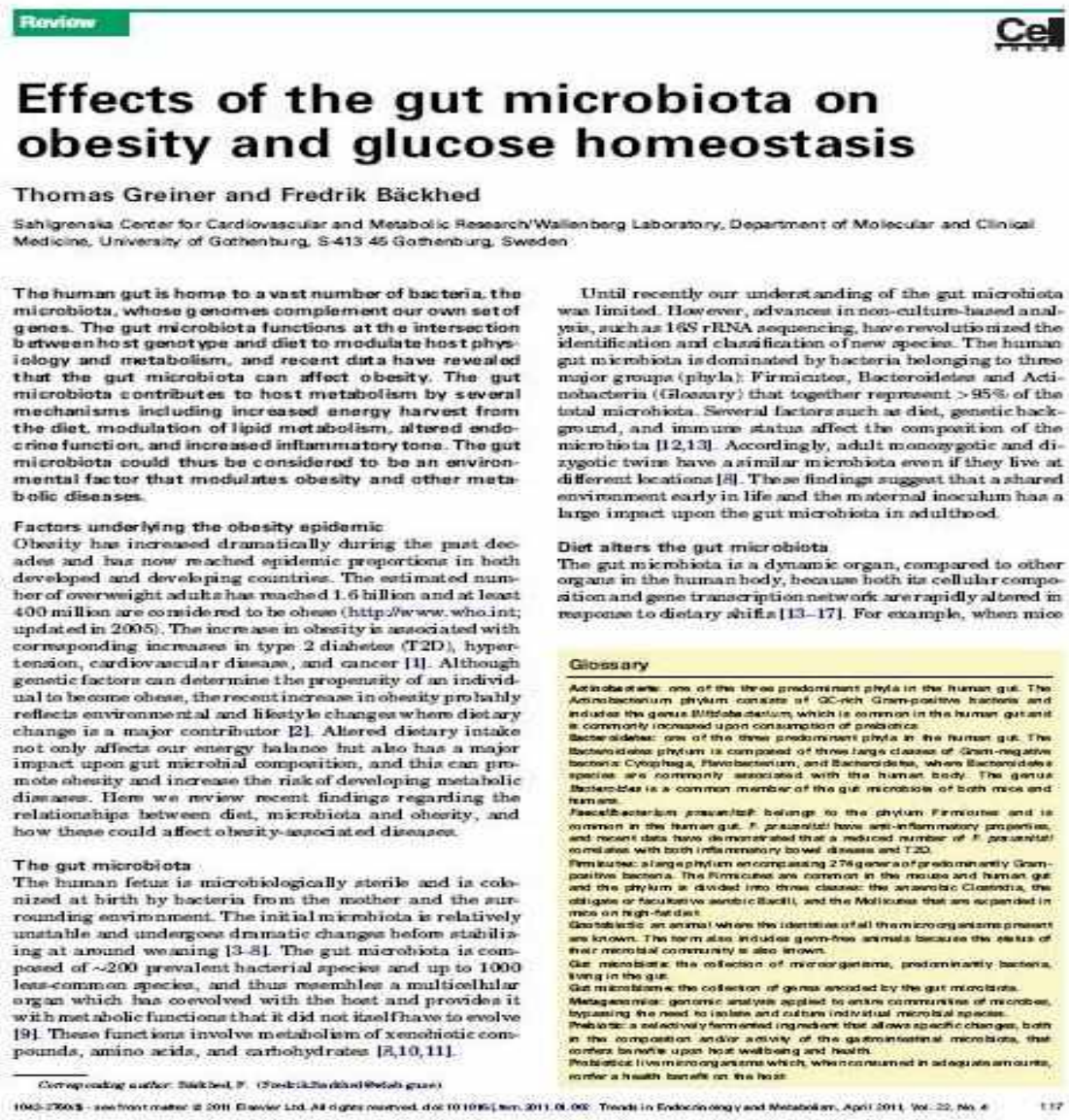
CONCLUSION: Th blood glucose levels.

PMID: 21843832 [Pub

These results suggest that passive static stretching of the skeletal muscles may be an alternative to exercise to help lower blood glucose levels.



"The gut microbiota could thus be considered to be an environmental factor that modulates obesity and other metabolic diseases."



Review

Cell press

Effects of the gut microbiota on obesity and glucose homeostasis

Thomas Greiner and Fredrik Bäckhed

Sahlgrenska Center for Cardiovascular and Metabolic Research/Wallenberg Laboratory, Department of Molecular and Clinical Medicine, University of Gothenburg, S-413 45 Gothenburg, Sweden

The human gut is home to a vast number of bacteria, the microbiota, whose genomes complement our own set of genes. The gut microbiota functions at the intersection between host genotype and diet to modulate host physiology and metabolism, and recent data have revealed that the gut microbiota can affect obesity. The gut microbiota contributes to host metabolism by several mechanisms including increased energy harvest from the diet, modulation of lipid metabolism, altered endocrine function, and increased inflammatory tone. The gut microbiota could thus be considered to be an environmental factor that modulates obesity and other metabolic diseases.

Factors underlying the obesity epidemic

Obesity has increased dramatically during the past decades and has now reached epidemic proportions in both developed and developing countries. The estimated number of overweight adults has reached 1.6 billion and at least 400 million are considered to be obese (http://www.who.int; updated in 2005). The increase in obesity is associated with corresponding increases in type 2 diabetes (T2D), hypertension, cardiovascular disease, and cancer [1]. Although genetic factors can determine the propensity of an individual to become obese, the recent increase in obesity probably reflects environmental and lifestyle changes where dietary change is a major contributor [2]. Altered dietary intake not only affects our energy balance but also has a major impact upon gut microbial composition, and this can promote obesity and increase the risk of developing metabolic diseases. Here we review recent findings regarding the relationships between diet, microbiota and obesity, and how these could affect obesity-associated diseases.

The gut microbiota

The human fetus is microbiologically sterile and is colonized at birth by bacteria from the mother and the surrounding environment. The initial microbiota is relatively unstable and undergoes dramatic changes before stabilizing at around weaning [3–8]. The gut microbiota is composed of ~200 prevalent bacterial species and up to 1000 less-common species, and thus resembles a multicellular organ which has coevolved with the host and provides it with metabolic functions that it did not itself have to evolve [9]. These functions involve metabolism of xenobiotic compounds, amino acids, and carbohydrates [8,10,11].

Until recently our understanding of the gut microbiota was limited. However, advances in non-culture-based analysis, such as 16S rRNA sequencing, have revolutionized the identification and classification of new species. The human gut microbiota is dominated by bacteria belonging to three major groups (phyla): Firmicutes, Bacteroidetes and Actinobacteria (Glossary) that together represent >95% of the total microbiota. Several factors such as diet, genetic background, and immune status affect the composition of the microbiota [12,13]. Accordingly, adult monozygotic and dizygotic twins have a similar microbiota even if they live at different locations [8]. These findings suggest that a shared environment early in life and the maternal inoculum has a large impact upon the gut microbiota in adulthood.

Diet alters the gut microbiota

The gut microbiota is a dynamic organ, compared to other organs in the human body, because both its cellular composition and gene transcription network are rapidly altered in response to dietary shifts [13–17]. For example, when mice

Glossary

Actinobacteria: one of the three predominant phyla in the human gut. The *Actinobacterium* phylum consists of GC-rich Gram-positive bacteria and includes the genus *Bifidobacterium*, which is common in the human gut and is commonly increased upon consumption of prebiotics.

Bacteroidetes: one of the three predominant phyla in the human gut. The Bacteroidetes phylum is composed of three large classes of Gram-negative bacteria: Cytophaga, Flavobacterium, and Bacteroidetes, where Bacteroidetes species are commonly associated with the human body. The genus *Bacteroides* is a common member of the gut microbiota of both mice and humans.

Faecalibacterium prausnitzii: belongs to the phylum Firmicutes and is common in the human gut. *F. prausnitzii* have anti-inflammatory properties, and recent data have demonstrated that a reduced number of *F. prausnitzii* correlates with both inflammatory bowel disease and T2D.

Firmicutes: a large phylum encompassing 274 genera of predominantly Gram-positive bacteria. The Firmicutes are common in the mouse and human gut and the phylum is divided into three classes: the anaerobic Clostridia, the obligate or facultative aerobic Bacilli, and the Mollicutes that are expanded in mice on high-fat diet.

Gnotobiotic: an animal where the identities of all the microorganisms present are known. The term also includes germ-free animals because the status of their microbial community is also known.

Gut microbiota: the collection of microorganisms, predominantly bacteria, living in the gut.

Gut microbiome: the collection of genes encoded by the gut microbiota.

Metagenomics: genomic analysis applied to entire communities of microbes, bypassing the need to isolate and culture individual microbial species.

Prebiotic: a selectively fermented ingredient that allows specific changes, both in the composition and/or activity of the gastrointestinal microbiota, that confers benefits upon host wellbeing and health.

Probiotics: live microorganisms which, when consumed in adequate amounts, confer a health benefit on the host.

Corresponding author: Bäckhed, F. (Fredrik.Backhed@wlab.gu.se)

1043-2760/$ - see front matter © 2011 Elsevier Ltd. All rights reserved. doi:10.1016/j.tem.2011.01.002 Trends in Endocrinology and Metabolism, April 2011, Vol. 22, No. 4

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

Received: 16 March 2011 / Accepted: 20 April 2011 / Published online: 11 May 2011

Abstract Obesity
health concern globa
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hand, the adoption
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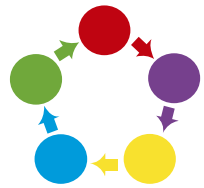
studies report an aber
and that gut microl
carbohydrate fermentation and bile acid metabolism, can impact on a number of mammalian physiological functions linked to obesity. The aim of this review is to present the evidence for a characteristic "obese-type" gut microbiota and to discuss studies linking 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

"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."

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



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

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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 [3] and Lorenza Putignani [1,*]

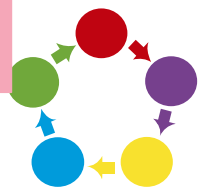
[1] Unit of Metagenomics, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio, Rome 400165, Italy; E-Mails: federica.delchierico@opbg.net (F.D.C.); pamela.vernocchi@opbg.net (P.V.)
[2] Interdepartmental Centre for Industrial Research-CIRI-AGRIFOOD, Alma Mater Studiorum, University of Bologna, Piazza Goidanich, Cesena-FC 47521, Italy
[3] Scientific Directorate, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio,

new tools, acting as a systems biology-based proof of evidence to evaluate MD effects on gut microbiota homeostasis. Data integration of food metabotypes and gut microbiota

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

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

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."



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 independent effect of the microbiota on fat accumulation has been demonstrated in mice, where transplantation of microbiota from obese mice or mice fed western diets to lean or germ-free mice produced fat accumulation among recipients. 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. Interestingly, certain probiotics are associated with weight gain both in animals and in humans. The effects are dependent on the probiotic strain, the host, and specific host characteristics, such as age and baseline nutritional status. Attention has recently been drawn to the association between antibiotic use and weight gain in children and adults. We herein review the studies describing the associations between the mic

Keywords: Fat, growth promoters, microbiota, obesity, probi
Article published online: 2 March 2013
Clin Microbiol Infect 2013; 19: 305–313

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

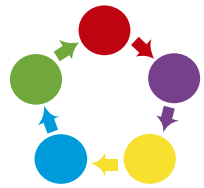
Introduction

Ten trillion to 100 trillion (10^{14}) microorganisms populate t
adult intestines [1,2]. The vast majority reside in the colo
where densities approach 10^{11}–10^{12} cells/mL. Almost all
these organisms are bacteria, and a minority are archaea
eukaryotes, and viruses [3,4]. Bacteria are classified from d
phylum to species level (Table 1). The two most abunda
bacterial phyla in humans and in mice are the *Firmicutes* (4
80%) and the *Bacteroidetes* (20–40%) [1,3,5]. Most of
representatives of these two phyla do not grow outside of the
host [1]. Babies acquire their initial microbiota from the
surrounding ecosystems, especially the maternal vaginal and
faecal microflora [2,6], and the human gut microbiome is shared
among family members [7,8]. The gut microbiota composition
depends on age, sex, geography, ethnicity, family, and diet, and
can be modulated by prebiotics, probiotics, and antibiotics.

The Association between Microbiota Composition and Obesity

Studies in mice have found a higher abundance of *Firmicutes* in obese mice and those fed on western diets, concomitant with

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.



Diabetes Metab Res Rev. 2016 Feb;32(2):143-68. doi: 10.1002/dmrr.2665. Epub 2015 Jul 1.

Probiotics as beneficial agents in the management of diabetes mellitus: a systematic review.

Razmpoosh E[1], Javadi M[1], Ejtahed HS[2,3], Mirmiran P[4,5].

Author information

Abstract

Probiotics have been suggested to play an important role in the management of diabetes. We conducted a systematic review on the role of probiotics in modulating parameters related to diabetes in animal and human experiments. We searched Pubmed, Scopus and Cochrane central until June 2014, concerning the effects of probiotics on hyperglycemia, hyperinsulinemia and their anti-diabetic efficacies by modulating the activities of proinflammatory and antioxidant factors. Our initial search retrieved 1120 reports. After screening titles and abstracts, 72 full-text articles were reviewed for eligibility. were, in particular, use studies showed signifi blood glucose, glycate significant changes in only one human and c demonstrated benefici parameters, although,

We found that probioitcs have beneficial effects on glycemic controls, as all human studies showed significant reductions in at least one of the primary outcome endpoints which were the levels of fasting plasma glucose, postprandial blood glucose, glycated haemoglobin, insulin, insulin resistance and onset of diabetes

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

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[5], 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 models consuming Westernized 'fast food' diet, and found $CD4^+$ T helper (Th)17-biased immunity and changes in microbial communities and abdominal fat with obesity after eating the Western chow. In striking contrast, eating probiotic yogurt together with Western chow inhibited age-associated weight gain. We went on to test whether a bacteria found in yogurt may serve to lessen fat pathology by using purified *Lactobacillus reuteri* ATCC 6475 in drinking water. 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. These beneficial microbe effects were transferable into naïve recipient animals by purified $CD4^+$ T cells alone. Specifically, bacterial effects depended upon active immune tolerance by induction of $Foxp3^+$ regulatory T cells (Treg) and interleukin (I)-10, without significantly changing the gut microbial ecology or reducing *ad libitum* caloric intake. Our finding that microbial targeting restored $CD4^+$ T cell balance and yielded significantly leaner animals regardless of their dietary 'fast food' indiscretions suggests population-based approaches for weight management and enhancing public health in industrialized societies.

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

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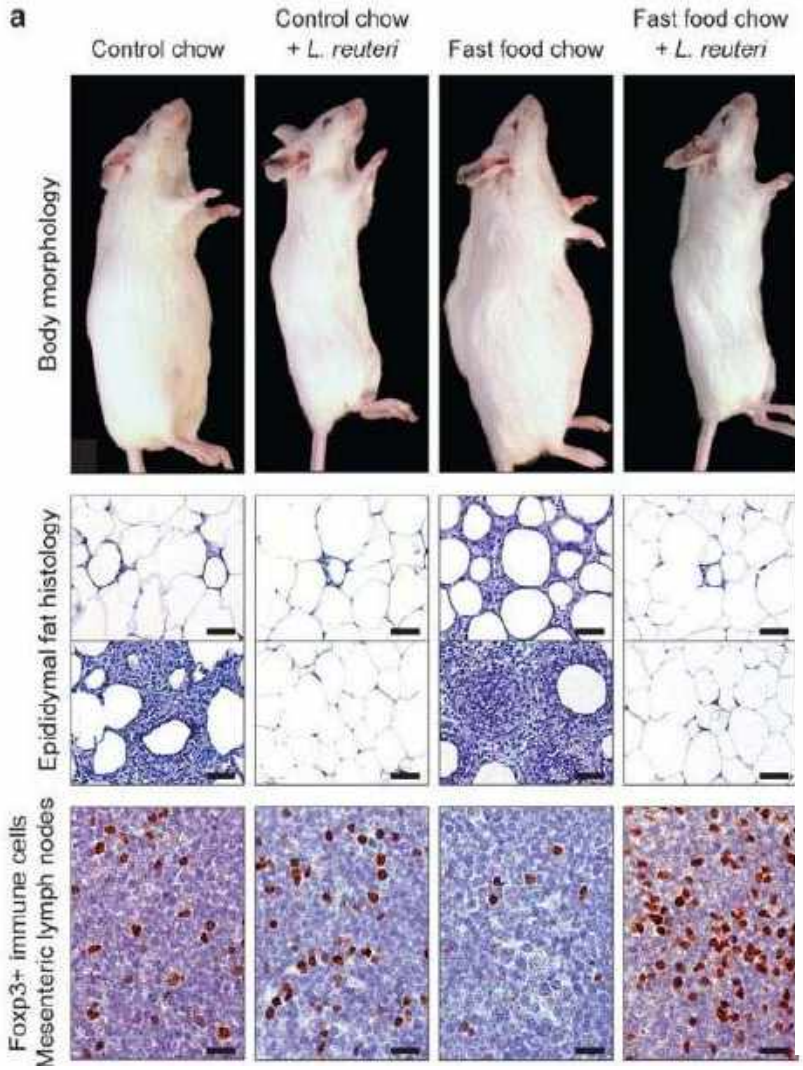
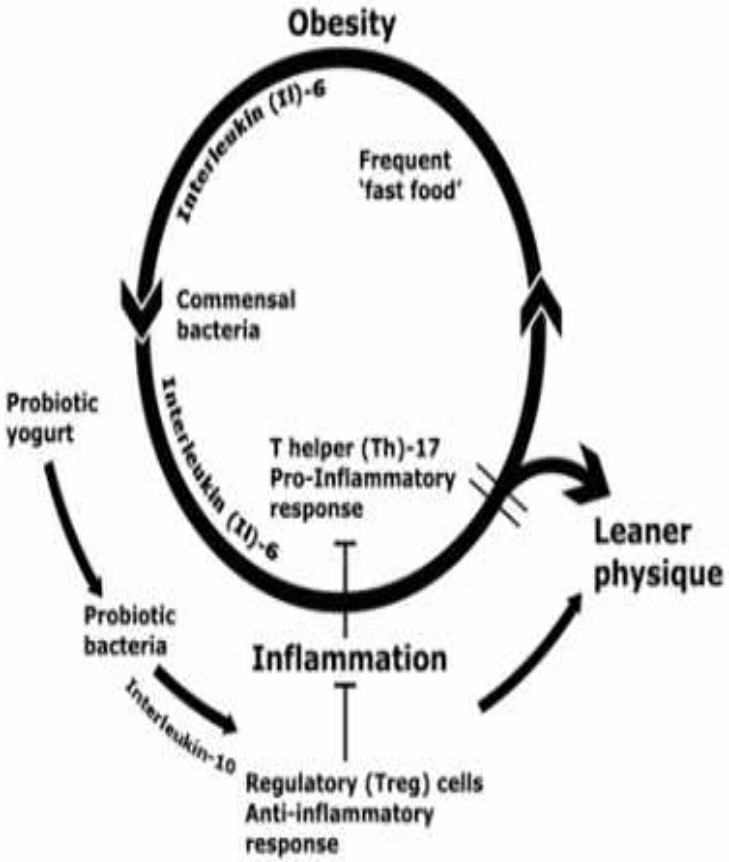
Introduction

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 experimental data suggest that the white adipose tissue of obese organisms is in a low-grade, persistent state of chronic inflammation that exerts adverse systemic effects [2–3]. The most prominent inflammatory cell type of the obesity-associated inflammation is the adipose tissue macrophage. Macrophages are recruited and surround dead adipocytes, thus creating the so-called crown-like structures (CLS). These cells along with hypertrophic adipocytes are thought to be the key cells initiating the unique subclinical pro-inflammatory signaling cascade encountered in obesity [2,4–5]. Macrophages, B and T lymphocytes, and up-regulated pro-inflammatory cytokines including TNF-α, 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 shows while dietary 'fast food' contributes to obesity, eating yogurt surprisingly prevents age-associated weight gain, though the mechanism is unknown. It has been thought that slenderizing outcomes of yogurt are due to a probiotic bacteria-mediated mechanism [1]. Dietary probiotic consumption alters gut microbiota and may be an effective strategy not only for weight loss but also for preventing weight regain after loss [11–14]. Furthermore, alterations in the composition of gut microbiota may affect not only gut health but also distant tissues and overall health and longevity via immune-mediated mechanisms [15–20].





Theofilos Poutahidis et al. Microbial Reprogramming Inhibits Western Diet-Associated Obesity. PLoS ONE 8(7): e68596. doi:10.1371/journal.pone.0068596.

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Original Article

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

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Department of Family Medicine, Obesity Clinic, Yeungnam University College of Medicine, Daegu; [1]R&D Center of Bioneer Corporation, Daejeon; [2]Department of Health Administration, Namseoul University, Cheonan; [3]Department of Physiology, Center of Metabolism and Obesity, Yeungnam University College of Medicine, Daegu, Korea

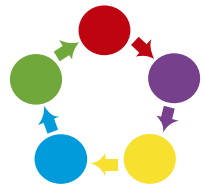
Background: *Lactobacillus gasseri* BNR17 is a type of probiotic strain isolated from human breast milk. A study was reported regarding the fact that BNR17 was an inhibitor of obesity and diabetic activities in the human body through previous animal experiments. This study was furthered to investigate the effect of BNR17, a probiotic strain isolated from human breast milk, on obese and overweight adults.

Methods: Sixty-two obese volunteers aged 19 to 60 with body mass index ≥ 23 kg/m^2 and fasting blood sugar ≥ 100 mg/dL 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



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 2 h blood glucose levels, as well as OGTT levels.

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

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Gut microbiota mediated low-grade inflammation is involved in the onset of type 2 diabetes (T2DM). In this study, we used a high fat sucrose (HFS) diet-induced pre-insulin resistance and a low dose-STZ-HFS rat models to study the effect and mechanism of *Lactobacillus casei* Zhang in protecting against T2DM onset. Hyperglycemia was favorably suppressed by *L. casei* Zhang treatment. Moreover, the hyperglycemia was connected with type1 immune response, high plasma bile acids and urine chloride ion loss. This chloride ion loss was significantly prevented by *L. casei* via upregulating of chloride ion-dependent genes (*CIC1-7, GlyRα1, SLC26A3, SLC26A6, GABAAα1, Bestrophin-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 chloride ions can act 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 lipopolysaccharide-binding protein[10]. One research showed that *B. animalis* 420 could prevent mice from obesity-induced T2DM through an improvement of bacterial translocation and overall inflammatory status[11]. Recently, the gut microbe, *Akkermansia muciniphila*, exhibited an insulin resistance-reducing effect and may have potential application in T2DM[12].

Our previous research showed that *L. casei* Zhang could improve impaired glucose tolerance in rats due to altered microbiota composition which led to an upregulation of osteocalcin level[13]. The aims of the present study were to investigate whether probiotic *L. casei* Zhang supplementation could prevent the symptoms of rat model of T2DM and identify its mechanisms.

Methods

Animals and housing. The protocol was approved by the Animal Care and Use Committee at Inner Mongolia Agricultural University in Hohhot, China. All the methods were carried out in accordance with the approved guidelines. Male sprague-dawley (SD) rats, initial weight

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.

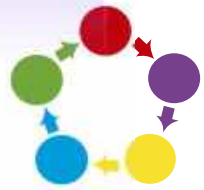
Rajkumar H[1], Mahmood N[1], Kumar M[1], Varikuti SR[1], Challa HR[1], My

Author information

Abstract

To evaluate the effects of probiotic (VSL#3) and omega-3 fatty ac and inflammation, we conducted a clinical trial in 60 overweight (BM years. After initial screening the subjects were randomized into fou groups received, respectively, placebo, omega-3 fatty acid, probic probiotic, for 6 weeks. Blood and fecal samples were collected at l probiotic (VSL#3) supplemented group had significant reduction in 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.

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



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journal homepage: www.nutritionjrnl.com

Pilot study

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

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Homocysteine
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ABSTRACT

Objective: Metabolic syndrome (MetS) in postmenopausal women is an important risk factor for cardiovascular morbidity, especially stroke and coronary heart disease and mortality. Preventing and treating MetS would be useful in preventing disability and promoting normal aging. Previous human studies have found some beneficial effects of *Lactobacillus* species on some isolated parameters of MetS. Nevertheless, we are not aware, to date, of any study which has verified the influence of probiotics in patients with MetS. Therefore, the aim of the present study was to evaluate the influence of fermented milk with *L. plantarum* in the classical parameters related to MetS, as well as in other parameters related to cardiovascular risk in postmenopausal women.
Methods: Twenty-four individuals were paired by age, ethnicity, and body mass index in two groups: Non-fermented milk (NFM – 12) 80 mL/d and fermented milk (FM – 12) 80 mL/d. Anthropometric and blood pressure measurements, biochemical, inflammatory, and immunologic

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

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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MICROBIAL ECOLOGY in Health and Disease

COMMENTARY

ENGIHR SUPPLEMENT

Manipulating the gut microbiota to maintain health and treat disease

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Background: The intestinal microbiota composition varies between healthy and diseased individuals for numerous diseases. Although any cause or effect relationship between the alterations in the gut microbiota and disease is not always clear, targeting the intestinal microbiota might offer new possibilities for prevention and/or treatment of disease.

Objective: Here we review some examples of manipulating the intestinal microbiota by prebiotics, probiotics, 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/*Eubacterium 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. Prebiotics 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, prebiotics, probiotics

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Microbes existed on Earth long before humans; therefore, it is logical that humans have learned to live with them, in fact co-evolved with them. All animals can be looked upon as dualistic "super-organisms", i.e. their selves and their microbiota. Establishment and maintenance of an intestinal microbiota is of utmost importance for health in all mammals.

In the last 2–3 decades, an increasing number of metagenomic analyses have provided us with information about differences in gut microbiota composition between healthy and diseased individuals. Generally, high microbial diversity is thought to be associated with a healthy gut microbiota, while loss of diversity seems to correlate with disease. Nowadays over 25 diseases or syndromes have been linked to an altered intestinal microbiome (1). These diseases range from gastrointestinal diseases like inflammatory bowel diseases (IBDs), irritable bowel syndrome, and colorectal cancer to metabolic diseases and potentially even to diseases like Alzheimer's disease, autistic spectrum disorders, chronic fatigue syndrome, Parkinson's disease, and autoimmune diseases like rheumatoid arthritis and multiple sclerosis. The most studied disease conditions in relation to intestinal microbiota are obesity, metabolic syndrome, and type II diabetes on

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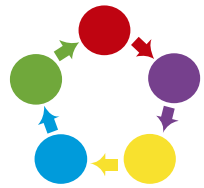
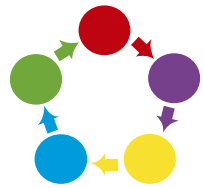
Prebiotics act to enhance the growth and/or activity of bacteria that are resident in the colon, acting as growth substrates to selectively boost numbers and/or activities of particular bacteria.

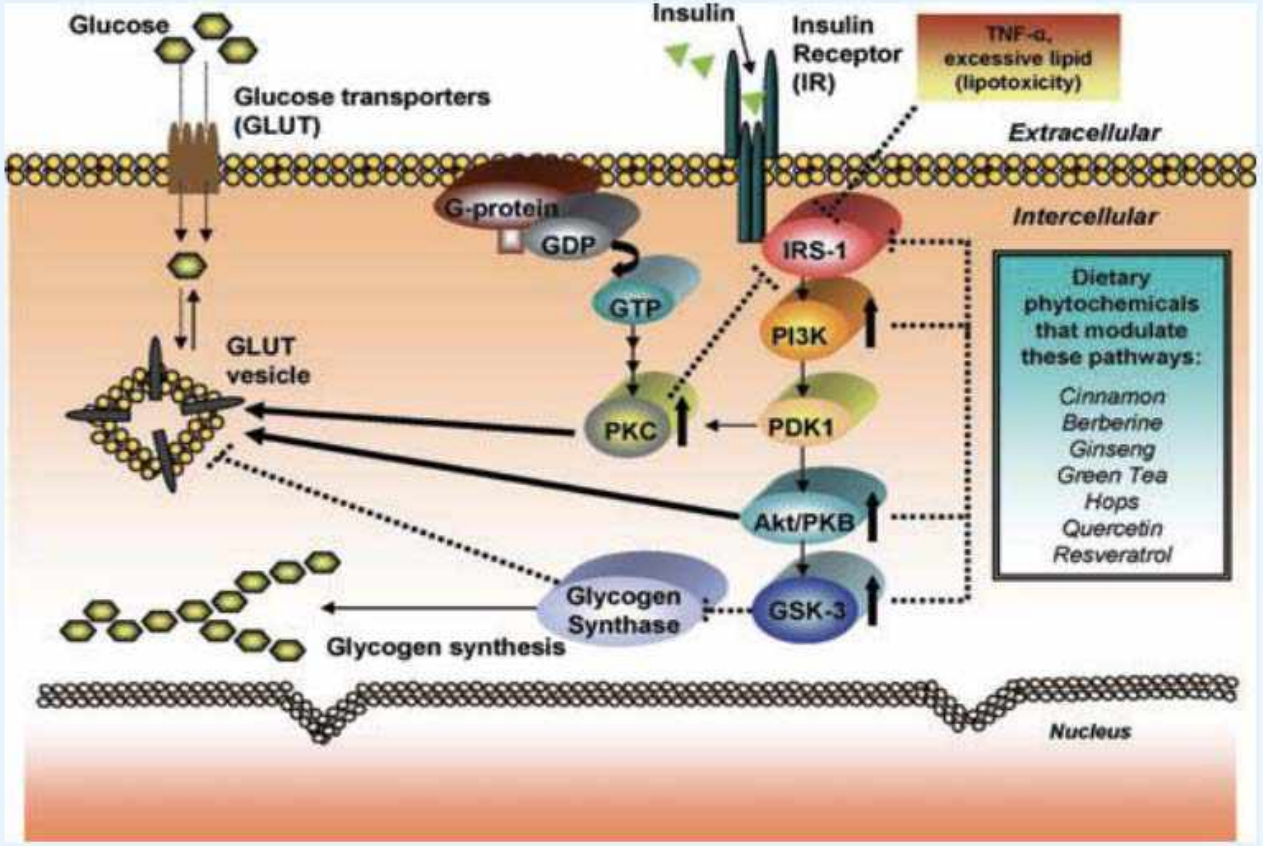


MANY PHYTOCHEMICALS WORK AS TISSUE SPECIFIC KINASE RESPONSE MODULATORS (SKRM'S)

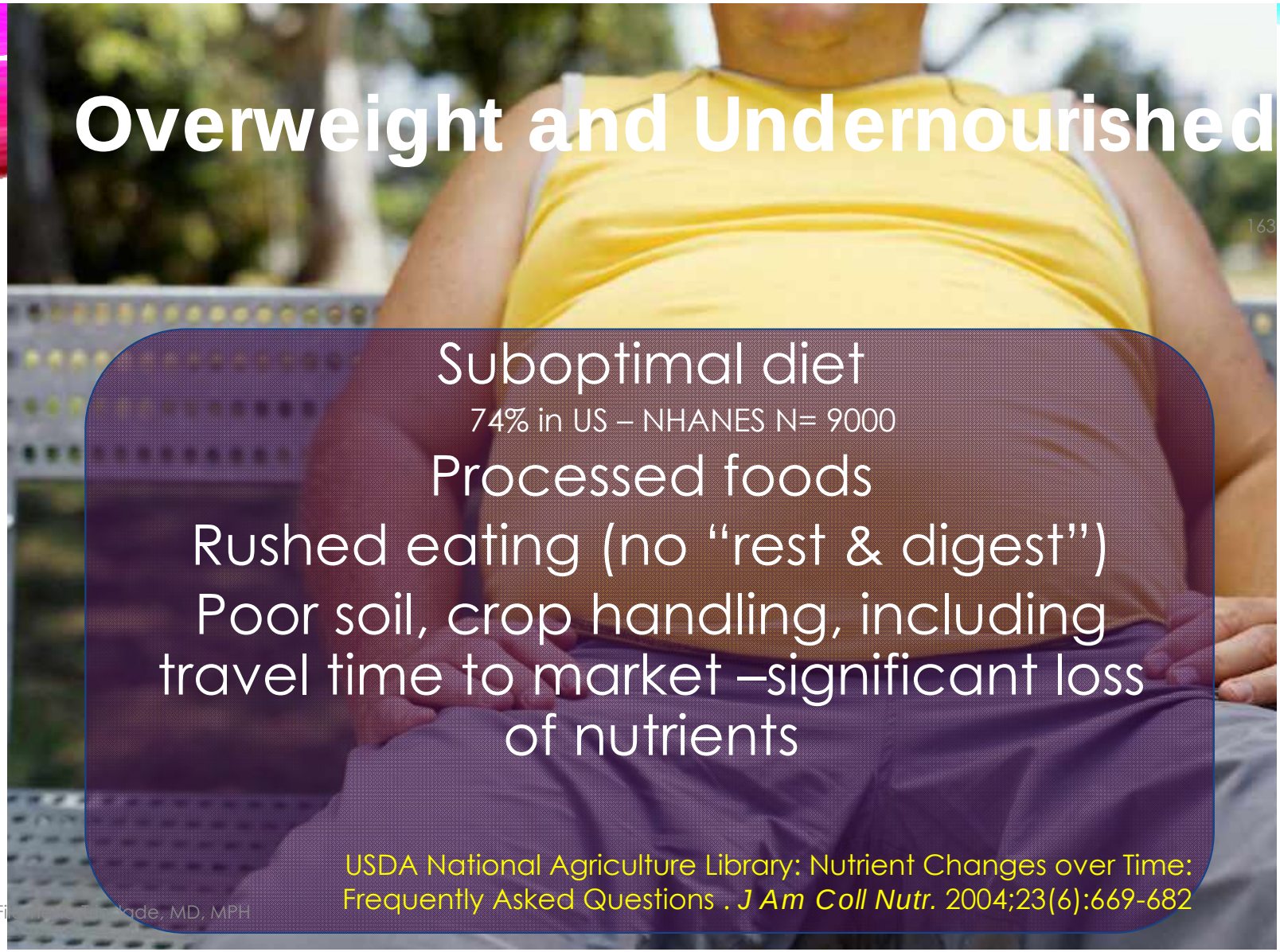


Dietary Recommendations for Insulin Resistance Beyond Macronutrients

Minich and Bland, Nutrition Reviews 2008 66(8):429-444.



Overweight and Undernourished



Suboptimal diet

74% in US – NHANES N= 9000

Processed foods

Rushed eating (no "rest & digest")

Poor soil, crop handling, including travel time to market –significant loss of nutrients

USDA National Agriculture Library: Nutrient Changes over Time: Frequently Asked Questions . *J Am Coll Nutr.* 2004;23(6):669-682

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]

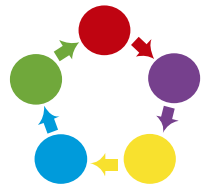
Sardines have the best ratio of Selenium/Mercury

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

NUTRIENTS KNOWN TO MODIFY INSULIN RESPONSIVENESS AT THE CELLULAR LEVEL

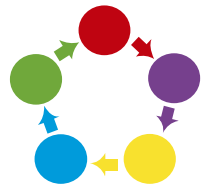
- Chromium
- Alpha-lipoic acid
- CoQ10
- Vitamin D
- Magnesium
- Vitamin C, vitamin E and other antioxidants
- Omega 3 fatty acids
- Curcumin
- Vanadium
- Serum kinase receptor modulators (SKRM's)



- 600 to 1800 mg/day of alpha lipoic acid (ALA) can improve insulin sensitivity in patients with type 2 diabetes.
- 600-1200 mg/day of ALA may improve microcirculation and diabetic polyneuropathy.

Jacob S, et al. Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo- controlled pilot trial. Free Radic Biol Med, 1999. 27(3-4): p. 309-14.

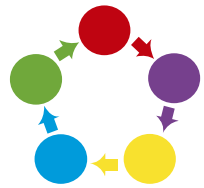
Haak E, et al. Effects of alpha-lipoic acid on microcirculation in patients with peripheral diabetic neuropathy. Exp Clin Endocrinol Diabetes, 2000. 108(3): p. 168-74.



- 120 mg/day of Coenzyme Q10 improves glycemic control and blood pressure in NIDDM
- 200mg of CoQ10 daily improved HgA1C and blood pressure in NIDDM patients.

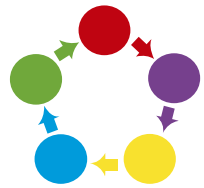
Singh RB, et al. Effect of hydrosoluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery disease. J Hum Hypertens, 1999. 13(3): p. 203-8.

Hodgson JM, et al. Coenzyme Q(10) improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. Eur J Clin Nutr, 2002. 56(11): p. 1137-42.



- Positive correlation of 25(OH)D concentration with insulin sensitivity.
- Negative effect of hypovitaminosis D on beta cell function.
- Subjects with hypovitaminosis D are at higher risk of insulin resistance and the metabolic syndrome.
- Increasing 25(OH)D from 10-30 ng/mL can improve insulin sensitivity by 60%.

Chiu KC, Chu A, Go VL, Saad MF Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr. 2004 May;79(5):820-5.



Cholecalciferol improves glycemic control in type 2 diabetic patients: a 6-month prospective interventional study

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Dalia A Shaheen[2]

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Background and purpose: To investigate the effects of vitamin D supplementation on glucose homeostasis and lipid profile in type 2 diabetic patients who have vitamin D deficiency.

Patients an

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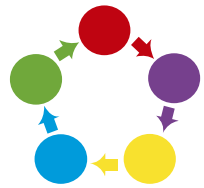
lipid profile were measured. Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated whenever fasting insulin (FI) was available. Forty-one patients (27 males and 14 females) were started on cholecalciferol replacement–45,000 units once weekly for 8 weeks and then 22,500 units once weekly for 16 weeks. Calcium carbonate tablets 500 mg once daily were also prescribed for the initial 2 months of treatment. Measured variables were reassessed after 6 months of replacement therapy. During the trial, subjects were instructed not to change their diabetes drugs or lifestyle.

"Cholecalciferol helps improve blood glucose control and cholesterol profile in vitamin D3-deficient type 2 diabetic patients".



- 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.

1. Barbagallo M, et al. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. Mol Aspects Med, 2003. **24**(1-3): p. 39-52

2. Guerrero-Romero F, et al: *Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. Diabetes Metab 2004;30:253–258*

OPEN ACCESS Freely available online

PLOS ONE

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

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Abstract

Background: Magnesium plays a role in glucose and insulin homeostasis and evidence suggests that magnesium intake is associated with insulin resistance (IR). However, data is inconsistent and most studies have not adequately controlled for critical confounding factors.

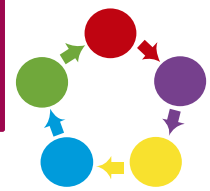
Objective: The study investigated the association between magnesium intake and IR in normal-weight (NW), overweight (OW) and obese (OB) along with pre- and post- menopausal women.

Design: A total of 2295 subjects (590 men and 1705 women) were recruited from the CODING study. Dietary magnesium intake was computed from the Willett Food Frequency Questionnaire (FFQ). Adiposity (NW, OW and OB) was classified by

"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."

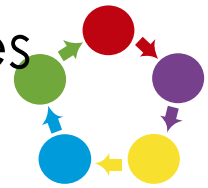
and the Canadian Institute for Health Research (operating grant: OOP-77984 to Guang Sun). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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



MICRONUTRIENT RECOMMENDATIONS

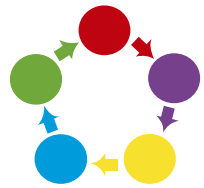
- Chromium: If using generally give 200mcg/daily if insulin resistant. Likely most effective if deficient, but difficult to test.
- Vitamin D: Test 25(OH)D and supplement as appropriate (or supplement 2000-5000) IU/daily
- Magnesium: Generally give 200-400 mg. Likely most effective if deficient, accurate 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.



CHROMIUM AND INSULIN RESISTANCE

- 92 pts with PCOS and infertility resistant to clomiphene
- "Chromium picolinate effectively reduced insulin resistant and treated hyperinsulinemia as well as hyperandrogenemia"
- Randomized clinical trial

Amooee, S. Metformin versus chromium picolinate in clomiphene citrate-resistant patients with PCOs: A double-blind randomized clinical trial. Iran J Reprod Med. 2013 Aug;11(8):611-8



Format: Abstract Send to

Arthritis Care Res (Hoboken). 2011 Sep;63(9):1295-306. doi: 10.1002/acr.20519.

Effect of oral vitamin C supplementation on serum uric acid: a meta-analysis of randomized controlled trials.

Juraschek SP[1], Miller ER 3rd, Gelber AC.

Author information

1 Johns Hopkins University School of Medicine, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21224, USA.

Abstract

OBJECTIVE: To assess the effect of vitamin C supplementation on serum uric acid (SUA) by pooling the findings from published randomized controlled trials (RCTs).

METHODS: A total of 2,082 publications identified through systematic search were subjected to the following inclusion criteria: 1) RCTs conducted on human subjects, 2) reported end-trial SUA means and variance, 3) study design with oral vitamin C supplementation and concurrent control groups, and 4) trial duration of at least 1 week. Trials that enrolled children or patients receiving dialysis were excluded. Two investigators independently abstracted trial and participant characteristics. SUA effects were pooled by random-effects models and weighted by inverse variance.

RESULTS: Thirteen RCTs were identified in the Medline, EMBase, and Cochrane Central Register of Controlled Trials databases. The total number of participants was 556, the median dosage of vitamin C was 500 mg/day, trial size ranged from 8-184 participants, and the median study duration was 30 days. Pretreatment SUA values ranged from 2.9-7.0 mg/dl (Système International d'Unités [SI units]: 172.5-416.4 μmoles/liter). The combined effect of these trials was a significant reduction in SUA of -0.35 mg/dl (95% confidence interval -0.66, -0.03 [P = 0.032]; SI units: -20.8 μmoles/liter). Trial heterogeneity was significant (I(2) = 77%, P < 0.0 reductions in uric acid in trials that were placebo controlled.

CONCLUSIONS: In aggregate, vitamin C supplementation significantly lov supplementation can reduce hyperuricemia or prevent incident and recurre

"vitamin C can lower serum uric acid"

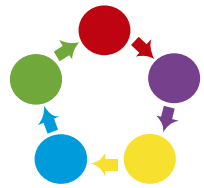
Comment in

Oral vitamin C supplementation and serum uric acid: comment on the article by Juraschek et al. [Arthritis Care Res (Hoboken). 2012]

PMID: 21671418 PMCID: PMC3169708 DOI: 10.1002/acr.20519

[Indexed for MEDLINE] **Free PMC Article**

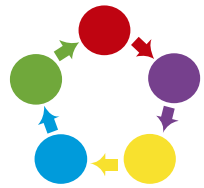
FILOMENA TRINDADE, MD, MPH



STRESS

- Autonomic dysfunction with sympathetic over-activity exacerbates insulin resistance and lipid and glucose metabolism and promotes central obesity.
- Techniques to enhance parasympathetic and reduce sympathetic activity, such as yoga or meditation, can have protective or even therapeutic benefit in metabolic syndrome and diabetes.

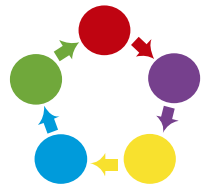
Rosmond R, Dallman MF, Bjorntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities.
J Clin Endocrinol Metab. 1998;83(6):1853-1859.



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

1. Health Psychol. 2016 Dec;35(12):1356-1363.
2. Oxid Med Cell Longev. 2017: 7928981



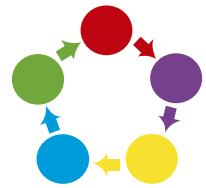
"Don't worry, be happy!"

Published in final edited form as:
Am Heart J. 2008 October ; 156(4): 759.e1–759.e7. doi:10.1016/j.ahj.2008.07.009.

Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men

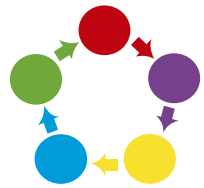
"Autonomic dysregulation leading to inflammation may represent one common pathway through which traditional risk factors promote development of CAD."

(Am Heart J. 2008 Oct;156(4):759.e1-7.)



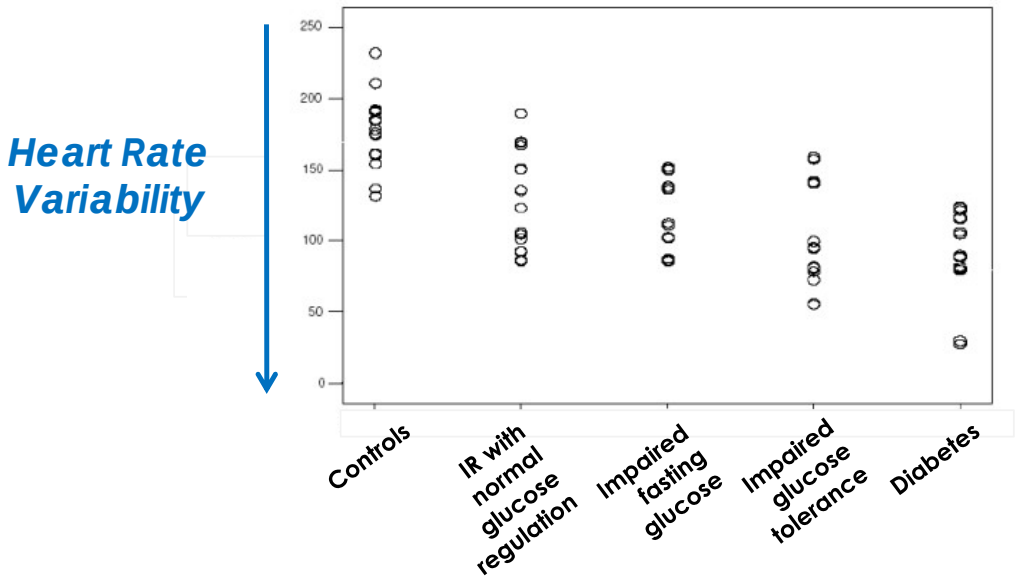
HEART RATE VARIABILITY (CONT.)

- Lower heart rate variability is associated with…
  - Hypertension
  - Abnormal cholesterol
  - Smoking
  - Physical inactivity
  - Obesity
  - Aging
  - Inflammation
  - Insulin resistance
  - Hyperglycemia and diabetes
  - Beta-cell impairment & higher levels of Proinsulin…



HRV & GLUCOSE REGULATION

- Autonomic dysfunction increases in parallel with worsenina alucose reaulation…

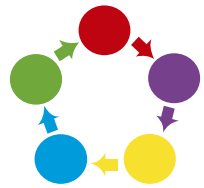


(BMC Cardiovasc Disord. 2006; 6: 19.)

TELEVISION AND DM [181]

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

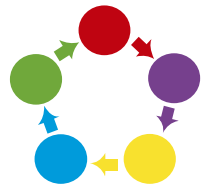
Screen time and metabolic risk factors among adolescents.Hardy LL, Arch Pediatr Adolesc Med. 2010 Jul;164(7):643-9. PMID:20603465



PASSIVE SMOKING AND DM

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

Passive smoking and risk of type 2 diabetes: a meta-analysis of prospective cohort studies.Wang Y, PLoS One. 2013 Jul 26;8(7):e69915. PMID:23922856



SLEEP AND INSULIN RESISTANCE

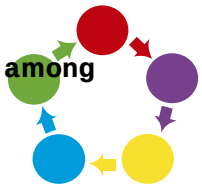
"Sleep deprivation may lead to **insulin resistance** and, subsequently, to diabetes mellitus."

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

DETOXIFICATION

- BPA, endocrine disruptors, POP's, metals
- Toxins induce IR and DM
- Toxins induce weight gain
- GGTP elevated or high normal > 30 start to monitor but is over 40 then definitely need to work on glutathione production.
- Increase antioxidants

1. **Endocrine disruptors in the etiology of type 2 diabetes mellitus.** Nat Rev Endocrinol. 2011 Jun;7(6):346-53
2. **Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes.** PLoS One. 2011 Jan 26;6(1):e15977.



PROGRESSION TO DIABETES

- Can be prevented
- Can be reversed
- Can be treated effectively
  - Goal: Identify underlying metabolic processes, before the patient is symptomatic