Anti-Inflammatory Effects of Omega 3 Fatty Acids in Metabolic Disorders: Role of Lipid Mediators and MicroRNAs
Presenters

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Metabolic Disorders

- Atherosclerosis
- Obesity
- Metabolic syndrome
- Diabetes
World diabetes cases expected to jump 55 percent by 2035

Current and projected cases of diabetes by region

<table>
<thead>
<tr>
<th>Region</th>
<th>2013</th>
<th>Projected 2035</th>
</tr>
</thead>
<tbody>
<tr>
<td>South and Central America</td>
<td>59.8%</td>
<td>109.6%</td>
</tr>
<tr>
<td>Africa</td>
<td>109.6%</td>
<td>209.1%</td>
</tr>
<tr>
<td>North America/Caribbean</td>
<td>37.3%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Middle East/North Africa</td>
<td>96.2%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Europe</td>
<td>22.4%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>70.6%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>46.0%</td>
<td>11.9%</td>
</tr>
</tbody>
</table>

Top 10 countries by number of people with diabetes in 2013, ages 20 to 79

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of People</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>98.4 million</td>
</tr>
<tr>
<td>India</td>
<td>65.1 million</td>
</tr>
<tr>
<td>U.S.</td>
<td>24.4 million</td>
</tr>
<tr>
<td>Brazil</td>
<td>11.9 million</td>
</tr>
<tr>
<td>Russia</td>
<td>10.9 million</td>
</tr>
<tr>
<td>Mexico</td>
<td>8.7 million</td>
</tr>
<tr>
<td>Indonesia</td>
<td>8.5 million</td>
</tr>
<tr>
<td>Germany</td>
<td>7.6 million</td>
</tr>
<tr>
<td>Egypt</td>
<td>7.5 million</td>
</tr>
<tr>
<td>Japan</td>
<td>7.2 million</td>
</tr>
</tbody>
</table>

Source: International Diabetes Federation
Diabetes Physiology

Hyperglycemia
- Insulin resistance
- Steatosis

Co-morbidities
- Retinopathy
- Neuropathy
- Defective wound healing

Sterile Inflammation
- IL-1β
- IL-1α
- TNFα
- IFNγ

Lipid Mediators

IL = Interleukin; TNF: Tumor Necrosis Factor; IFN: Interferon
Lipid Mediators (PAF)

Cancer

Carcinoma (mouth and uterus)

Type 1 Diabetes

Melanoma

Metabolic Syndrome (PAFR KO)

Platelet Activating Factor (PAF)

Arachidonic Acid

Prostaglandins

Leukotrienes

Thromboxanes

5-LO

COX

TXAS

LTB4

Membrane Phospholipid

Normal cells

Cancer cells
PAFR and Metabolic Homeostasis
PAFR and Metabolic Homeostasis

Macrophage

- PAF receptor
- Anti-inflammatory phenotype

Steatosis in PAFR KO

Inflammatory macrophage infiltration in adipose tissue in PAFR KO mice

- Filgueiras LR et al., *Clinical Science*, 2016

Insulin Resistance in PAFR KO mice
PAFR and Metabolic Homeostasis

Filgueiras LR et al., *Clinical Science*, 2016
LTB4 in Type 1 Diabetes
Lipid Mediators (LTB4)

Type 1 Diabetes
Streptozotocin model

Platelet Activating Factor (PAF)
Arachidonic Acid

5-LO

COX

TXAS

Prostaglandins
Thromboxanes

Membrane Phospholipid

Pancreatic islets

PLA2
LTB4 in Type 1 Diabetes

LTB4 promotes sterile inflammation

Filgueiras LR et al., Sci Sign, 2015
Ramalho TR et al, Unpublished, 2017
LTB4 in Type 1 Diabetes

Filgueiras LR et al., Sci Sign, 2015
Filgueiras LR et al., J Diabetes Comp, 2016
Ramarho TR et al, Unpublished, 2017
1. TTU and USP team met in Summer 2016 at the International Immunology meeting in Australia

2. Jancar's Postdoc Luciano attended the 2016 FAPESP meeting at TTU, presented the SPRINT project and visited Moustaid-Moussa’s lab

3. TTU Team visited USP in March 2017 and Moustaid-Moussa gave an invited lecture in the dept. of Immunology, USP

4. Visiting scholar (Theresa) at TTU for one year (funded by CAPES, Brazil)

5. Invited presentation by AFMR, April 2017, and invited peer-reviewed manuscript in press

6. Poster presentations at the Immuno-metabolism and Chronic Disease conference, Fiji, Aug 2017
Obesity, a global & complex disease
Obesity

- **Complex disease**
  - 1/3 of American adults
  - Medical costs
    - *Per capita medical spending* $2,741 higher

- **Increases risk for metabolic diseases**
  - Health Disparities

- **Linked to changes in metabolism/inflammation**
  - (sterile inflammation)

Ministry of Health Brazil

17.9% Obesity

52.5% Overweight

cdc.gov
CONTRIBUTORS TO ENERGY STORAGE

Inside the Person
- Disordered Eating (night eating syndrome, binge eating, "food addiction")
- Hyper-reactivity to Environmental Food Cues
- Delayed Satiety
- Emotional Coping
- Age Related Changes (i.e. menopause, mobility decline, hormones)
- Pathological Sources of Endocrine Dysregulation (i.e. thyroid dysfunction, PCOS, Cushing's Syndrome)
- Central & Peripheral Regulators of Appetite & Adipose Tissue
- Self-regulatory & Coping Deficits
- Mood Disturbance (i.e. depression, anxiety, bipolar etc.)
- Mental Disabilities
- Thermogenesis
- Gut Microbiota
- Pain Sensitivity
- Physical Disabilities (i.e. functional impairments and regulatory dysfunction)
- Social Anxiety (i.e. exercise avoidance)

Outside the Person
- Increased Availability of Energy Dense, Nutrient Poor Foods & Beverages
- Larger Portion Sizes
- Increased Intake
- Breast Feeding and/or Related Factors
- Maternal Employment
- Maternal Smoking
- Maternal Obesity
- Delayed Prenatal Care
- Maternal Over-nutrition During Pregnancy
- Market Economy
- Food Surplus
- Pervasive Food Advertising
- Eating Away From Home
- Skipping Meals
- Food Insecurity
- Diet Patterns
- Maternal Strass
- Non-parental Childcare
- Having Children (for women)
- Infection (i.e. human adenovirus 36)
- Weight Gain Including Drugs
- Maternal Stress
- Maternal Smoking
- Family Conflict (i.e. absence of medical care, self esteem, teasing history)
- Westernization & Economic Development
- Lack of Health Care Provider Support/Knowledge & Inadequate Access to Care
- Social Networks
- Entering into a Romantic Relationship
- Lack of Employer Preparedness to Assist with Obesity
- Low SES & Nutrition Support
- Living in Crime-prone Areas
- Consistent Temperature (i.e. air conditioning/heating, thermoregulation)
- Increased Sedentary Time (i.e. inactive leisure "screen" time, inactive job requirements)
- Built Environment (i.e. star/viv design/access, building design, absence of or poor sidewalks)
- Labor Saving Devices
- Decreased Opportunity for Non-exercised Based Physical Activity (i.e. driving vs. walking to work and school, sedentary jobs)
- Pre-natal Air Pollution

Contributors/Influencers
- Environmental Pressures on Physical Activity
- Biological/Medical
- Maternal/Developmental
- Economic
- Food and Beverage Behavior/Environment
- Psychological
- Social

* Potential contributors indicate anything that has been put forth in the research literature as a question of investigation and is not intended to be a verification of whether or not, or to the extent which, each may or may not contribute.

Obesity Society
Research. Education. Action.
www.obesity.org
Obesity and the Metabolic Syndrome

- Hyperglycemia
- Abdominal Obesity
- Reduced HDL
- Elevated Triglycerides
- Elevated Blood Pressure
- Type 2 Diabetes
- CVD

Prevalence: 35-40% (AHA/NHLBI, IDF, 2005)

Alberti et al., Circulation, 2009
Obesity and inflammation

Adapted from: Kalupahana and Moustaid-Moussa. Obesity Reviews, 2011

IL-10
Adiponectin
TNFα
Ang II
IL-6
PAI-1
Resistin
MCP-1

T_{n1}
T_{n2}
T_{reg}

Stem cells/preadipocytes
Adipocyte
Blood Vessel
M1 macrophage
M2 macrophage
Effector T cell

Diet (ω 3-PUFAs), genetics, pharmacology

LEAN
OBESE
Pathogenesis of obesity-associated insulin resistance

Pancreas
Glucose
Glycogenolysis
Gluconeogenesis
Liver
Lipolysis
Lipolysis
Adipose Tissue
Inflammation
Cytokines
Insulin
Free fatty acids
Intestine
Glycogenolysis
Gluconeogenesis
Skeletal muscle
Ectopic fat
Insulin resistance

Kalupahana, Moustaid-Moussa and Claycombe. Molecular Aspects of Medicine 2012
Dietary/genetic regulation of adipose tissue inflammation

Food and Plant Bioactives

(Omega 3’s, tart cherry anthocyanins, tocotrienols, Switchgrass extracts)

Cells, animals, model organisms, bariatric patients

Endocrine systems (Renin Angiotensin System)

Metabolic Syndrome

Breast Cancer

Obesity

Small Adipocytes

Large inflamed Adipocytes

Mechanisms linking adipocyte inflammation to metabolic disorders
Omega 3 fatty acids prevent diet-induced obesity and inflammation
Lipid Mediators

Omega 3 fatty acids: hypotriglyceridemic, cardioprotective and anti-inflammatory

Metabolic Syndrome (PAFR KO)

Platelet Activating Factor (PAF)

Arachidonic Acid

Membrane Phospholipid

PLA2

Prostaglandins

Leukotrienes

Thromboxanes

COX

TXAS

5-LO

LTB4

BLT1?

Omega 3 fatty acids (EPA)

Anti-inflammatory mediators

T1 Diabetes

Omega 3 fatty acids: hypotriglyceridemic, cardioprotective and anti-inflammatory
OBESITY/T2 Diabetes
INFLAMMATION

High fat diet
Lipogenesis
Adipogenesis

Lipid mediators?
T1 Diabetes

Adipocyte Hypertrophy

MCP-1
TNFα
IL-6

MACROPHAGE RECRUITMENT

Research Hypothesis
Study design

Male C57BL/6J mice

- LF: Low-fat diet (10% fat, 70% CHO, 20% proteins)
- HF: High-fat diet (45% fat, 35% CHO, 20% proteins)
- HF-EPA-P: EPA diet (HF with 36g/kg EPA)
- HF-EPA-R: High-fat diet

Tissue collection and analyses

- Metabolic Changes
  - Cell Culture Experiments
- Gene Expression
  - Microarray
  - qRT-PCR
- Inflammation
  - Macrophage infiltration
  - Adipokines secretion
EPA reduces body weight and restores glucose tolerance

EPA Lowers TG Deposition in Liver

Kalupahana et al. J Nutr 2010
EPA reduces adipose macrophages independent of adiposity


Labeled means without a common letter differ, \( P < 0.05 \)
Omega 3 fatty acids target specific miRNAs and genes related to inflammation and lipid mediators (unpublished)

We thank members of Prof. Jancar and Prof Moustaid-Moussa’s lab for their contributions to this SPRINT project.
Future studies

- Validation of gene and miRNA findings
- Effects of EPA on LTB4 in adipose tissue
- Inhibition of LTB4/BLT1 and PAFR in wild type, obese and diabetic animals to determine effects on:
  - Inflammation
  - Target genes and miRNAs
- Research Manuscript
- Funding after research publication: NIH-FAPESP and other funding agencies
Thank you!

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https://www.depts.ttu.edu/hs/obesityresearch/
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