The three faces of metabolic syndrome

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AAP, Mar 9, 2023
Disclosures

I have the following financial relationships with the manufacturer(s) of commercial product(s) and provider of commercial services discussed in this CME activity:

Chief Medical Officer: BioLumen, Kalin Health, Foogal, Perfect
Advisory Board: Levels Health, ReadOut Health, Simplex Health, Myka Bio

I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

All relevant financial relationships have been reviewed and mitigated by AAP-OC Chapter’s CME Committee.
Life expectancy, 1970 to 2021

Source: UN WPP (2022); Zijdeman et al. (2015); Riley (2005)

Note: Shown is the ‘period life expectancy’. This is the average number of years a newborn would live if age-specific mortality rates in the current year were to stay the same throughout its life.
US Longevity Tax: 8 yr
Obesity Longevity Tax: 15 yr
Metabolic Syndrome Tax: 20 yr

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Only 7% of American Adults Have Good Cardiometabolic Health

Tufts researchers find that most U.S. adults rate poorly across five components of heart and metabolic health, with clear racial disparities.
US Longevity Tax: 8 yr
Obesity Longevity Tax: 15 yr
Metabolic Syndrome Tax: 20 yr
The money is not going to hospitals, physicians, or Big Pharma
The money is not going to hospitals, physicians, or Big Pharma

It’s going to chronic metabolic disease
TIME

CHOLESTEROL

1984
Fat for Life?
Six Million Kids Are Seriously Overweight. What Families Can Do.

By Geoffrey Cowley & Sharon Begley
Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity

Sarah E. Hampl, MD, FAAP; Sandra G. Hassink, MD, FAAP; Ashley C. Skinner, PhD; Sarah C. Armstrong, MD, FAAP; Sarah E. Barlow, MD, MPH, FAAP; Christopher E. Boiling, MD, FAAP; Kimberly C. Avila Edwards, MD, FAAP; Ihuoma Eneli, MD, MS, FAAP; Robin Hamre, MPH; Madeline M. Joseph, MD, FAAP; Doug Unstorf, MD; Eneida Mendonca, MD, PhD, FAAP; Marc P. Michalsky, MD, MBA, FAAP; Nazrat Mirza, MD, ScD, FAAP; Eduardo R. Ochoa, Jr., MD, FAAP; Mona Sharifi, MD, MPH, FAAP; Amanda E. Stalano, PhD, MPP; Ashley E. Weedn, MD, MPH, FAAP; Susan K. Flinn, MA; Jeanne Lindros, MPH; Kymika Okwuchukwu, MPA

Hampl et al. Pediatrics 151: e2022060640, 2023
New guidelines for treating childhood obesity include medications and surgery for first time.

The guidelines say that pediatricians should offer weight-loss drugs for children age 12 and up with obesity.

Four drugs are now approved for obesity treatment in adolescents starting at age 12 – Orlistat, Saxenda, Qsymia and Wegovy – and one, phentermine, for teens age 16 and older. Another drug, called setmelanotide (brand name Imcivree), has been approved for kids age 6 and older who have Barde-Biedl syndrome, a genetic disease that causes obesity.
The Fiction

“Beating obesity will take action by all of us, based on one simple common sense fact: All calories count, no matter where they come from, including Coca-Cola and everything else with calories…”

-The Coca Cola Company, “Coming Together”, 2013
It’s about calories and obesity — or is it?

It’s about calories and obesity — or is it?
It’s about calories and obesity — or is it?
It’s about calories and obesity — or is it?
Obesity is the problem (?)

• Obesity is increasing worldwide by 2.78% per year 1975-2015  
  Lancet Oct 10, 2017  
  http://dx.doi.org/10.1016/S0140-6736(14)60460-8

• Diabetes is increasing worldwide by 4.07% per year  
  1980-2014  
  Lancet Apr 6, 2016  
  http://dx.doi.org/10.1016/S0140-6736(16)00618-8
Secular trend in diabetes among U.S. adults, 1988-2012

Secular trend in diabetes among U.S. adults, 1988-2012

25% increase in obese

Secular trend in diabetes among U.S. adults, 1988-2012

- 25% increase in obese
- 25% increase in nl wt
Meta-analysis: 25% of pediatric T2DM are normal weight

All studies

Stratified by race

Cloana et al. JAMA Network Open 5(12):e2247186, 2022
THE LITTLE WOMEN OF LOJA — GROWTH HORMONE–RECEPTOR DEFICIENCY IN AN INBRED POPULATION OF SOUTHERN ECUADOR

ARLAN L. ROSENBLOOM, M.D., JAIME GUEVARA AGUIRRE, M.D., RON G. ROSENFELD, M.D., AND PAUL J. FIELDER, PH.D.

The Little Women of Loja are obese yet insulin sensitive

| Table 1. Anthropometric Data, Lipid Metabolism, Carbohydrate Metabolism, and Insulin Sensitivity Measures for 35 Controls and 27 GHRD Subjects |
|---------------------------------|--------|--------|--------|
|                                 | Controls | GHRD   | P       |
| **Anthropometrics**             |         |        |        |
| Age, y                         | 39.8 (13) | 34.5 (11) | 0.09   |
| SDS ht                         | −1.7 (1.2) | −7.4 (1.2) | <.0001 |
| BMI, kg/m²                     | 29.4 (4.4) | 27.6 (5.6) | .16    |
| AVG Fat                        | 1.08 (0.18) | 1.97 (0.09) | .79    |
| % Fat                          | 41.1 (6.6) | 47.7 (8.9) | .0014  |
| LF                             | 1.48 (0.47) | 1.18 (0.48) | .016   |
| **Lipids**                     |         |        |        |
| Total C, mg/dL                 | 199 (43.9) | 229 (47.3) | .0124  |
| HDL, mg/dL                     | 43.5 (13.7) | 50.9 (12.8) | .034   |
| HDL-C, mg/dL                   | 4.87 (1.33) | 4.65 (1.10) | .49    |
| LDL, mg/dL                     | 123.1 (37.5) | 157.6 (37.4) | <.0001 |
| Apo A, g/L                     | 1.24 (0.23) | 1.34 (0.23) | .0007  |
| Apo B, g/L                     | 0.95 (0.24) | 1.085 (0.23) | .029   |
| VLDL, mg/dL                    | 31.5 (18.7) | 20.2 (7.6) | .0044  |
| TG, mg/dL                      | 158.3 (95.3) | 100.7 (37.8) | .0001  |
| **Carbohydrate metabolism, adipocytokines** |         |        |        |
| Fasting glucose, mg/dL         | 93.2 (22.4) | 88.6 (10.6) | .34    |
| Postprandial glucose, mg/dL    | 94.1 (35.4) | 77.1 (13.4) | .027   |
| Fasting insulin, μU/mL         | 13.6 (15.5) | 4.29 (0.74) | .0034  |
| HOMA2%β                       | 141 (103) | 90 (48) | .0026  |
| HOMA2%IR                      | 108 (87) | 261 (133) | <.0001 |
| Leptin, mg/mL                  | 10.36 (5.24) | 7.32 (4.7) | .0212  |
| Adiponectin, mg/L              | 6.92 (4.41) | 9.94 (4.84) | .0128  |
| HMW adiponectin, mg/L          | 4.29 (2.89) | 7.59 (4.07) | .0004  |

Abbreviations: SDS ht, SD score for height; C, cholesterol. Data are shown as mean (SD). Conversion factors: glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945; LDL and VLDL to mmol/L, multiply by 0.0259; TGs to mmol/L, multiply by 0.0113.

The Little Women of Loja are obese yet insulin sensitive

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Familial Partial Lipodystrophy: Dunningan or Type 2

- X-linked or autosomal dominant
- Absence of limb fat
  - Easily visible veins
  - Defined musculature
- Normal or excess facial fat
- Cushingoid facies (moon facies)
- Dorsocervical fat pad
- Acanthosis nigricans
“Exclusive” view of obesity and metabolic dysfunction

260 million adults in U.S.

110 million
Obese (42.4%)

150 million
Normal weight or overweight (57.6%)

Chen et al. J Clin Endocrinol Metab 100:4082, 2015
https://www.cdc.gov/nchs/products/databriefs/db360.htm
“Exclusive” view of obesity and metabolic dysfunction

260 million adults in U.S.

110 million
Obese (42.4%)

Obese and sick (80% of 42.4%)

86 million

150 million
Normal weight or overweight (57.6%)

Chen et al. J Clin Endocrinol Metab 100:4082, 2015
https://www.cdc.gov/nchs/products/databriefs/db360.htm
“Exclusive” view of obesity and metabolic dysfunction

260 million adults in U.S.

- 110 million Obese (42.4%)
- 86 million Obese and sick (80% of 42.4%)
- 90 million Normal weight or overweight (57.6%)
- 150 million Normal or overweight and sick (60% of 57.6%)

Total: 176 million sick

Source:
Chen et al. J Clin Endocrinol Metab 100:4082, 2015
https://www.cdc.gov/nchs/products/databriefs/db360.htm
Relation between visceral and subcutaneous obesity: **TOFI** (thin on the outside, fat on the inside)

Obesity is not the problem
Obesity is not the problem

Metabolic Syndrome: where all the money goes
(75% of all healthcare dollars)
Obesity is not the problem

Metabolic Syndrome: where all the money goes
(75% of all healthcare dollars)

- Diabetes
- Hypertension
- Lipid abnormalities
- Cardiovascular disease
- Non-alcoholic fatty liver disease
- Polycystic ovarian disease
- Cancer
- Dementia
Metabolic syndrome is difficult to define in adults

- WHO 1998
- EGIR 1998
- NCEP/ATPIII 2001
- AACE 2003
- IDF 2005
- AHA 2005
Metabolic syndrome is difficult to define in adults

- WHO 1998
- EGIR 1998
- NCEP/ATPIII 2001

And even more difficult to define in children

AHA Scientific Statement

Progress and Challenges in Metabolic Syndrome in Children and Adolescents

A Scientific Statement From the American Heart Association
Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism

Julia Steinberger, MD, MS, Chair; Stephen R. Daniels, MD, PhD, FAHA; Robert H. Eckel, MD, FAHA; Laura Hayman, PhD, RN, FAHA; Robert H. Lustig, MD; Brian McCrindle, MD, MPH, FAHA; Michele L. Mietus-Snyder, MD

Circulation 119:628, 2009
Because each of these definitions sought to define the metabolic syndrome phenomenologically, with cutoffs
Because each of these definitions sought to define the metabolic syndrome phenomenologically, with cutoffs.

It is easier to define the metabolic syndrome mechanismically.

Where’s the insulin resistance?
OGTT in ‘healthy’ volunteers from ~1970 till 2014
OGTT in ‘healthy’ volunteers from ~1970 till 2014

So in 40-50 years our need for insulin increased 2-4 fold: e.g. did we become 2-4 fold more insulin resistant?
The standard model of insulin resistance
The standard model of insulin resistance
The standard model of insulin resistance
Subcutaneous Fat
Relationship between BMI and insulin sensitivity (N=220)

Insulin sensitivity/resistance is more determinant of morbidity and mortality than obesity/normal weight.

Meigs et al. J Clin Endocrinol Metab 97:2906, 2006
Calgori et al. Diab Care 34:210, 2011
Or it could be visceral fat, due to chronic stress

Acute Stress (norepi): Brown Adipocyte
- Lipolysis
- Proliferation
- \( \beta \)-ADR
- Thermogenesis
- Burn fat, lose weight

Chronic Stress (cortisol): White Adipocyte
- Lipid storage
- Angiogenesis
- Preadipocyte proliferation, Adipocyte differentiation
- Grow fat, gain weight

Zukowska, Science 2008
Ectopic Fat: Familial Partial Lipodystrophy

- X-linked or autosomal dominant
- Absence of limb fat
  - Easily visible veins
  - Defined musculature
- Minimal visceral fat
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- Metabolic Syndrome

Comparison between lipodystrophy and obesity

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So the metabolic syndrome can arise from too much, or too little fat i.e. it’s not the fat that counts

Obesity and lipodystrophy share insulin resistance
Intrahepatic fat explains metabolic perturbation better than visceral fat

Hepatic Insulin Sensitivity Index

Insulin Stimulated Glucose Disposal Rate

Insulin Stimulated Palmitate Suppression Rate

VLDL Secretion Rate

Contribution Of Free Fatty Acids To VLDL

Fabbrini et al. Proc Natl Acad Sci 106:15430, 2009
Obese
Low Liver Fat = 2.6%
Obese
Low Liver Fat = 2.6%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%

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High Liver Fat = 24%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%

Thin
High Liver Fat = 23%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%

Thin
High Liver Fat = 23%
NAFLD is a worldwide problem, even in normal weight people.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n</th>
<th>Mode of diagnosis</th>
<th>NAFLD prevalence BMI &lt;25</th>
<th>NAFLD prevalence BMI &gt;25</th>
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<td>Younossi et al. 2012</td>
<td>United States</td>
<td>11,613</td>
<td>Ultrasound</td>
<td>9.6%</td>
<td>28.8%</td>
</tr>
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<td>Xu et al. 2013</td>
<td>China</td>
<td>6,905</td>
<td>Ultrasound</td>
<td>7.2%</td>
<td>Not studied</td>
</tr>
<tr>
<td>Das et al. 2010</td>
<td>India</td>
<td>1,911</td>
<td>Ultrasound/CT</td>
<td>5.1%</td>
<td>31.7%</td>
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<td>Kwon et al. 2012</td>
<td>Korea</td>
<td>29,994</td>
<td>Ultrasound</td>
<td>12.6%</td>
<td>50.1%</td>
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<tr>
<td>Bellentani et al. 2000</td>
<td>Italy</td>
<td>257</td>
<td>Ultrasound</td>
<td>16.4%</td>
<td>75.8%</td>
</tr>
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<td>Sinn et al. 2012</td>
<td>Korea</td>
<td>5,878</td>
<td>Ultrasound</td>
<td>27% (BMI 20-25) 16% (BMI &lt;20)</td>
<td>Not studied</td>
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<td>Wei et al. 2015</td>
<td>Hong Kong</td>
<td>911</td>
<td>Magnetic Resonance</td>
<td>19.3%</td>
<td>60.5%</td>
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Kumar and Mohan, J Clin Trans Hepat 5:216, 2017
NAFLD is associated with diabetes, even in normal weight people

NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances

Mazen Noureddin MD, MHSc, Aarshi Vipani MD, Catherine Bresee MS, Tsuyoshi Todo MD, Irene K. Kim MD, Naim Alkhouri MD, Veronica Wendy Setiawan PhD, Tram Tran MD, Walid S. Ayoub MD, Shelly C. Lu MD, Andrew S. Klein MD, Vinay Sundaram MD & Nicholas N. Nissen MD
Insulin Receptor Knockouts (IRKO)
Kahn Lab, Joslin 1998-present

Obesity, Metabolic Syndrome
Liver (LIRKO)
Brain (NIRKO)

Protected from Obesity
Muscle (MIRKO)
White Adipose Tissue (FIRKO)
Brown Adipose Tissue (BATIRKO)
$\beta$-cell ($\beta$IRKO)
Vascular Smooth Muscle (VSMCIRKO)
Glomerular Podocyte (PODIRKO)

Insulin has two effects on the liver
Result: Obesity
Hyperglycemia, hyperinsulinemia, DM
Low TG, VLDL
Normal BP
NOT Metabolic Syndrome
Result: Obesity
Hyperglycemia, hyperinsulinemia, DM
High TG, VLDL
Low BP
Metabolic Syndrome
In order to explain Metabolic Syndrome:

• We are looking for a ubiquitous factor that
  – promotes obesity (preferably visceral)
  – promotes hypertension
  – induces selective hepatic insulin resistance
    • blocks Foxo1 to promote gluconeogenesis
      (hyperglycemia, hyperinsulinemia, and diabetes)
    • stimulates de novo lipogenesis
      (dyslipidemia, atherosclerosis)
NOVA I

NOVA II

NOVA III

NOVA IV
Only NOVA IV correlates with chronic disease.
Original article

Consumption of ultra-processed foods associated with weight gain and obesity in adults: A multi-national cohort study

Reynalda Cordova a,b, Nathalie Kliemann a, Inge Huybrechts a, Fernanda Rauber c,d, Eszter P. Vamos e, Renata Bertazzi Levy c,d, Karl-Heinz Wagner b, Vivian Viallon a, Corinne Casagrande a, Geneviève Nicolas a, Christina C. Dahm f, Jie Zhang f, Jytte Halkjær g, Anne Tjønneland g,h, Marie-Christine Boutron-Ruault i,j, Francesca Romana Mancini i,j, Nasser Laouali i,j, Verena Katzke k, Bernard Srour k, Franziska Jannasch l,m,n, Matthias B. Schulze l,o, Giovanna Masala p, Sara Grioni q, Salvatore Panico r, Yvonne T. van der Schouw s, Jeroen W.G. Derksen s, Charlotta Rylander t, Guri Skeie t, Paula Jakszyn u,v, Miguel Rodriguez-Barranco w,x,y, José María Huerta z,aa, Aurelio Barricarte y,ab,ac, Louise Brunckwall ad, Stina Ramne ad, Stina Bodén ae, Aurora Perez-Cornago af, Alicia K. Heath e, Paolo Vineis e, Elisabete Weiderpass a, Carlos Augusto Monteiro c,d, Marc J. Gunter a, Christopher Millett e, Heinz Freising a,*
Ultra-Processed Food Consumption Associated with Incident Hypertension among Chinese Adults—Results from China Health and Nutrition Survey 1997–2015

Ming Li 1,* and Zumin Shi 2△
Ultraprocessed Food Consumption and Risk of Type 2 Diabetes Among Participants of the NutriNet-Santé Prospective Cohort

Bernard Srour, PharmD, MPH, PhD; Léopold K. Fezeu, MD, PhD; Emmanuelle Kesse-Guyot, MSc, PhD; Benjamin Allès, PhD; Charlotte Debras, MSc; Nathalie Druesne-Pecollo, PhD; Eloi Chazelas, MSc; Mélanie Deschasaux, MSc, PhD; Serge Hercberg, MD, PhD; Pilar Galan, MD, PhD; Carlos A. Monteiro, MD, PhD; Chantal Julia, MD, MPH, PhD; Mathilde Touvier, PhD, MSc, MPH
Associations of ultra-processed food consumption with cardiovascular disease and all-cause mortality: UK Biobank

Xuanli Chen, Jiadong Chu, Wei Hu, Na Sun, Qida He, Siyuan Liu, Zhaolong Feng, Tongxing Li, Qiang Han, Yueping Shen
Association between ultra-processed foods consumption and risk of non-alcoholic fatty liver disease: a population-based analysis of NHANES 2011–2018

Zhening Liu, Hangkai Huang, Yan Zeng, Yishu Chen and Chengfu Xu*

Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou 310003, People’s Republic of China
Ultra-processed food consumption and metabolic syndrome: a cross-sectional study in Quilombola communities of Alagoas, Brazil

Lídia Bezerra Barbosa¹ ², Nancy Borges Rodrigues Vasconcelos¹ ld, Ewerton Amorim dos Santos³ ld, Tamara Rodrigues dos Santos¹ ld, Thays Ataide-Silva² ld and Haroldo da Silva Ferreira²* ld
Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort

Thibault Fiolet,¹ Bernard Srour,¹ Laury Sellem,¹ Emmanuelle Kesse-Guyot,¹ Benjamin Allès,¹ Caroline Méjean,² Mélanie Deschasaux,¹ Philippine Fassier,¹ Paule Latino-Martel,¹ Marie Beslay,¹ Serge Hercberg,¹,⁴ Céline Lavalette,¹ Carlos A Monteiro,³ Chantal Julia,¹,⁴ Mathilde Touvier¹
Association of Ultraprocessed Food Consumption With Risk of Dementia: A Prospective Cohort Study

Huiping Li, Shu Li, Hongxi Yang, Yuan Zhang, Shunming Zhang, Yue Ma, Yabing Hou, Xinyu Zhang, Kaijun Niu, Yan Borné, Yaogang Wang

First published July 27, 2022, DOI: https://doi.org/10.1212/WNL.0000000000200871
Premature Deaths Attributable to the Consumption of Ultraprocessed Foods in Brazil

Eduardo A.F. Nilson, ScD, Gerson Ferrari, PhD, Maria Laura C. Louzada, PhD, Renata B. Levy, PhD, Carlos A. Monteiro, PhD, Leandro F.M. Rezende, ScD
'Ultra-processed' products now half of all UK family food purchases

Exclusive: health experts warn increasing popularity of industrially-made food will lead to negative effects such as obesity and poor health

Sarah Boseley Health editor

doi: 10.1101/2021.05.22.21257615

Americans Are Eating More Ultra-Processed Foods: How to Cut Down on Them

Fast food such as hamburgers are among the ultra-processed foods that people are eating more often. Evrim Ertik/Getty Images

57% of US consumption
73% of the US food supply
Detrimental Effects of Fructose

Fructose → ATP
Fructokinase
Fructose-1-P
πGNG
πGlucose
πForko1

Hyperglycemia

Leptin Resistance

Fructose-6-P
Fructose-1,6-bis-P
Glyceraldehyde
Dihydroxyacetone-P

Inflammation

JNK1
IRS-1
pSer-IRS-1

Insulin

Hepatic IR
FFA
Dys-lipidemia
Muscle IR

Lipid droplet

Acetyl-CoA
Malonyl-CoA

TCA cycle

O₂
ATP
CO₂

TG
Obesity

PP2A
PKC

PGC-1β

MKK7

Fructose-6-P *
PFK

Fructose-1,6-bis-P

ChREBP
SREBP1c

ACL
ACC
FAS

VLDL

MTP

LCPL
Sugar is toxic unrelated to calories

Isocaloric Fructose Restriction and Metabolic Improvement in Children with Obesity and Metabolic Syndrome


Short-term isocaloric fructose restriction lowers apoC-III levels and yields less atherogenic lipoprotein profiles in children with obesity and metabolic syndrome


Effects of Dietary Fructose Restriction on Liver Fat, De Novo Lipogenesis, and Insulin Kinetics in Children With Obesity

Schwarz et al. Gastroenterology 153:743, 2017
Strategy

- Isocaloric fructose restriction x 9 days in children who are habitual sugar consumers
- No change in weight
- Substitute complex carbs for sugar
- Maintain baseline macronutrient composition of the diet
- Study in PCRC at Day 0 and Day 10
- Assess changes in organ fat, de novo lipogenesis, and metabolic health
## Fasting Labs

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 10</th>
<th><strong>β-coefficient</strong> (Adjusted Change) [95% CI]</th>
<th><strong>p value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>83.1 ± 10.7</td>
<td>80.1 ± 11.3</td>
<td>-2.8 [-6.5, +0.9]</td>
<td>0.13</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>122.6 ± 10.5</td>
<td>121.1 ± 9.9</td>
<td>-1.39 [-4.9, +2.1]</td>
<td>0.43</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>68.8 ± 8.9</td>
<td>63.7 ± 7.5</td>
<td>-4.9 [-8.1, -1.8]</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Fasting lactate (mmol/L)</td>
<td>1.2 ± 0.4</td>
<td>0.9 ± 0.3</td>
<td>-0.3 [-0.5, -0.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate AUC (mM/120 min)</td>
<td>160.0 ± 34.5</td>
<td>129.0 ± 34.5</td>
<td>-31.2 [-41.9, -20.5]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>7.9 ± 4.8</td>
<td>5.2 ± 2.6</td>
<td>-2.7 [-3.8, -1.5]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/L) *</td>
<td>27.4 ± 14.1</td>
<td>23.8 ± 8.9</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>ALT (U/L) *</td>
<td>28.9 ± 22.8</td>
<td>26.7 ± 19.6</td>
<td>-2.2 [-4.7, +0.3]</td>
<td>0.09</td>
</tr>
<tr>
<td>Fasting TG (mM)</td>
<td>1.4 ± 0.9</td>
<td>1.0 ± 0.5</td>
<td>-0.4 [-0.6, -0.2]</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting LDL-C (mM)</td>
<td>2.4 ± 0.6</td>
<td>2.1 ± 0.6</td>
<td>-0.3 [-0.4, -0.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting HDL-C (mM)</td>
<td>1.2 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>-0.1 [-0.2, -0.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting FFA (mM)</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>+0.1 [+0.1, +0.2]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
DNL is the Conversion of Dietary Carbohydrates into Lipids

Sugar into Fat (lipids)

Fructose $\xrightarrow{\text{Acetate}}$ Palmitate

New Tracer Method using MIDA: Hellerstein and Neese, AJP 1999
DNL AUC Pre and Post Fructose Restriction

Endocrine Society, March 5, 2015
Oral glucose tolerance test before and after isocaloric fructose restriction

Lustig et al. Obesity Society Nov. 4, 2015
Changes in liver, visceral, and subcutaneous fat
(n = 37)
De novo Lipogenesis

Glycerol-P → TG* → VLDL*

Ac CoA* → Malonyl CoA → Fatty Acid* → TG* → VLDL*
De novo Lipogenesis

DNL

Glycerol-P

Ac CoA*

Malonyl CoA

Fatty Acid*

TG*

VLDL*

9 days fructose restriction
De novo Lipogenesis

DNL

Glycerol-P

TGF*

Ac CoA* → Malonyl CoA → Fatty Acid*

VLDDL*

9 days fructose restriction

LIVER

FAT

DNL

VLDDL*

Visceral fat
De novo Lipogenesis

DNL

Ac CoA* ➔ Malonyl CoA ➔ Fatty Acid* ➔ TG* ➔ VLDL*

9 days fructose restriction

Improved Insulin kinetics

Liver Fat

DNL

VLDL*

Visceral fat
Independent Confirmation

Preliminary Communication
January 22, 2019

Effect of a Low Free Sugar Diet vs Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys
A Randomized Clinical Trial

Jeffrey B. Schwimmer, MD¹,²; Patricia Ugalde-Nicalo, MD¹; Jean A. Welsh, PhD, MPH, RN³,⁴,⁵; et al

Author Affiliations
Fructose reduces liver mitochondrial function, while glucose stimulates it

"The most important takeaway of this study is that high fructose in the diet is bad," says Dr. Kahn. "It's not bad because it's more calories, but because it has effects on liver metabolism to make it worse at burning fat. As a result, adding fructose to the diet makes the liver store more fat, and this is bad for the liver and bad for whole body metabolism."

Dr. C. Ronald Kahn, CEO, Joslin Diabetes Center
A different model of insulin resistance

- Cytokines
- Fructose
- Fatty liver
- Sensitivity
- Hepatic insulin resistance
A different model of insulin resistance

- Cytokines
- Fructose
- Fatty liver
- Sensitivity
- Hepatic insulin resistance
- Increased Portal FFA
- Decreased Insulin Sensitivity
A different model of insulin resistance

- Fructose
- Cytokines
- Fatty liver
- Sensitivity
- Decreased Insulin Sensitivity
- Increased Portal FFA
- Fat
- Further Hyperinsulinemia
- Islet Cells
- Decreased Glucose Uptake
- Skeletal Muscle
- Increased Peripheral Insulin Resistance
- Hyperinsulinemia
• Sugar is the payload

• Ultraprocessed food is the vehicle
Assessment of metabolic syndrome

• History: esp. FHx, BW, BF, ACE’s
• Physical: esp. WC, BP
• Labs:
  – Fasting insulin
  – Lipid Profile, esp. TG:HDL (LDL not imp), ApoB
  – ALT
  – Uric Acid
  – Lactate
  – Fasting glucose, HbA$_1c$ – last thing to change!
  – Uncommon tests, e.g. hs-CRP, TNF-\(\alpha\)
• Do not draw leptin
REFRAMING THE DEBATE
REFRAMING THE DEBATE

Obesity doesn’t CAUSE metabolic syndrome

Obesity is a MARKER for metabolic syndrome
REFRAMING THE DEBATE

Obesity doesn’t CAUSE metabolic syndrome

Obesity is a MARKER for metabolic syndrome

OBESITY IS A “RED HERRING”
EVERYONE IS AT RISK OF METABOLIC SYNDROME
The three faces of metabolic syndrome

- **SQ fat — the ”bucket” hypothesis**
  - get the insulin down (reduce CHO, sugar)

- **Visceral fat — the “stress” hypothesis**
  - mindfulness, exercise, sleep

- **Liver fat — the “mainlining” hypothesis**
  - reduce sugar, alcohol, branched chain amino acids, trans-fats
Collaborators

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Guggenheim Partners
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