

## Entry Level Clinical Nutrition Part XIX

### Carbohydrate-protein imbalances and the impact of fructose

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Neuroscience  
The Journal of Physiology

2012, 590, 2485–2499

**'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition**

Rubal Agrawal<sup>1</sup> and Francisco Gomez-Pinilla<sup>1,2</sup>

<sup>1</sup>Department of Physiology and <sup>2</sup>Neurology, University of Washington, Seattle, WA 98195, USA

**Abstract**

Metabolic syndrome is a cluster of conditions that increase the risk of heart disease, stroke, and type 2 diabetes. It is characterized by abdominal obesity, high blood pressure, high blood sugar, high triglycerides, and low levels of HDL cholesterol. In the brain, metabolic syndrome is associated with insulin resistance, which can lead to cognitive dysfunction. This study investigated the effects of dietary n-3 fatty acid deficiency on insulin receptor signaling and cognition in a mouse model of metabolic syndrome. Results showed that dietary n-3 fatty acid deficiency exacerbates insulin resistance and cognitive dysfunction in mice with metabolic syndrome. The study also found that dietary n-3 fatty acid supplementation can improve insulin receptor signaling and cognitive function in these mice.

**Key messages**

- The present study provides evidence for the effects of metabolic dysfunction on brain function using the mouse model of metabolic syndrome induced by high fructose diet.
- We observed that the different components of metabolic disease induce not the parallel impairment of insulin receptor signaling in a single cell.
- High sugar consumption impairs cognitive abilities and disrupted insulin signaling in the brain, which is exacerbated in mice with dietary n-3 fatty acid deficiency. However, in mice, the brain function was restored by dietary n-3 fatty acid supplementation.

**Introduction**

Metabolic syndrome is a cluster of conditions that increase the risk of heart disease, stroke, and type 2 diabetes. It is characterized by abdominal obesity, high blood pressure, high blood sugar, high triglycerides, and low levels of HDL cholesterol. In the brain, metabolic syndrome is associated with insulin resistance, which can lead to cognitive dysfunction. This study investigated the effects of dietary n-3 fatty acid deficiency on insulin receptor signaling and cognition in a mouse model of metabolic syndrome. Results showed that dietary n-3 fatty acid deficiency exacerbates insulin resistance and cognitive dysfunction in mice with metabolic syndrome. The study also found that dietary n-3 fatty acid supplementation can improve insulin receptor signaling and cognitive function in these mice.

**Conclusions**

The study found that dietary n-3 fatty acid deficiency exacerbates insulin resistance and cognitive dysfunction in mice with metabolic syndrome. The study also found that dietary n-3 fatty acid supplementation can improve insulin receptor signaling and cognitive function in these mice.

**References**

1. Agrawal R & Gomez-Pinilla F. 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition, *J Physiology*, Vol. 590, No. 10, pp. 2485-2499, 2012.

2. All parameters of metabolic dysfunction related to fructose treatment were ameliorated by the presence of dietary n-3 fatty acid. Results showed that dietary n-3 fatty acid deficiency elevates the vulnerability to metabolic dysfunction and impaired cognitive functions by modulating insulin receptor signalling and synaptic plasticity.

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60 MINUTES

60 Minutes – Sunday, April 1, 2012

Is sugar toxic?



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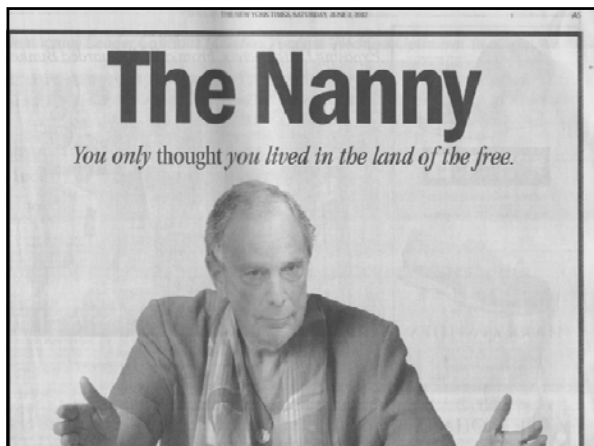
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USA TODAY hopes to serve as a forum for better understanding and only to help make the USA truly one nation."

John A. Thompson, President, June 10, 2012

USA TODAY

Today's debate: Obesity

### 16 ounces of prevention is no cure for pounds

If Mayor Michael Bloomberg says his new health law, which bans New Yorkers from eating or drinking more than 16 ounces, will curb obesity, he's wrong. It's not a cure for obesity, but it's a step in the right direction.

It's for sure, America's waistline is getting out of control. Obesity rates are skyrocketing, and obesity is the leading cause of death in the United States. And Bloomberg's law is a step in the right direction.

But there are some things to be aware of. For one, the law only applies to restaurants and food service establishments. It doesn't cover fast-food restaurants, which are a major source of obesity. And it doesn't cover schools, which are another major source of obesity.

NYC's portion caps won't do it all. But it's a start. And it's a step in the right direction.

### Big portions yield big waistlines

By Michael A. Bloomberg

It takes 12 inches for a large beverage at a typical fast-food restaurant, not a 16-ounce cup. And it takes 12 inches for a large beverage at a typical fast-food restaurant, not a 16-ounce cup. And it takes 12 inches for a large beverage at a typical fast-food restaurant, not a 16-ounce cup.

Reaction follows familiar pattern

Under our proposal, people would still choose to drink as much soda as they want. If it's necessary, people would still choose to drink as much soda as they want. If it's necessary, people would still choose to drink as much soda as they want.

USA Today, June 4, 2012

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Daily Hampshire Gazette, June 4, 2012

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## Promoting Nutrition, Disney to Restrict Junk-Food Ads

By BROOKS BARNES

LOS ANGELES — The Walt Disney Company, in an effort to address concerns about entertainment's role in childhood obesity, plans to

**The New York Times, June 5, 2012**

dis stations and Web sites must comply with a strict new set of nutritional standards.

The restrictions on ads extend to Saturday-morning cartoons on ABC stations owned by Disney. Under the new rules, products like Capri Sun drinks and Knott Lunchables meals — both current Disney advertisers — along with a wide range of candy, sugared cereal and fast food, will no longer be acceptable advertising material.

The initiative, which Dis-

ney plans to detail Tuesday at a Washington news conference with the first lady, Michelle Obama, stretches into other areas. For instance, Disney will reduce the amount of sodium in its eat-

ery at its theme parks, and create what it calls "fun" public service announcements promoting child exercise and healthy eating.

The move follows the announcement last week of a plan by New York City to ban the sale of large sodas and other sugary drinks amid in-

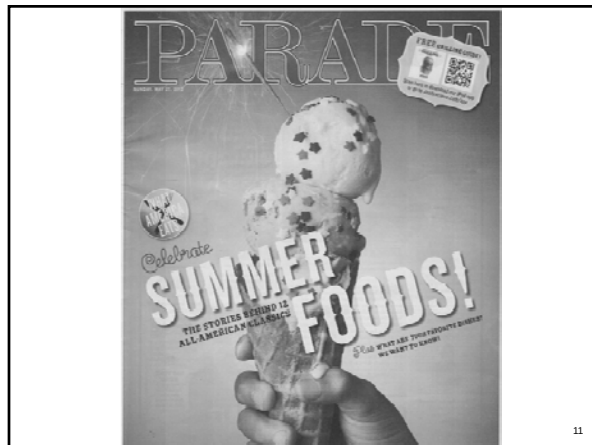
creasing concern about childhood obesity in America.

Disney said that in adopting the new advertising standards it was largely following recommendations



A fruit cart at a Disney theme park featuring fresh produce for sale. Disney's new commercial restrictions will bar some current advertisers.

Continued on Page 9



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**WHOLEPIECES**  
The new WholePieces ice cream is made with real fruit and is the only ice cream in the world that is 100% natural. It's the perfect treat for the whole family.

**CALIFORNIA DOP**  
The new California Dop ice cream is made with real fruit and is the only ice cream in the world that is 100% natural. It's the perfect treat for the whole family.

**CHEWY**  
The new Chewy ice cream is made with real fruit and is the only ice cream in the world that is 100% natural. It's the perfect treat for the whole family.

**HANDMADE**  
The new Handmade ice cream is made with real fruit and is the only ice cream in the world that is 100% natural. It's the perfect treat for the whole family.

**Edy's Slow Churned**  
One for all  
All for one

Whether the ice is Edy's Slow Churned, it's the perfect treat for the whole family. It's the perfect treat for the whole family.




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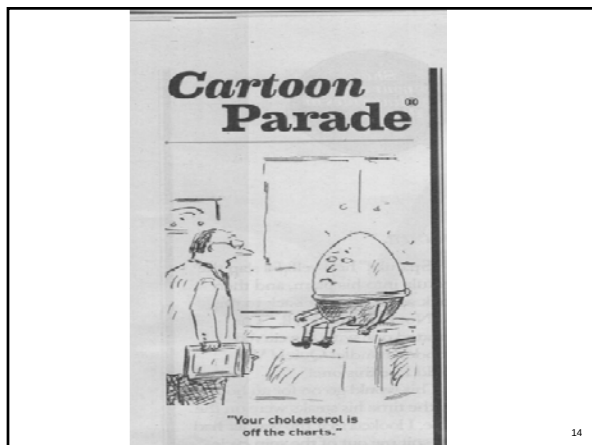
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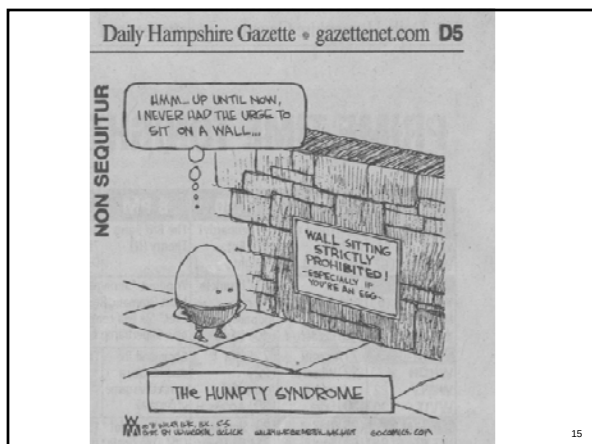
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**Quality of life issues are the major concerns more than ever now.**

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Summer of Work Exposes Medical Students to System's Ills, The New York Times

September 9, 2009

Summer of Work Exposes Medical Students to System's Ills

By David A. Asch, M.D., and David A. Asch, M.D.

The students learned not only to deliver patient care, but also to deliver patient care in a system that is broken. The students learned not only to deliver patient care, but also to deliver patient care in a system that is broken. The students learned not only to deliver patient care, but also to deliver patient care in a system that is broken.

**"...a tidal wave of chronic illness..."**

For 12 years, the University of Washington School of Medicine has required incoming second-year students to complete a course in patient care. The course is designed to teach students how to deliver patient care in a system that is broken. The course is designed to teach students how to deliver patient care in a system that is broken.

http://www.nytimes.com/2009/09/09/us/politics/09washington.html?\_r=1&ref=nytimes.com

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Nestlé Nutrition Workshop Series  
Clinical & Performance Program, Vol. 8

**Nutrition and Critical Care**

Luc Cynober  
Frederick A. Moore

Baracos VE. Overview on metabolic adaptation to stress, pp. 1-13.

"An understanding of the nature of stress is fundamental to the rational design of nutrient mixtures to feed patients whose homeostasis has been altered by one or more stressors."

"All stresses may be presumed to be associated with characteristic modifications in the metabolism of lipids, carbohydrates, amino acids, and micronutrients."

KARGER Nestlé NUTRITION

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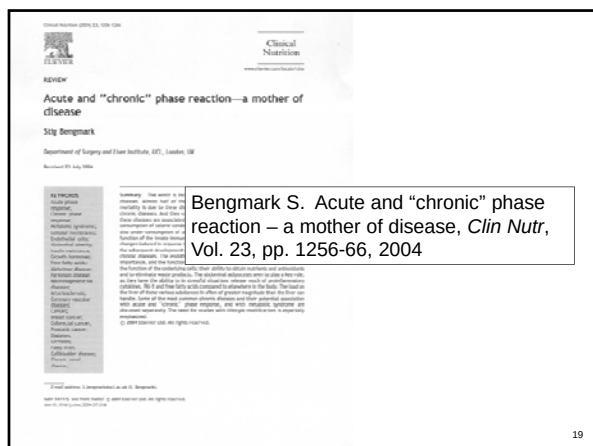
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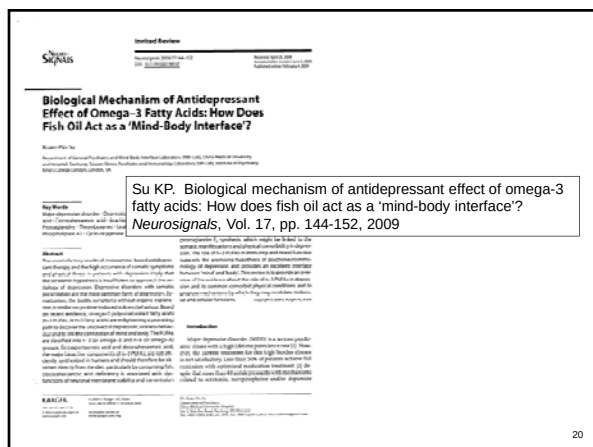
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Bengmark S. Acute and "chronic" phase reaction – a mother of disease, *Clin Nutr*, Vol. 23, pp. 1256-66, 2004



Su KP. Biological mechanism of antidepressant effect of omega-3 fatty acids: How does fish oil act as a 'mind-body interface'? *Neurosignals*, Vol. 17, pp. 144-152, 2009

**Table 1.** Overlapping of symptoms of acute sickness behaviour associated with IFN- $\alpha$  therapy and the somatic symptoms in MDD

| Symptoms                  | Prevalence in IFN- $\alpha$ therapy <sup>a</sup> , % | Prevalence in MDD <sup>b</sup> , % |
|---------------------------|------------------------------------------------------|------------------------------------|
| Fatigue/asthenia          | 39–90                                                | 73                                 |
| Headache                  | 27–67                                                | 33 <sup>c</sup>                    |
| Gastrointestinal symptoms | 50 <sup>c</sup> –1                                   | 34–47 <sup>f</sup>                 |
| Psychomotor slowing       | 40 <sup>c</sup>                                      | 59–65 <sup>f</sup>                 |
| Insomnia                  | 20–39 <sup>d</sup>                                   | 63                                 |
| Irritability              | 35 <sup>d</sup>                                      | 50                                 |
| Arthralgia                | 9–36                                                 | 31 <sup>e</sup>                    |
| Musculoskeletal pain      | 26–32                                                | 62–80 <sup>e, i</sup>              |
| Abdominal pain            | 15–20                                                | 21 <sup>e</sup>                    |
| Anorexia                  | 13–19                                                | 40                                 |
| Anxiety                   | 13–18 <sup>d</sup>                                   | 57                                 |
| Poor concentration        | 14 <sup>d</sup>                                      | 51                                 |

<sup>a</sup> [46], unless otherwise specified; <sup>b</sup> [99], unless otherwise specified; <sup>c</sup> [100]; <sup>d</sup> [101]; <sup>e</sup> [102]; <sup>f</sup> [103]; <sup>g</sup> [104].  
<sup>1</sup> Nausea, vomiting, bowel problems.  
<sup>2</sup> Result from depressed inpatient population.

### Key metabolic imbalances seen with the acute phase response

- Metabolic acidosis
- Loss of lean body mass (sarcopenia)
- Insulin resistance
- Inflamm-aging (Increased innate immunity and decreased adaptive immunity)
- Suboptimal caloric intake and carbohydrate:protein ratio (Refeeding syndrome)
- Gastrointestinal dysfunction/gut atrophy
- Deficiencies of key micronutrients such as zinc, selenium, and vitamin D

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### Underlying hypotheses of Entry Level Clinical Nutrition:

- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

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### Entry Level Clinical Nutrition:

A new model of functional medicine that incorporates allostatic load and the “chronic” acute phase response

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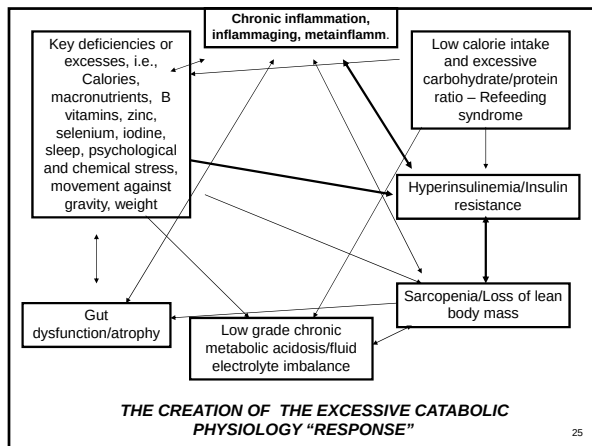
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## Refeeding syndrome

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**REVIEW**  
**Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment**  
 Z Stanga<sup>1,2</sup>, A Bressan<sup>3,4</sup>, M Eisenberg<sup>5</sup>, M Cazzola<sup>6</sup>, A Maccioni<sup>7</sup> and CH Kohn<sup>8</sup>

<sup>1</sup>Department of Clinical Nutrition, University Hospital Bonn, Germany; <sup>2</sup>Clinical Nutrition Team, Division of Endocrinology, Endocrine and Clinical Nutrition, University Hospital Bonn, Germany; <sup>3</sup>Section of Human Nutrition, Faculty of Medicine, University of Bonn, Germany; <sup>4</sup>Department of Endocrinology, University Hospital Bonn, Germany; <sup>5</sup>Department of Endocrinology, University Hospital Bonn, Germany; <sup>6</sup>Department of Endocrinology, University Hospital Bonn, Germany; <sup>7</sup>Department of Endocrinology, University Hospital Bonn, Germany; <sup>8</sup>Department of Endocrinology, University Hospital Bonn, Germany

**Abstract**  
 The refeeding syndrome (RS) is a life-threatening condition that occurs when severely malnourished patients are refed. It is characterized by a rapid shift in fluid and electrolyte balance, leading to hypophosphatemia, hypokalemia, and hypomagnesemia. These electrolyte imbalances can lead to complications such as respiratory failure, cardiac arrhythmias, and neurological symptoms. The pathogenesis of RS is multifactorial, involving insulin resistance, hormonal changes, and depletion of electrolyte stores. Prevention and early recognition are crucial for a favorable outcome. This review provides illustrative cases and guidelines for the prevention and treatment of RS in clinical practice.

**Keywords:** refeeding syndrome, hypophosphatemia, hypokalemia, hypomagnesemia, electrolyte imbalance, clinical nutrition, guidelines.

**Introduction**  
 The refeeding syndrome (RS) is a life-threatening condition that occurs when severely malnourished patients are refed. It is characterized by a rapid shift in fluid and electrolyte balance, leading to hypophosphatemia, hypokalemia, and hypomagnesemia. These electrolyte imbalances can lead to complications such as respiratory failure, cardiac arrhythmias, and neurological symptoms. The pathogenesis of RS is multifactorial, involving insulin resistance, hormonal changes, and depletion of electrolyte stores. Prevention and early recognition are crucial for a favorable outcome. This review provides illustrative cases and guidelines for the prevention and treatment of RS in clinical practice.

**Conclusion**  
 The refeeding syndrome (RS) is a life-threatening condition that occurs when severely malnourished patients are refed. It is characterized by a rapid shift in fluid and electrolyte balance, leading to hypophosphatemia, hypokalemia, and hypomagnesemia. These electrolyte imbalances can lead to complications such as respiratory failure, cardiac arrhythmias, and neurological symptoms. The pathogenesis of RS is multifactorial, involving insulin resistance, hormonal changes, and depletion of electrolyte stores. Prevention and early recognition are crucial for a favorable outcome. This review provides illustrative cases and guidelines for the prevention and treatment of RS in clinical practice.

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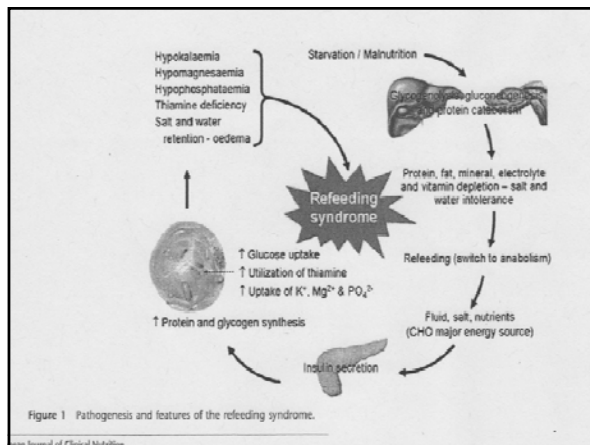
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- "The refeeding syndrome was first reported among those released from concentration camps following the Second World War."
- "Oral feeding of these grossly malnourished individuals often resulted in fatal diarrhea, heart failure and neurological complications, including coma and convulsions."
- "Milder symptoms were later reported by Keys *et al.* during the refeeding of healthy volunteers with a mean weight loss of 23% after starvation."

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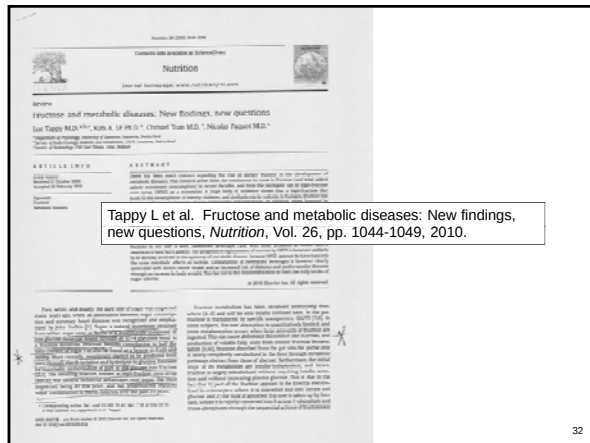


| Table 1 Some groups of malnourished patients at particular risk of developing the refeeding syndrome |  |
|------------------------------------------------------------------------------------------------------|--|
| <b>Unintentional weight loss</b>                                                                     |  |
| Loss of >5% of body weight in 1 month                                                                |  |
| Loss of >7.5% of body weight in 3 months                                                             |  |
| Loss of >10% of body weight in 6 months                                                              |  |
| <b>Low nutrient intake</b>                                                                           |  |
| Patients starved for >7 days                                                                         |  |
| Prolonged hypocaloric feeding or fasting                                                             |  |
| Chronic swallowing problems and other neurological disorders                                         |  |
| Anorexia nervosa                                                                                     |  |
| Chronic alcoholism                                                                                   |  |
| Depression in the elderly                                                                            |  |
| Patients with cancer                                                                                 |  |
| Chronic infectious diseases (AIDS, tuberculosis)                                                     |  |
| During convalescence from catabolic illness                                                          |  |
| Postoperative patients                                                                               |  |
| Diabetic hyperosmolar states                                                                         |  |
| Morbid obesity with profound weight loss                                                             |  |
| Homelessness, social deprivation                                                                     |  |
| Idiosyncratic/eccentric diets                                                                        |  |
| Hunger strikers                                                                                      |  |
| <b>Increased nutrient losses/decreased nutrient absorption</b>                                       |  |
| Significant vomiting and/or diarrhoea                                                                |  |
| Dysfunction or inflammation of the gastrointestinal tract                                            |  |
| Chronic pancreatitis                                                                                 |  |
| Chronic antacid users (these bind minerals)                                                          |  |
| Chronic high-dose diuretic users                                                                     |  |
| After bariatric surgery                                                                              |  |

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## Skiping meals and then binging on fructose-laden refined foods: Is it more fuel on the fire?

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Tappy L et al. Fructose and metabolic diseases: New findings, new questions, *Nutrition*, Vol. 26, pp. 1044-1049, 2010.

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## Basic information on fructose

- “Sugar, a natural sweetener obtained from either sugar cane or beets, is a disaccharide composed of one glucose molecule linked through an  $\alpha$ 1-4 glycoside bond to a fructose molecule.”
- “Fructose besides contributing to half the total content of sugar, can also be found as a hexose in fruits and honey.”

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- “More recently, sweeteners started to be produced from corn through starch isolation and hydrolysis to glucose, followed by enzymatic isomerization of part of the glucose into fructose.”
- “The resulting mixture, known as high-fructose corn syrup (HFCS), has several industrial advantages over sugar, the most important being its low price, and has progressively replaced sugar consumption in North America over the past 30 years.”

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### Intestinal metabolism of fructose

- “In the gut, fructose is transported by specific transporters , GLUT5.”
- “In some subjects, fructose absorption is quantitatively limited, and some malabsorption occurs when large amounts of fructose are ingested.”
- “This can cause abdominal discomfort and diarrhea, and production of volatile fatty acids from colonic fructose fermentation.”

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- “Fructose absorbed from the gut into the portal vein is nearly completely metabolized in the liver through metabolic pathways distinct from those of glucose; furthermore, the initial steps of its metabolism are insulin-independent, and hence, fructose is largely metabolized without requiring insulin secretion and without increasing plasma glucose.”

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- “This is due to the fact that 1) part of the fructose appears to be directly metabolized in enterocytes, where it is converted into lactate and glucose, and 2) the bulk of absorbed fructose is taken up by liver cells, where it is rapidly converted into fructose 1-phosphate and triose-phosphates through the sequential actions of fructokinase and aldolase B and triokinase.”

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- “Fructokinase and aldolase B are not inhibited by ADP and citrate and hence are not regulated by the cellular energy status.”
- “In fact, fructose differs from glucose, because the ADP and citrate concentrations exert a negative feedback control of the initial steps of glycolysis.”

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- “Because fructose metabolism is not dependent on insulin secretion, at least in its initial steps, and because fructose ingestion causes only a limited rise in glycemia, fructose was initially proposed as a natural substitute of sucrose for diabetic patients.”
- “It however became rapidly apparent that an increased dietary intake of fructose had serious adverse metabolic effects in both rodents and humans.”

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***“Thus it was recognized that a high-fructose intake is associated with increased plasma triglyceride concentrations, hepatic steatosis, impaired glucose tolerance and insulin resistance, and even high blood pressure.”***

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## Dietary fructose vs. HFCS

- “In our everyday diet, naturally occurring, free fructose (essentially with fruits and honey) is a modest component of energy intake.”
- “Furthermore, there is some evidence that consumption of fructose with fruits or honey does not produce the same adverse metabolic effects as added fructose.”

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- “This may be due to the presence of natural antioxidants and/or dietary fibers with fruits and honey.”
- “The vast majority of fructose in our diet corresponds to added sugars, the two main sources being sucrose (containing 50% fructose) and HFCS (containing 42%-55% fructose).”
- “As a consequence, the intakes of fructose and glucose always vary simultaneously, and therefore, high-fructose consumers are also high-glucose consumers.”

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## Overall conclusions

- “There is compelling evidence that a hypercaloric, high fructose diet can induce, not only in animal models, but also in humans, a whole range of metabolic alterations, the most prominent being a disturbance of hepatic lipid metabolism and of plasma lipid profile.”
- “It appears therefore sound at this stage to advise limiting consumption of sugar calories to less than 140 kcal/d for men and 100 kcal/d for women (corresponding to about one can of sweetened beverage/d), as recently proposed by the American Heart Association.”

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## Fructose and systemic health: The work of Robert Lustig, MD

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## The case against Robert Lustig

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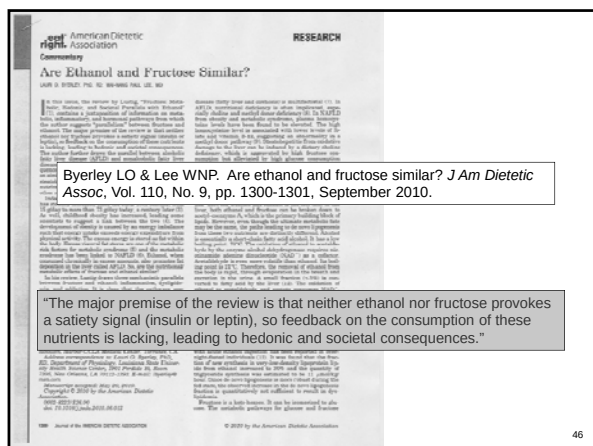
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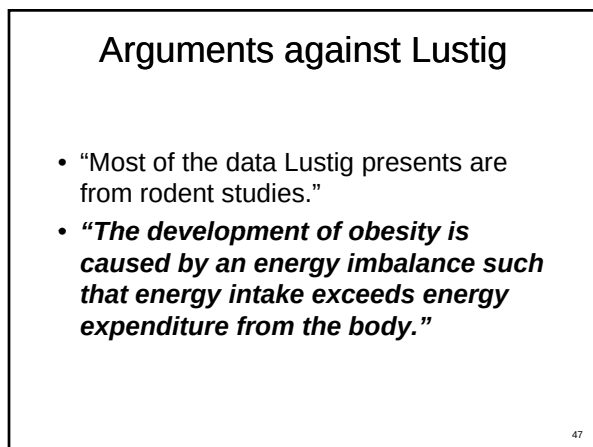
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- “The authority figures in obesity and nutrition are so fixed on the simplistic calorie-balance idea that they’re willing to ignore virtually any science to hold on to it.”
- “The first and most obvious mistake they make is embracing the notion that the only way foods can influence how fat we get is through the amount of energy-calories they contain.”

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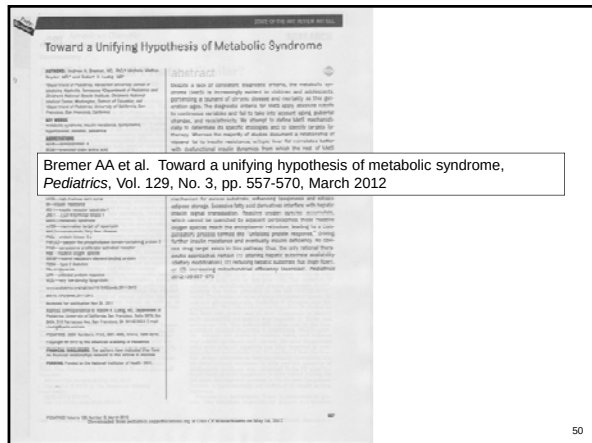
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Bremer AA et al. Toward a unifying hypothesis of metabolic syndrome, *Pediatrics*, Vol. 129, No. 3, pp. 557-570, March 2012

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- “Whereas the majority of studies document a relationship of visceral fat to insulin resistance, ectopic liver fat correlates better with dysfunctional insulin dynamics from which the rest of metabolic syndrome derives.”
- “In contrast to the systemic metabolism of glucose, the liver is the primary metabolic clearinghouse for 4 specific foodstuffs that have been associated with the development of metabolic syndrome: trans-fats, branched-chain amino acids, ethanol, and fructose.”

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***“These 4 substrates (1) are not insulin regulated and (2) deliver metabolic intermediates to hepatic mitochondria with an appropriate ‘pop-off’ mechanism for excess substrate, enhancing lipogenesis and ectopic adipose storage.”***

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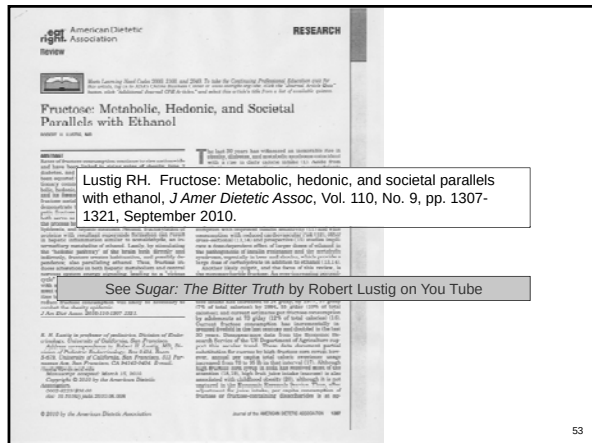
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- “Elucidation of fructose metabolism in liver and fructose action in brain demonstrate three parallelisms with ethanol.”
- “First, hepatic fructose metabolism is similar to ethanol, as they both serve as substrates for de novo lipogenesis, and in the process both promote hepatic insulin resistance, dyslipidemia, and hepatic steatosis.”
- “Second, fructosylation of proteins with resultant superoxide formation can result in hepatic inflammation similar to acetaldehyde, and intermediary metabolite of ethanol.”

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- “Lastly, by stimulating the ‘hedonic pathway’ of the brain both directly and indirectly, fructose creates habituation, and possibly dependence; also paralleling ethanol.”
- “Thus, fructose induces alterations in both hepatic metabolism and central nervous system energy signaling, leading to a ‘vicious cycle’ of excessive consumption and disease consistent with metabolic syndrome.”

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## Epidemiologic data

- “...our absolute consumption of dietary fat has not changed in these last 30 years, and high-fat, low-carbohydrate diets appear to be protective against the metabolic syndrome.”
- “Before 1900, Americans consumed approximately 15g/day fructose (4% of total calories, mainly through fruits and vegetables.”

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- “Before World War II, fructose intake had increased to 24 g/day; by 1977, 37 g/day (7% of total calories); by 1994, 55 g/day (10% of total calories); and current estimates put fructose consumption by adolescents at 73 g/day (12% of total calories).”
- “Although high-fructose corn syrup in soda has received most of the attention, high fruit juice intake (sucrose) is also associated with childhood obesity, although it is not captured in the Economic Research Service.”

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- “Thus, after adjustment for juice intake, per capita consumption of fructose or fructose-containing disaccharides is at approximately 156 lb/year or 0.4 lb/day for the average American.”

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“To explain the dichotomy of selective insulin resistance in the pathogenesis of metabolic syndrome, it is essential to delineate the hepatic metabolism of three energy substrates: glucose, ethanol, and fructose.”

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Hepatic glucose metabolism

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- “Upon ingestion of 120 kcal of glucose (eg, two slices of white bread), plasma glucose levels rise and insulin is released by the pancreas through glucose stimulation of  $\beta$ -cell depolarization via the Glut2 transporter.”
- “Ninety-six kilocalories (80%) of the glucose bolus are utilized by other organs immediately.”
- “Only 24 kcal (20%) enter the liver through the Glut2 transporter.”

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- “The liver can store large amounts of glycogen without experiencing dysfunction or damage, as demonstrated by the continued normal hepatic function into adulthood of patients with glycogen storage diseases.”
- “Only a small amount of glucose-6-phosphate (the exact amount is dependent on quantity of other substrates, and magnitude of insulin action) is broken down by the Embden-Meyerhoff glycolytic pathway to pyruvate.”

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- “Pyruvate enters the mitochondria, where it is converted to acetyl-CoA, which then participates in the Krebs tricarboxylic acid (TCA) cycle to generate adenosine triphosphate, the chemical storage form of energy, carbon dioxide, and water.”
- “The hepatic TCA cycle has a relatively fixed maximum velocity, modulated only by thyroid status, cold exposure, altitude, and exercise.”

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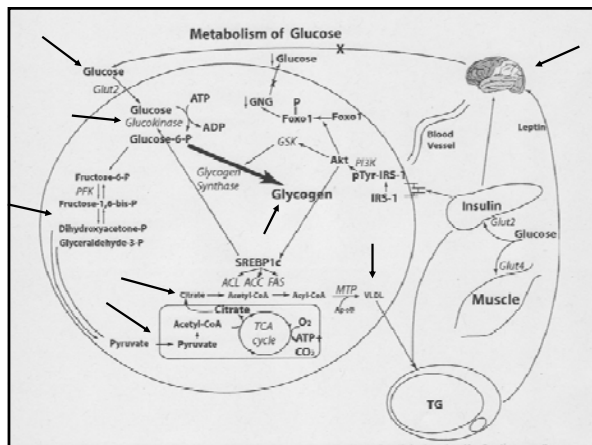
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- “Thus, whatever tiny fraction of pyruvate is not metabolized by the mitochondria exits back into the cytoplasm as citrate through the ‘citrate shuttle’.
- “This small amount of cytoplasmic citrate can serve as substrate for the process of de novo lipogenesis (DNL).”
- “...only a tiny fraction of glucose can be hepatically metabolized to VLDL, which could contribute slowly to cardiovascular disease during a lifetime.”

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## Hepatic ethanol metabolism

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- “Upon oral ingestion of 120 kcal of ethanol (eg, 1.5 oz hard spirits at 80 proof, or 40%), approximately 10% is metabolized by the stomach and stomach and intestine in a ‘first-pass’ effect before entry into the portal circulation.”
- “Another 10% are metabolized by muscle and kidney.”
- “So approximately 96 calories reach the liver accounting for four times the substrate as for glucose.”

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- “Ethanol enters the hepatocyte through osmosis and does not stimulate insulin secretion.”
- “Once inside the liver, ethanol bypasses glycolysis and is converted by alcohol dehydrogenase 1B to form acetaldehyde, which, because of its free aldehyde, can generate reactive oxygen species (ROS) formation and toxic damage if not quenched by hepatic antioxidants such as glutathione or ascorbic acid.”

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- “Acetaldehyde is then quickly metabolized by the enzyme aldehyde dehydrogenase 2 to the intermediary acetic acid.”
- “From there, acetic acid is metabolized by the enzyme acyl-CoA synthetase short-chain family member 2 to form acetyl-CoA, which can then enter the mitochondrial TCA cycle; or, in the presence of other caloric substrate, it is more likely to participate in synthesis of fatty acids through DNL.”

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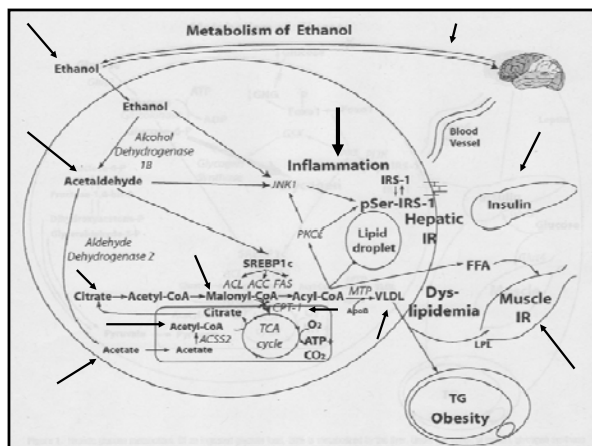
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- “In the process of DNL, the intermediary malonyl-CoA is formed in excess.”
- “However, malonyl-CoA is a steric inhibitor of the mitochondrial enzyme carnitine palmitoyl transferase-1.”
- “Carnitine palmitoyl transferase-1 is the key rate-limiting and regulatory step in mitochondrial  $\beta$ -oxidation; the fatty acid transporter carnitine must be regenerated for transesterification and import of fatty acids into the mitochondrial matrix to generate two-carbon fragments for ketone formation.”

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- **“Thus, increased DNL inhibits intrahepatic lipid  $\beta$ -oxidation, resulting in further intrahepatic lipid buildup.”**
- **“Lastly, ethanol is a known contributor to hepatic insulin resistance.”**

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## Hepatic fructose metabolism

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- “Upon ingestion of 120 kcal of sucrose (eg, 8 oz of orange juice; composed of 60 kcal fructose and 60 kcal glucose), the overwhelming majority of the 60-kcal fructose bolus reaches the liver, along with 20% of the glucose bolus (12 kcal), for a total of 72 kcal; thus, the liver must handle triple the substrate as it did for glucose alone.”
- “In the liver, fructose is converted to fructose 1-phosphate by the enzyme fructokinase.”

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- “This is an adenosine triphosphate-requiring reaction, depleting available intracellular phosphate.”
- “Phosphorylation of this large substrate load leads to activation of the scavenger enzyme adenosine monophosphate deaminase-1, which...[leads] to the cellular waste product uric acid.”
- “Buildup of urate in the circulation inhibits endothelial nitric oxide synthase, resulting in decreased nitric oxide in the vasculature.”

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- “In contrast to glucose’s conversion to glycogen, the fructose-1-phosphate load enters the Embden-Meyerhoff glycolytic cascade.”
- “The majority of fructose-1-phosphate is metabolized directly to pyruvate, with the resultant large volume of acetyl-CoA entering the mitochondrial TCA cycle.”
- “The liver mitochondria cannot metabolize the entire fructose-derived pyruvate/acetyl-CoA substrate excess; any extra will exit the mitochondria into the cytoplasm as citrate via the ‘citrate shuttle.’”

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### Fructose and de novo lipogenesis (DNL)

- “DNL is markedly increased by excess dietary CHO, rather than excess dietary fat.”
- “For example, if total CHO energy intake exceeds total energy expenditure, hepatic DNL is incremented 10-fold.”
- “Similarly, on a high-CHO diet, DNL synthesis is 27 times increased in the fasting state as compared with a low-CHO diet, and 4 times increased in the fed state.”

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- “Fructose is a primary driver of DNL.”
- “Human studies demonstrate a rate of fractional DNL of 2% with glucose and 10% after 6 days of high-fructose feeding.”
- “A recent human study demonstrated that fructose feeding increased fractional DNL to 17%.”
- “Elevated circulating VLDL in animal models of high-fructose feeding may be a result of overproduction driven by insulin resistance; increased triglyceride flux and hepatic inflammation; and decreased clearance.”

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- “Animal studies demonstrate increased hepatic lipid deposition in response to high-fructose feeding.”
- “In human studies, eucaloric replacement of glucose with fructose increased intrahepatic lipid levels by 38% within 8 days, as measured by magnetic resonance spectroscopy.”
- “Our group also has found a correlation between soft drink consumption and alanine aminotransferase levels in obese children.”

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## Fructose and insulin resistance

- “Numerous human studies demonstrate the induction of hepatic insulin resistance in response to increased fructose feeding and, in particular, peripheral markers of inflammation.”
- “Excessive FFA exported from the liver leads to increased uptake into skeletal muscle.”
- “There, diacylglycerides reassembled from FFA, reduces glucose transport, resulting in skeletal muscle resistance.”

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## Fructose and hyperinsulinemia

- “Hepatic and skeletal muscle insulin resistance, through increases FFA levels, promotes reciprocal hyperinsulinemia.”
- “Thus, fructose’s action on the liver is unique among carbohydrates and appears independent of insulin.”
- “Fructose metabolism gives rise to the phenotype of ‘selective hepatic insulin resistance’ typical of metabolic syndrome...”

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## Fructose vs. ethanol

- “Thus, hepatic metabolism of either fructose or ethanol results in energy substrate conversion to acetyl-CoA, with any insulin regulation and with limited diversion to nontoxic intermediaries such as glycogen.”
- “The overwhelming majority of the acetyl-CoA produced will find its way into DNL, generating intrahepatic lipid, inflammation, and insulin resistance.”

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## Some final thoughts from Lustig

- “Ethanol is manufactured by fermentation of fructose; the only difference is that for fructose, humans perform the glycolysis, while for ethanol, yeast have already performed the glycolysis.”

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- “Aside from restriction of intake there are two ‘antidotes’ to the hepatic effects of fructose.”
- Exercise – “By increasing hepatic TCA cycle maximal velocity, less acetyl-CoA will be converted to citrate, providing less substrate for DNL and reducing fructose’s downstream effects.”
- “Fiber...enjoys two benefits. By reducing glycemic load and rate of carbohydrate absorption, fiber reduces the bolus of energy substrate the liver has to metabolize acutely, thereby reducing the rate of DNL and improving insulin sensitivity. Fiber also increases satiety, reducing further consumption.”

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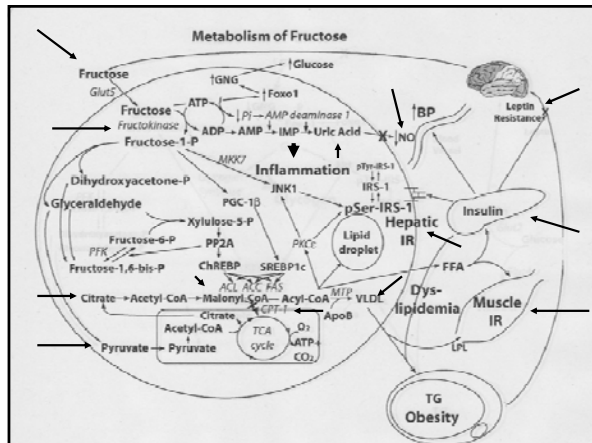
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***“Health care providers must recognize the differences between glucose and fructose and that despite fructose’s classification as a carbohydrate, it is metabolized more like a fat.”***

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**Fructose and leaky gut**

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REVIEWS

The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome

Lim JS et al. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat Rev Gastroenterol Hepatol*, Vol. 7, pp. 251-264, May 2010.

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- “Fructose consumption may also contribute to bacterial overgrowth and increased intestinal permeability.”
- “Animal and human studies suggest that non-alcoholic fatty liver disease (NAFLD) is associated with small intestinal bacterial overgrowth, which is linked to circulating endotoxemia and inflammatory cytokines.”
- “The presence of these factors in the blood has also been reported in patients with alcoholic fatty liver disease.”
- “Translocation of bacterial endotoxins through a leaky gut lumen to the portal blood increases the exposure of the liver to inflammation and injury.”

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- “The gut microflora, therefore, may be a key link between fructose feeding, plasma endotoxin levels, and systemic and hepatic inflammation associated with the metabolic syndrome.”

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Parting word

***HORMESIS***

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*Thank you!!*

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