

과당독성 및 연관질환

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연수강좌

I. Fructotoxicity, Insulin resistance and Obesity

Obesity cause medical problems

Table 3. Comorbid Conditions in Obesity and Evidence for Amelioration With Weight Reduction

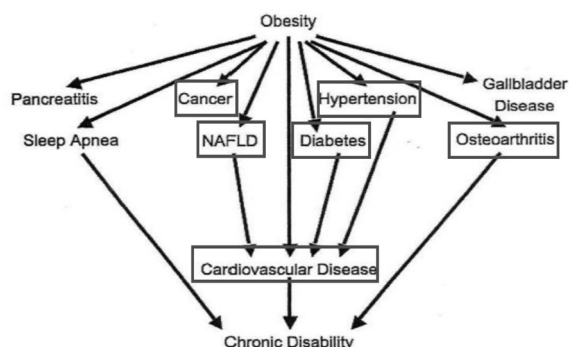
Comorbidity	Improvement After Weight Loss	First Author, Year (Ref)
T2DM	Yes	Cohen, 2012 (132); Mingrone, 2012 (133)*; Schauer, 2012 (134); Buchwald, 2009 (135)
Hypertension	Yes	Ilane-Parikka, 2008 (136); Phelan, 2007 (137); Zanella, 2006 (138)
Dyslipidemia and metabolic syndrome	Yes	Ilane-Parikka, 2008 (136); Phelan, 2007 (137); Zanella, 2006 (138)
Cardiovascular disease	Yes	Wannamethee, 2005 (139)
NAFLD	Variable outcomes	Andersen, 1991 (140); Huang, 2005 (141); Palmer, 1990 (142); Ueno, 1997 (143)
Osteoarthritis	Yes	Christensen, 2007 (144); Fransen, 2004 (145); Huang, 2000 (146); Messier, 2004 (147); van Gool, 2005 (148)
Cancer	Yes	Adams, 2009 (149); Sjöström, 2009 (150)
Major depression	Insufficient evidence	
Sleep apnea	Yes	Kuna, 2013 (151)

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

* This study showed that weight gain within the normal-weight BMI category (ie, increase from 23 to 25 kg/m²) increased risk of T2DM 4-fold.

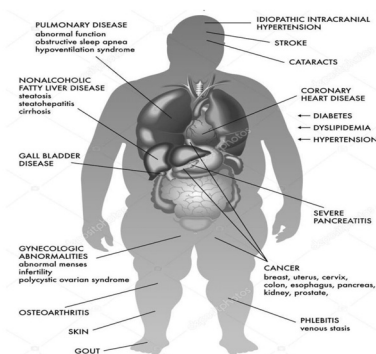
Apovian CM. et al. J Clin Endocrinol Metab., 2015;100(2):342–362

Obesity cause medical problems



Pi-Sunyer X. et al. Postgrad Med. 2009 Nov;121(6):21-33

Metabolic Syndrome



Why are we getting FAT?

- Eating too much
- Eat wrong kinds of food (sugar, low fat milk, juice, whole wheat)
- Lack of exercise
- Disease (hypothyroid)
- Medicine
 - Steroids, Oral contraceptives, Anti-depressant and anti-psychotic
- Lack of good bacteria in the bowels

Glucose and Fructose

- Excess Fructose
 - Fructose can be converted into glucose, triglyceride, and LDL-cholesterol in the liver.
 - Excess fructose consumption can cause obesity, insulin resistance, hypertension, and metabolic syndrome.
- Glucose and Fructose
 - Both fructose and glucose are hexose with the same chemical formula, $C_6H_{12}O_6$. However, their molecular structures and metabolism pathways are different.

FRUCTOSE SUGAR is NOT FRUITS

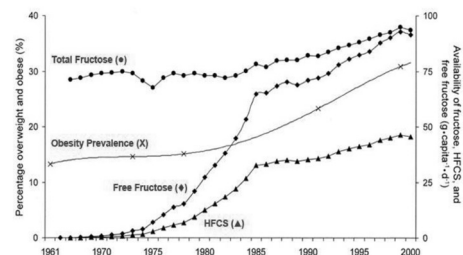
- Fructose
 - Low glycemic index
 - No stimulate insulin production
 - Fructose in regular diet
 - Fruit and honey, or as pure fructose of sucrose.
 - Fruits
 - Fruits contain fibers that slow down sugar absorption and help the growth of probiotics.
 - Consuming fruits containing fructose in moderate amount is safe.
- ➡ However, we are consuming too much fructose lately in the form of pure fructose or fructose corn syrup!

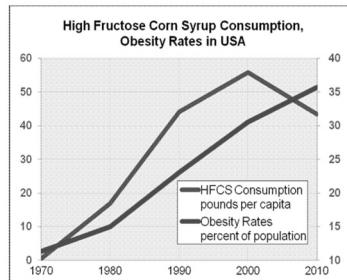
High fructose corn syrups

- High fructose corn syrups(HFCS)
 - It is corn syrups that has undergone enzymatic processing to convert some of its glucose into fructose to produce a desired sweetness.
- HFCS price is low compared to sugar, and because it won't stimulate leptin, a satiety hormone, that means increasing production sale.
- Now HFCS has become a predominant sweetener used in process food and soft drink.

One Bottle of Soda Contains 35 Gram of Fructose

Diets	35 gram of fructose
Soda beverage	1 bottle = 20 Oz
Honey	4 oz
Mango	2 mangoes
Apple	3 apples
Date	4 dates
Banana	5 bananas
Peach	6 peaches
Mandarin orange	7 oranges
Pineapple	8 slices
Strawberries	9 cups

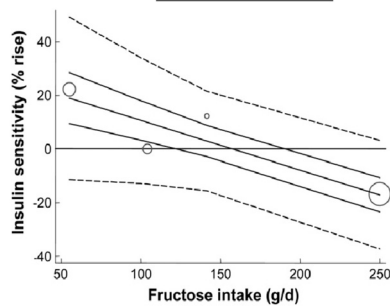




- The average American increased their consumption of HFCS (mostly from sugar sweetened drinks and processed food) from zero to over 60 pounds per person per year.

- During that time period, obesity rates have more than tripled and diabetes incidence has increased more than seven fold. Not perhaps the only cause, but a fact that cannot be ignored.

Since the invention of HFCS, excessive fructose consumption (> 250 g/d) became health hazardous problem that can lead to insulin resistance



J. Nutr. 2009; 139:12465-12525

Paradoxical Effects of Fruit on Obesity

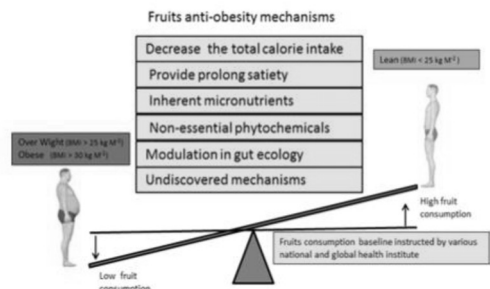
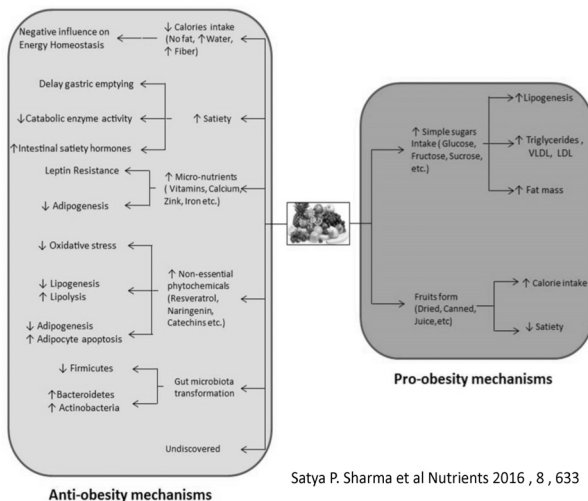


Figure 1. Higher consumption of daily fruit is recommended by health organizations as a key factor for maintaining a healthy body weight via various mechanisms.

Satya P. Sharma et al Nutrients 2016 , 8 , 633



Satya P. Sharma et al Nutrients 2016 , 8 , 633

Obesity and Gut flora

- gut bugs fall: Bacteroidetes and Firmicutes.
- A Washington Univ. research team found more Firmicutes in the gut flora of obese mice than in normal-weight mice; when gut flora from obese mice were transferred to germ-free normal-weight mice, the slim mice gained weight, without an increase in caloric intake.
- The team then studied the gut flora of 12 obese people and found an unusually high proportion of Firmicutes. As the participants lost weight through caloric restriction, the proportion of Firmicutes dropped.

Bajzer M and Seeley RJ. Nature 2006 Dec 21/28; 444:1009-10.

Obesity and Gut flora

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez¹, Tal Korem^{2*}, David Zeevi^{2*}, Gili Zilberman-Schapira^{3*}, Christoph A. Thaiss¹, Ori Maza¹, David Israeli¹, Niv Zmora^{4,5,6}, Shlomit Gilad⁷, Adina Weinberger², Yael Kuperman⁸, Alon Harmelin⁹, Ilana Kolodkin-Gal¹, Hagit Shapiro¹, Zamir Halpern^{1,6}, Eran Segal¹ & Eran Elinav¹

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 transferable 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.

Bajzer M and Seeley RJ. Nature 2006 Dec 21/28; 444:1009-10.

II. Fructotoxicity, Hyperuricemia and CKD

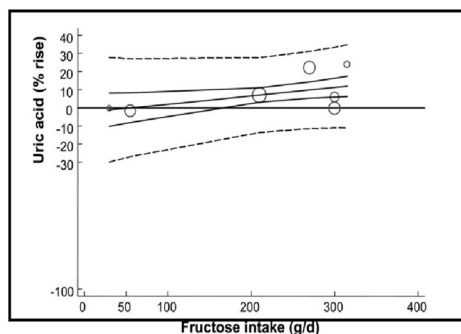
Causes of Hyperuricemia

- Genetics
- Drugs (diuretics, salicylates, pirazinamide, cyclosporine, nicotinic acid)
- Excess intake of purine rich foods such as meats, poultry, and animal internal organs.
- Alcohols
- Malignancies
- Lead Toxicity
- Chronic Kidney Disease
- High dietary fructose intake

Consequences of Hyperuricemia

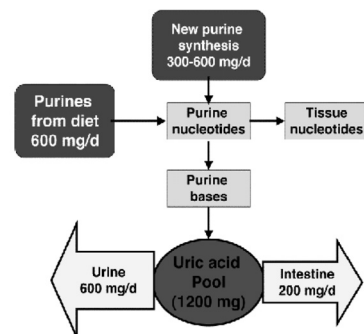
- Gout
- Uric Acid Stone
- Uric Acid Nephropathy
- Endothelial Dysfunction
- Hypertension
- Chronic Kidney disease

Fructose consumption and Uric Acid Levels



J Nutr 2009; 139:1246S

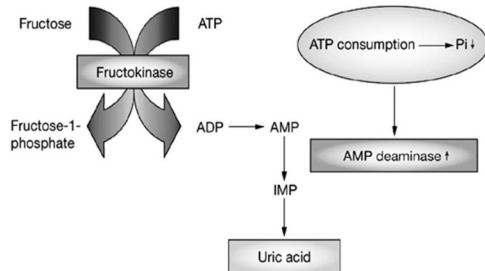
Uric Acid Homeostasis



70% of uric elimination occurs through the kidney and the rest via gastrointestinal tract.

Uric Acid Level and Fructose

- Fructose-induced production of uric acid in the hepatocyte



Nakagawa T et al. (2005) Nat Clin Pract Nephrol 1: 80-86

Dietary and serum Uric acid levels

- Severe reduction in dietary purine intake can accomplish NO MORE THAN a 1 mg/dL decrease in serum uric acid.
- High consumption of purine-rich vegetables has NO association with serum uric acid.
- Fructose is the only carbohydrate that influences purine metabolism. So, apple cider is NOT good for gout. Ingestion of 5 apples resulted in 35% increase in serum uric acid within 6 hours!

Choi HK et al. NEJM 2004;350:1093-1101

Choi HK et al. Lancet 2004;353:1277-1281

Lotito SB and Frei B Free Radic Biol Med 2004;37:251-258

Uric Acid and Hypertension

(N Engl J Med 2008;359:1811-21)

- Elevated uric acid level predicts the development of hypertension
- Elevated uric acid level is observed in 25%-60% of patients with essential hypertension.
- Elevated uric acid level is observed in nearly 90% of adolescents with essential hypertension.
- Reducing uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset.

Chronic Kidney Disease and Uric Acid Levels

- Uric acid > 7 mg/dL increased CKD risk 2.14 fold in men and 3.12 fold in women.
- Uric acid > 8 mg/dL increased CKD risk three fold in men and 10 fold in women.
- Each 1 mg/dL increase in uric acid increase risk of CKD 7%-11%
- Each 1 mg/dL increase in uric acid associated with 1.28 odds ratio of reduced eGFR at 5 years.
- Uric acid > 6.5 mg/dL in men and > 5.3 mg/dL in women, associated with hazard ratio of 1.36 for all cause mortality and 2.14 for incident CKD

World J Nephrol 2013;2:17-25

Guidelines for management of hyperuricemia

- Patient education on diet (including fructose reduction) and lifestyle is recommended.
- Xanthine oxidase inhibitor therapy with allopurinol or febuxostat is recommended
- Target serum urate level should be lower than 6 mg/dl
- Prior to initiation of allopurinol, HLA-B58 testing should be considered.
- In patients who can not tolerate allopurinol, febuxostat can be another alternative.

Take Home message

- Consuming fructose in excessive doses can be harmful and can causes metabolic syndrome, diabetes, and CKD.
- Fructose over-consumption can cause uric acid overproduction and gout. Vegetarian can have hyperuricemia too!
- Hyperuricemia is a treatable factor for delaying CKD progression, so uric acid levels should be tested in every patient with renal failure.