Fructose in Insulin Resistance- Focused on Diabetes

순천향대학교 부천병원
내분비내과
정 찬희

Introduction

Unique characteristics of Fructose Metabolism

Mechanism for Fructose-Induced Insulin Resistance

Epidemiological Studies
: Fructose intake and Type 2 diabetes

Summary

Fructose

- While virtually absent in our diet a few hundred years ago, fructose has now become a major constituent of our modern diet.
- Old hypothesis

  Excessive intake of sugar, and in particular fructose, may be an important cause of T2DM.

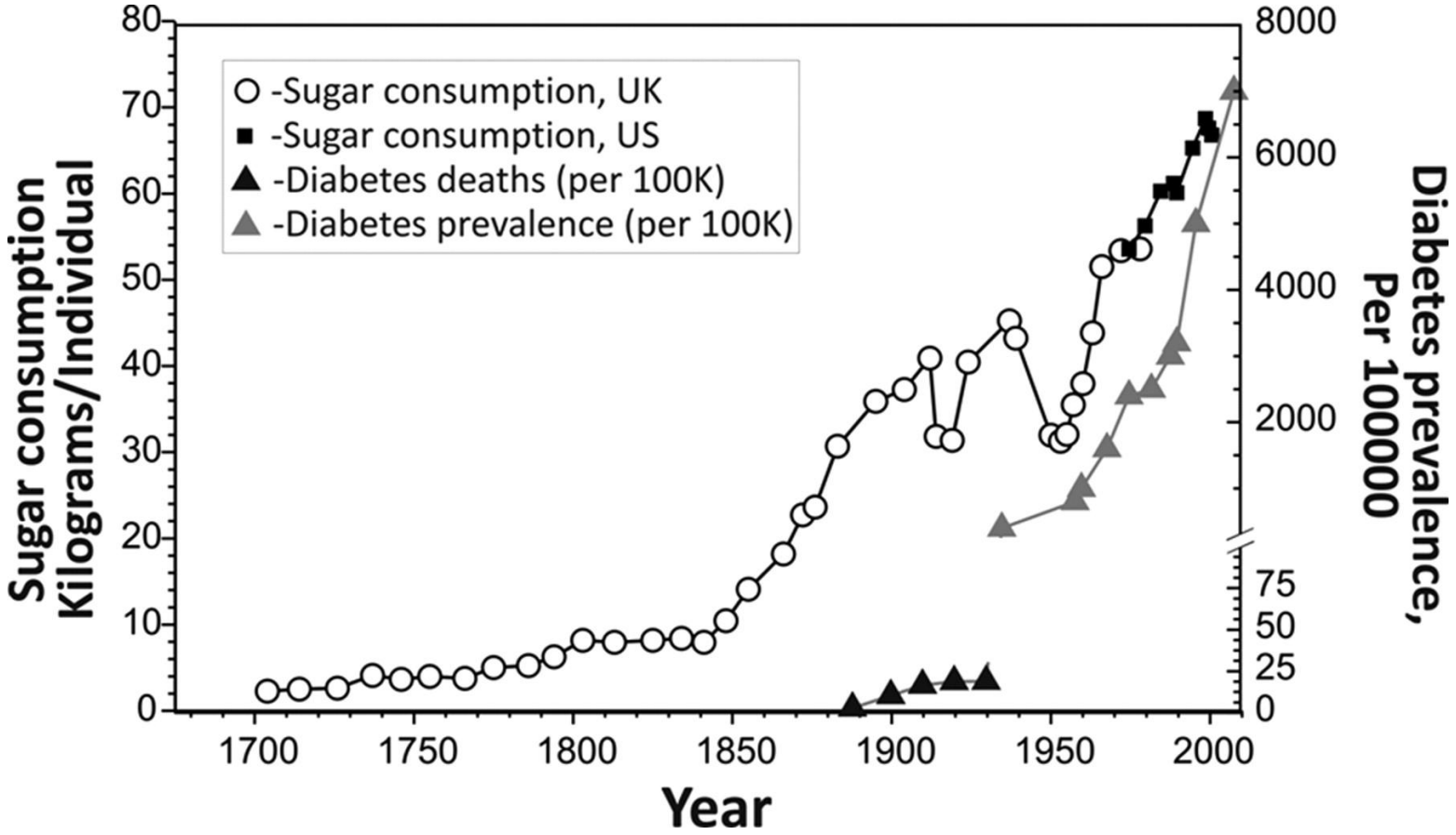
  =by Frederick Allen (1910년대)

  =In 1960s, Campbell and Yudkin resurrected

  =after, largely been eschewed

  Restriction of sugar had not been recommended as a means to prevent diabetes by the ADA before

Parallel epidemic of diabetes and sugar consumption



Johnson R J et al. Endocrine Reviews 2009;30:96-116

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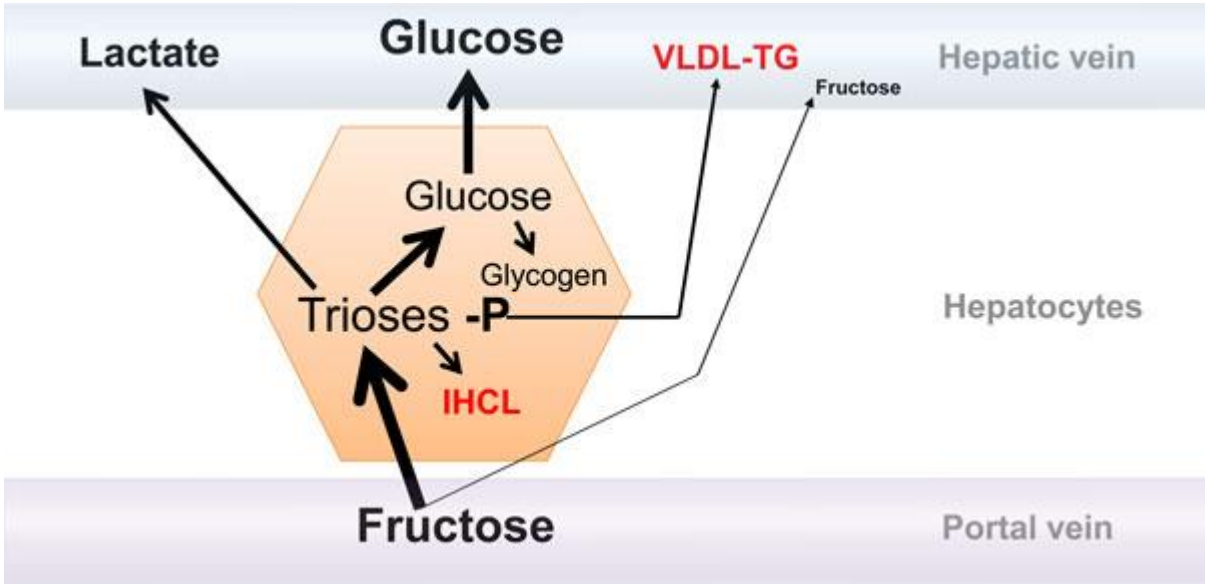
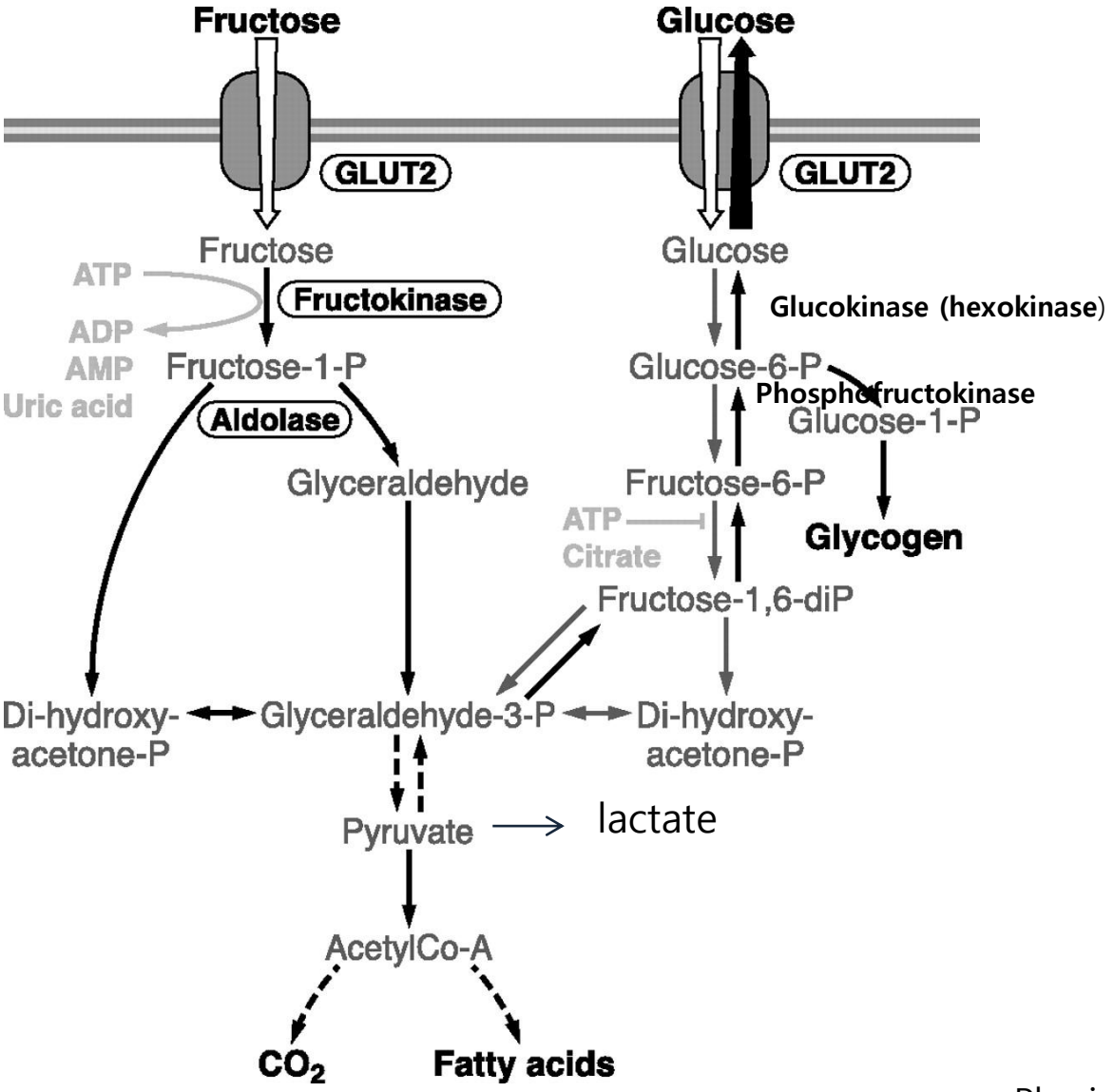
Conclusions

Metabolism of fructose in the liver



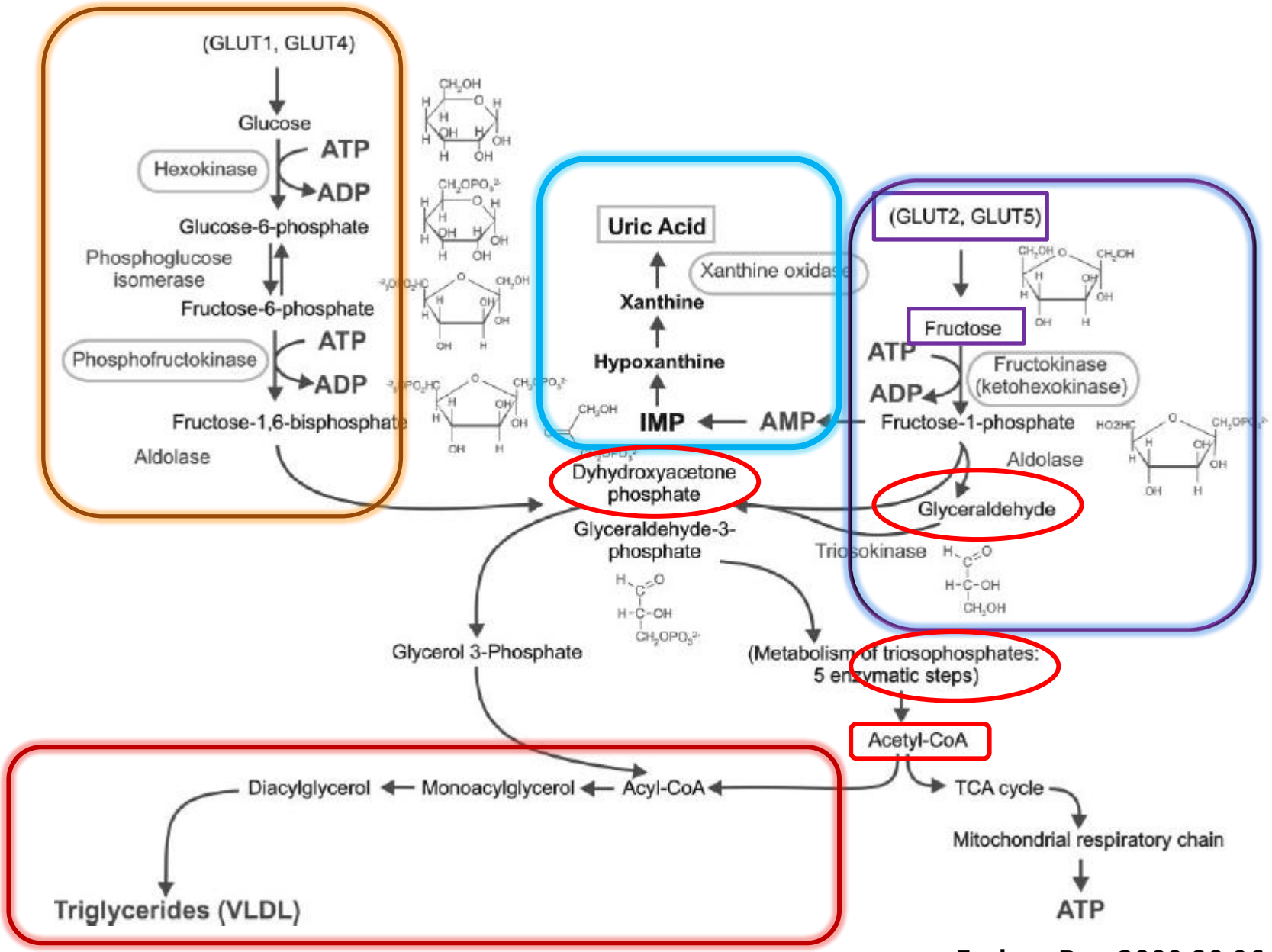
BMC Biology 2012;10:42

Metabolism of fructose in the liver



Physiol Rev 2010:90:23

Unique characteristics of Fructose metabolism



Endocr Rev 2009:30:96

- **Fructose differs from glucose in metabolism**
  - Different transporters and enzymes involved in its metabolism
  - Positive feedback system in which fructose up-regulates its transporter as well as fructokinase
  - Highly lipogenic
  - Stimulate uric acid production
  - Does not signal insulin release or require insulin
    : catalytic concept

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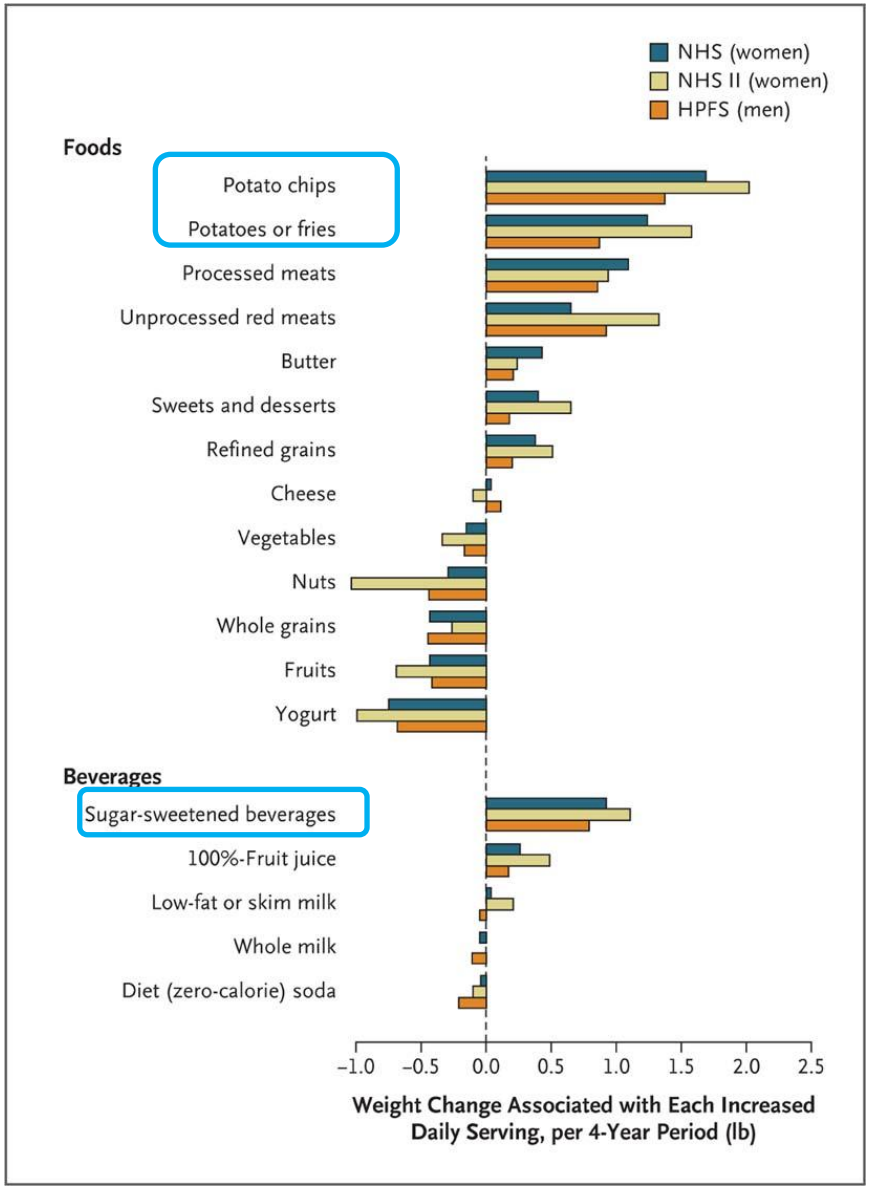
- Classic obesity-associated mechanisms
  - Fructose ingestion and satiety responses
- Independent of weight gain or differences in energy intake
  - Fructose-induced dyslipidemia
  - Fructose-induced hyperuricemia
  - Fructose-induced inflammation
  - Fructose-induced leptin resistance
  - Role of the gut in mediating the fructose response : endotoxin

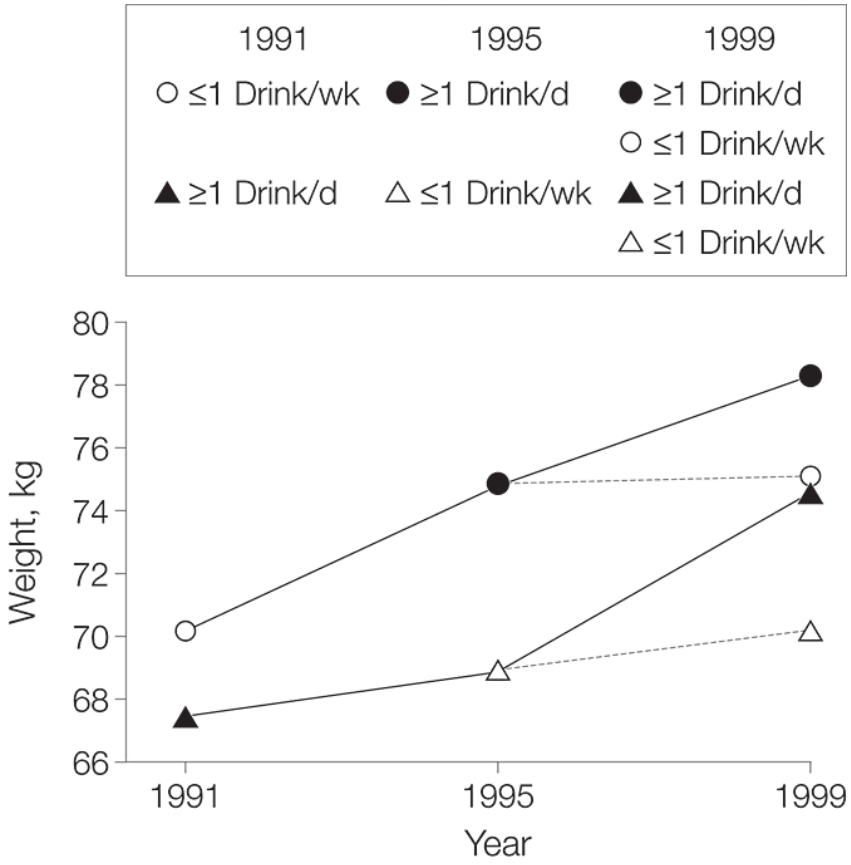
Changes in diet and lifestyle and long-term weight gain in women and men



N=120,877,
1986 to 2006

NEJM 2011;364:2392

Sugar-Sweetened Beverages and weight gain

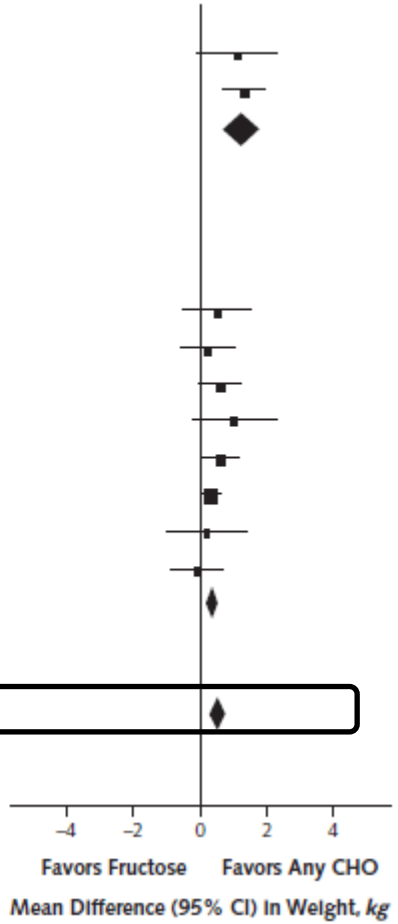


Mean weight in 1991, 1995, and 1999 according to trends in sugar-sweetened soft drink consumption in 1969 women who changed consumption from 1991 to 1995 and either changed or maintained level of consumption until 1999 : Nurses Health Study II

JAMA 2004;292:927

Effect of fructose on body weight in controlled feeding trials

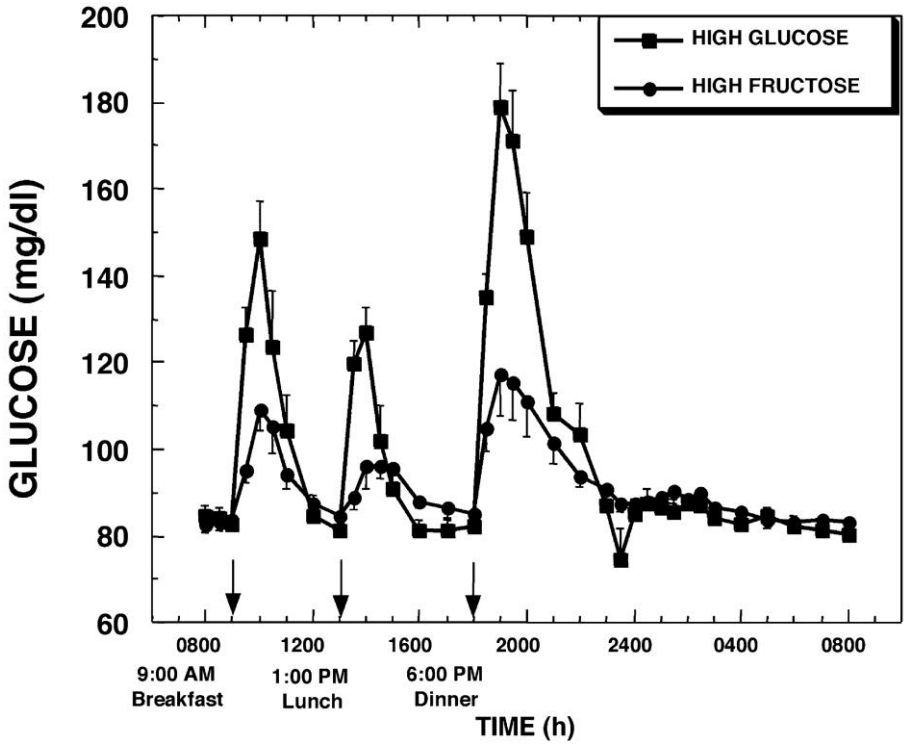
Subgroup and Study, Year (Reference)	Any CHO, *n*	Fructose, *n*	Mean Difference (95% CI) In Weight, *kg*
Overweight/obese			
Rizkalla et al, 1986 (58)	7	7	1.10 (–0.08 to 2.28)
Stanhope et al, 2009 (45)	17	17	1.30 (0.67 to 1.93)
Subtotal			1.26 (0.70 to 1.81)
Heterogeneity: tau-square = 0.00; chi-square = 0.09; $P = 0.77$; $I^2 = 0\%$			
Test for overall effect: $Z = 4.44$; $P < 0.00001$			
Normal-weight			
Beck-Nielsen et al, 1980 (50)	8	8	0.50 (–0.54 to 1.54)
Lê et al, 2006 (59)	7	7	0.20 (–0.61 to 1.01)
Le et al, 2009 (60) (ODM2)	8	8	1.00 (–0.26 to 2.26)
Le et al, 2009 (60) (N)	16	16	0.60 (–0.00 to 1.20)
Ngo Sock et al, 2010 (53)	11	11	0.60 (0.07 to 1.13)
Sobrecases et al, 2010 (61)	12	12	0.30 (–0.01 to 0.61)
Silbernagel et al, 2011 (56)	10	10	0.20 (–0.98 to 1.38)
Stanhope et al, 2011 (57)	16	16	–0.10 (–0.87 to 0.67)
Subtotal			0.37 (0.15 to 0.58)
Heterogeneity: tau-square = 0.00; chi-square = 4.19; $P = 0.76$; $I^2 = 0\%$			
Test for overall effect: $Z = 3.46$; $P < 0.00$			
Total			0.53 (0.26 to 0.79)
Heterogeneity: tau-square = 0.05; chi-square = 12.79; $P = 0.17$; $I^2 = 30\%$			
Test for overall effect: $Z = 3.91$; $P < 0.001$			

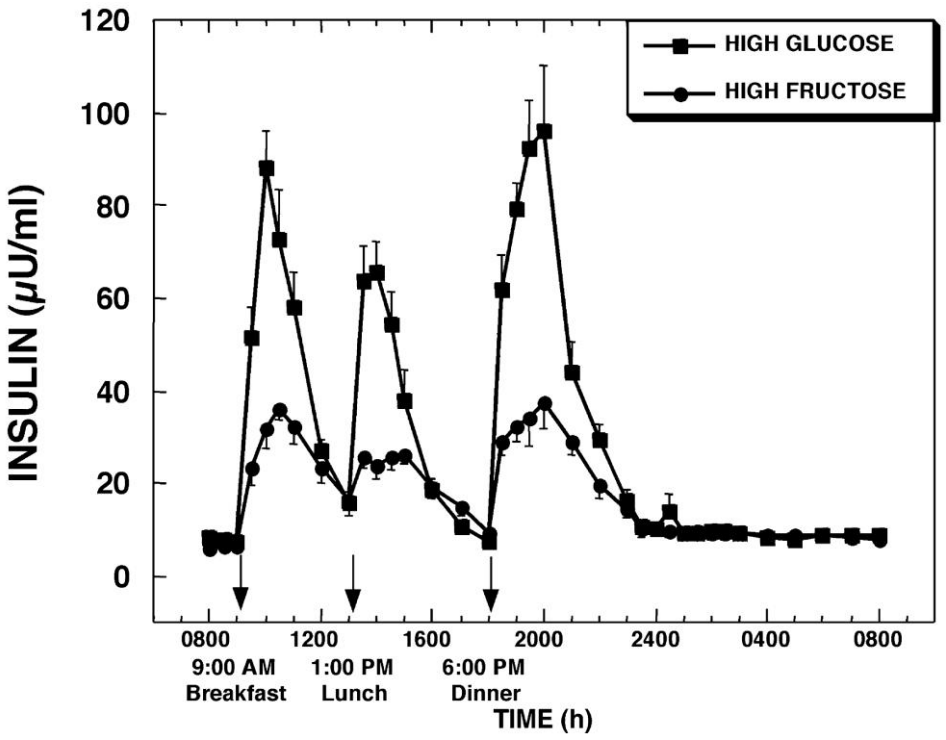


Ann Intern Med 2012;156:291

Fructose ingestion and Satiety Responses

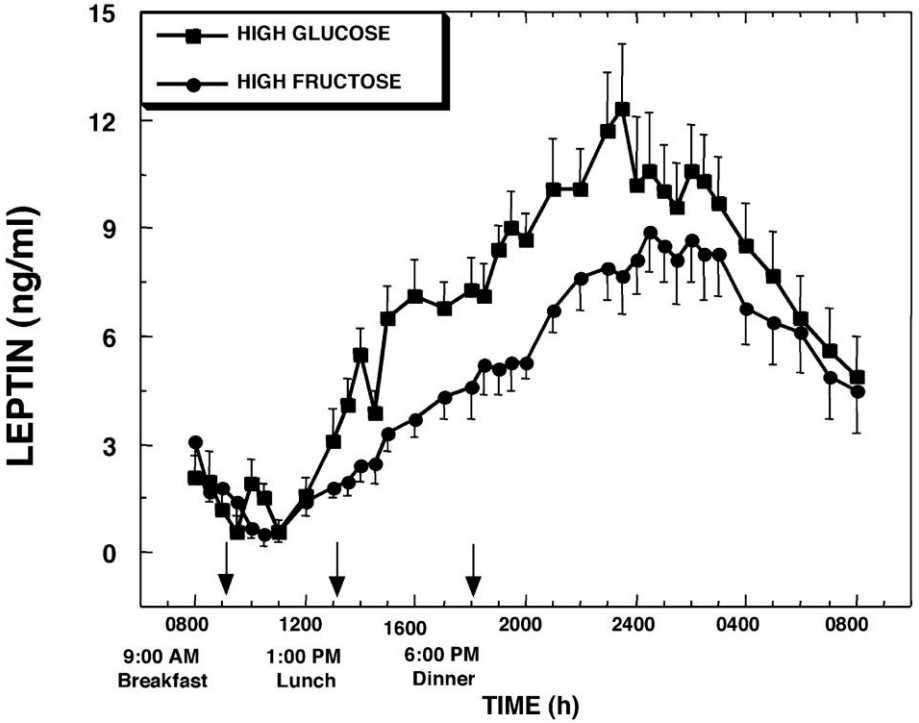
Plasma glucose and insulin concentrations during a 24-h period in 12 women consuming HGl or HFr beverages with each meal.

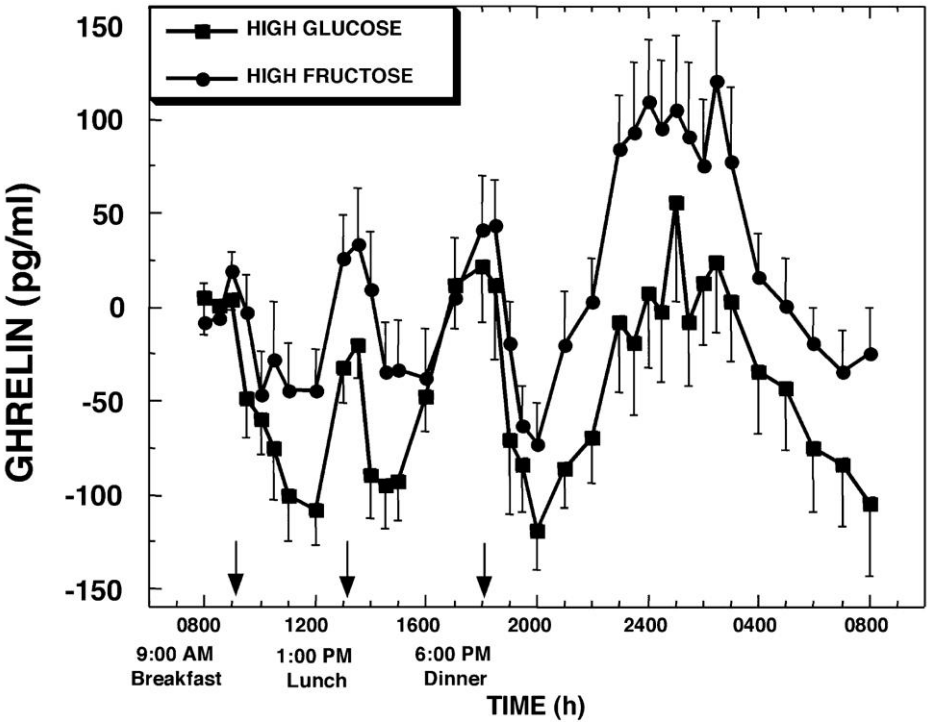




Teff K L et al. JCEM 2004;89:2963-2972

Change of plasma leptin and ghrelin concentrations in 12 women consuming HGl or HFr beverages with each meal.

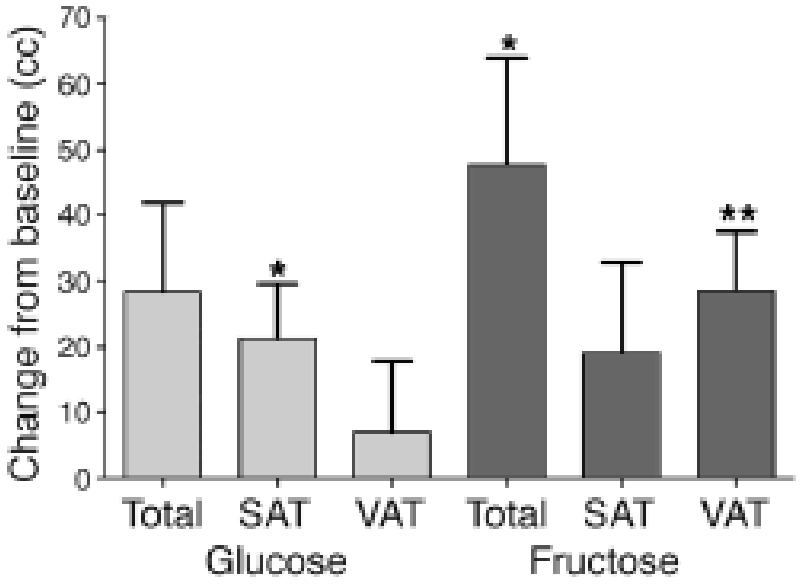




Teff K L et al. JCEM 2004;89:2963-2972

Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight /obese humans

Beverages providing 25% of energy requirements for 10 weeks



J Clin Invest 2009;119:1322

Fructose-Induced Insulin Resistance

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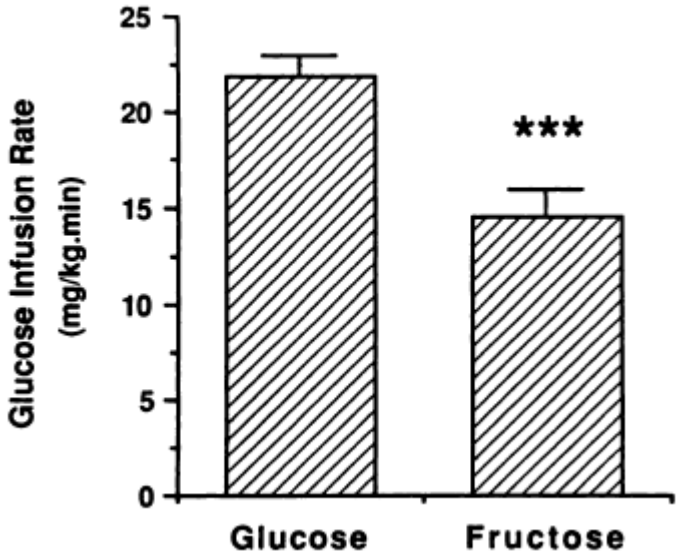
- Independent of weight gain or differences in energy intake
  - Fructose-induced dyslipidemia
  - Fructose-induced hyperuricemia
  - Fructose-induced inflammation, oxidative stress
  - Fructose-induced leptin resistance
  - Role of the gut in mediating the fructose response : endotoxin

Fructose-induced in vivo insulin resistance in rats

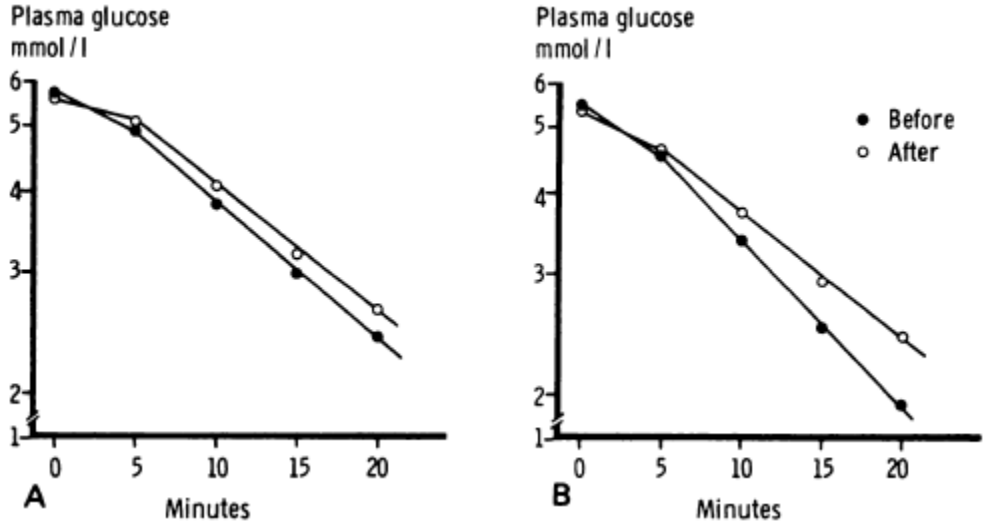


Insulin action was assessed by using the hyperinsulinemic clamp in rats fed equal amounts of glucose or fructose (35% of calories) for 4 wks

Am J Clin Nutr 1989;49:1155

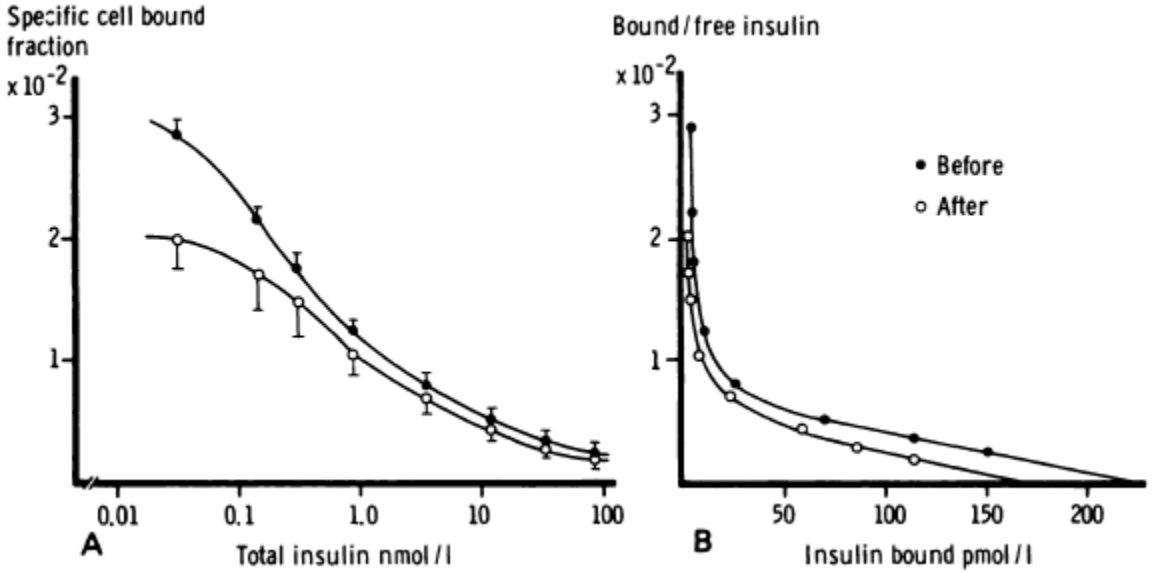
Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects

Diet and 1000kcal extra for 1wks



Insulin tolerance test
A: High glucose feeding
B: High fructose feeding

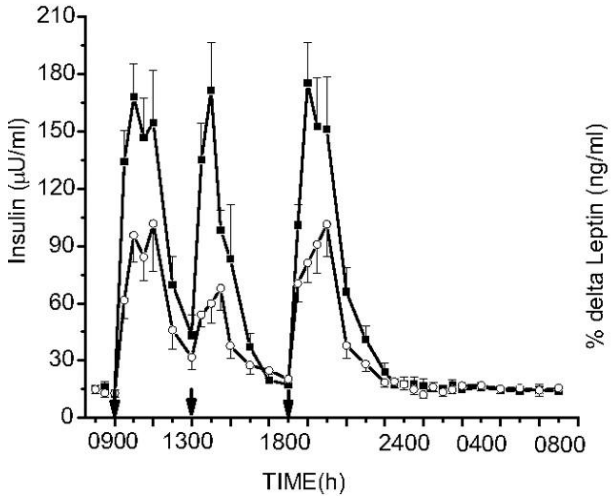
Insulin binding to monocytes from high-frutose feeding

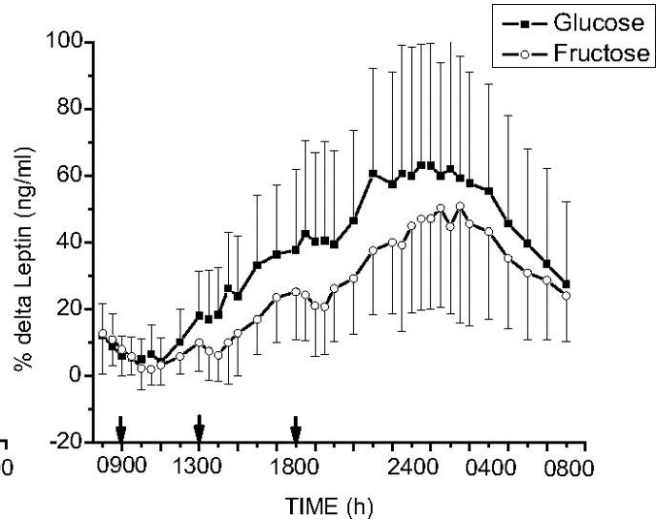


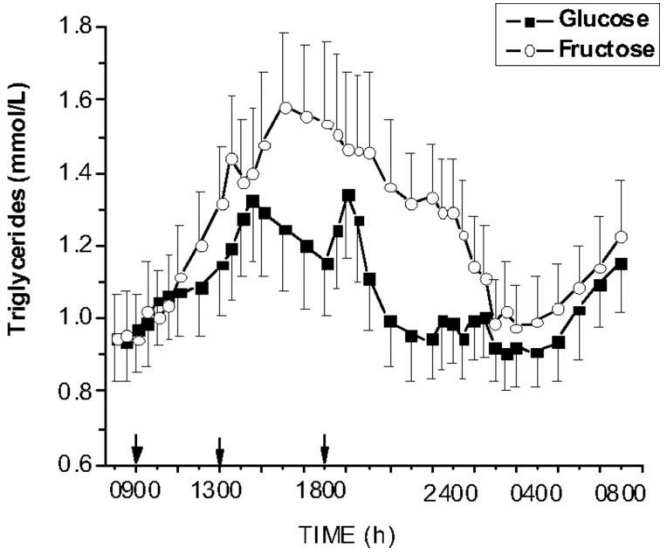
Am J Clin Nutr 1980;33:273

Influence of Insulin resistance on plasma Triglyceride responses

consuming Fructose-and Glucose-Sweetened Beverages with meals in obese men and women (n=17, 30% of total calories)



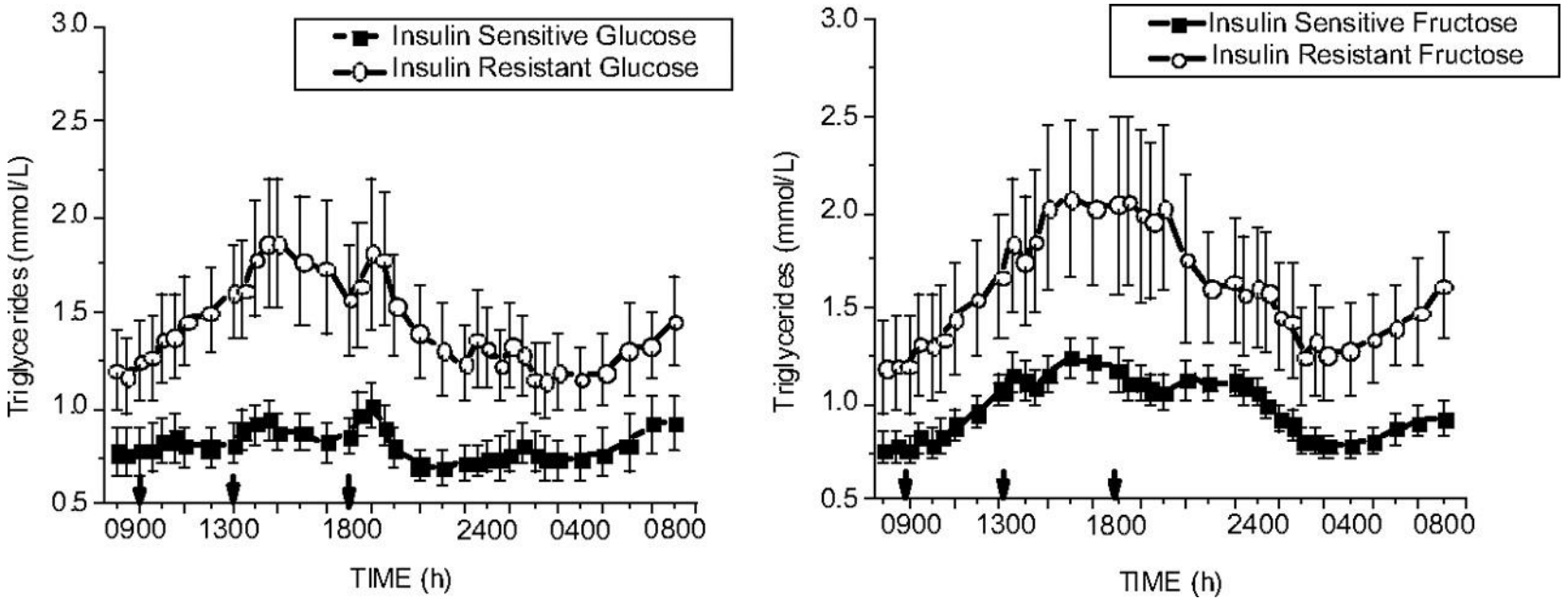




Teff K L et al. JCEM 2009;94:1562-1569

Influence of Insulin resistance on plasma Triglyceride responses

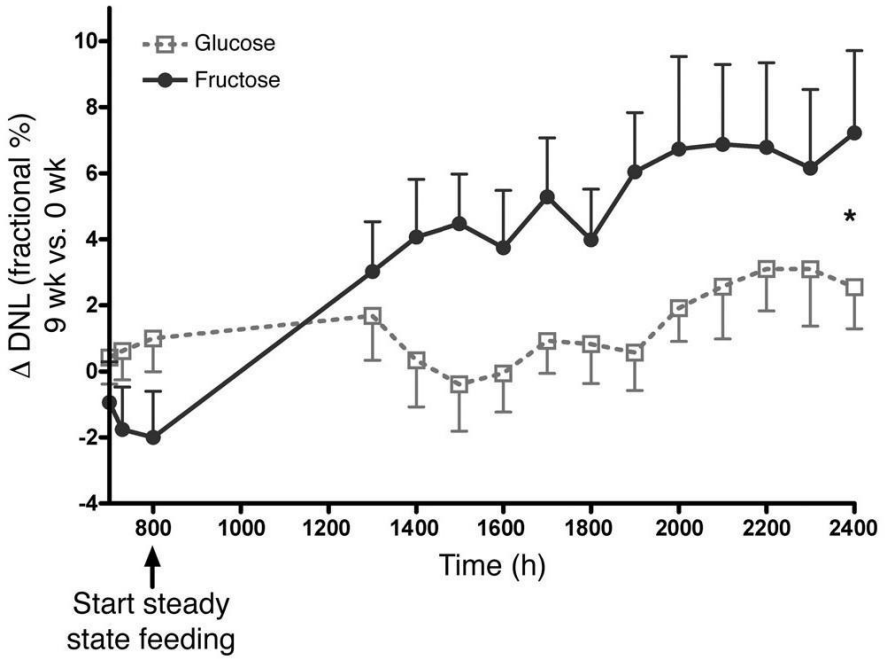
TG responses to consumption of glucose-sweetened and fructose-sweetened beverages with meals in insulin-sensitive (n = 10) and insulin-resistant obese subjects (n = 7).



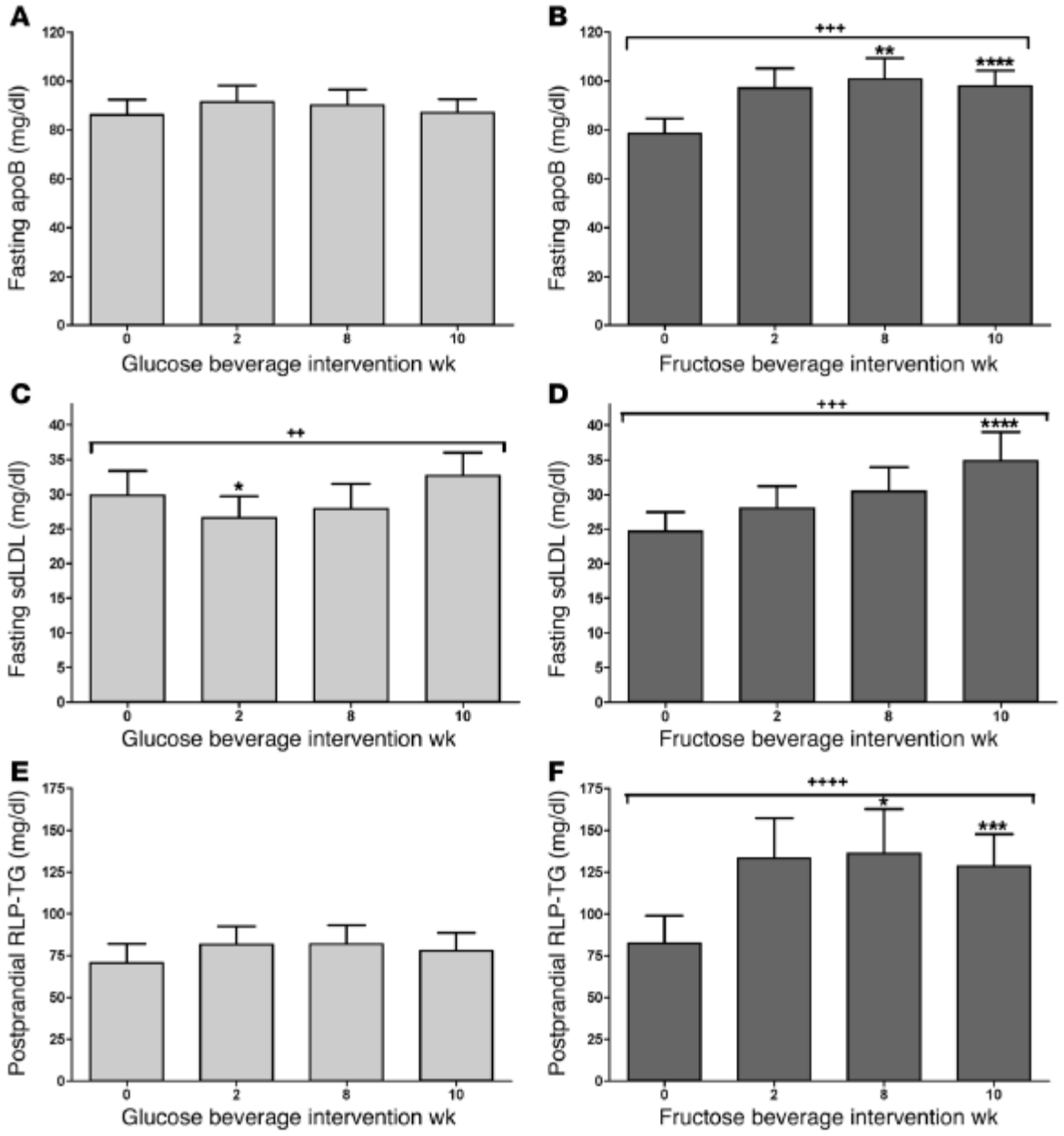
Teff K L et al. JCEM 2009;94:1562-1569

Consuming fructose-sweetened, not glucose-sweetened, beverages increases lipids in overweight /obese humans

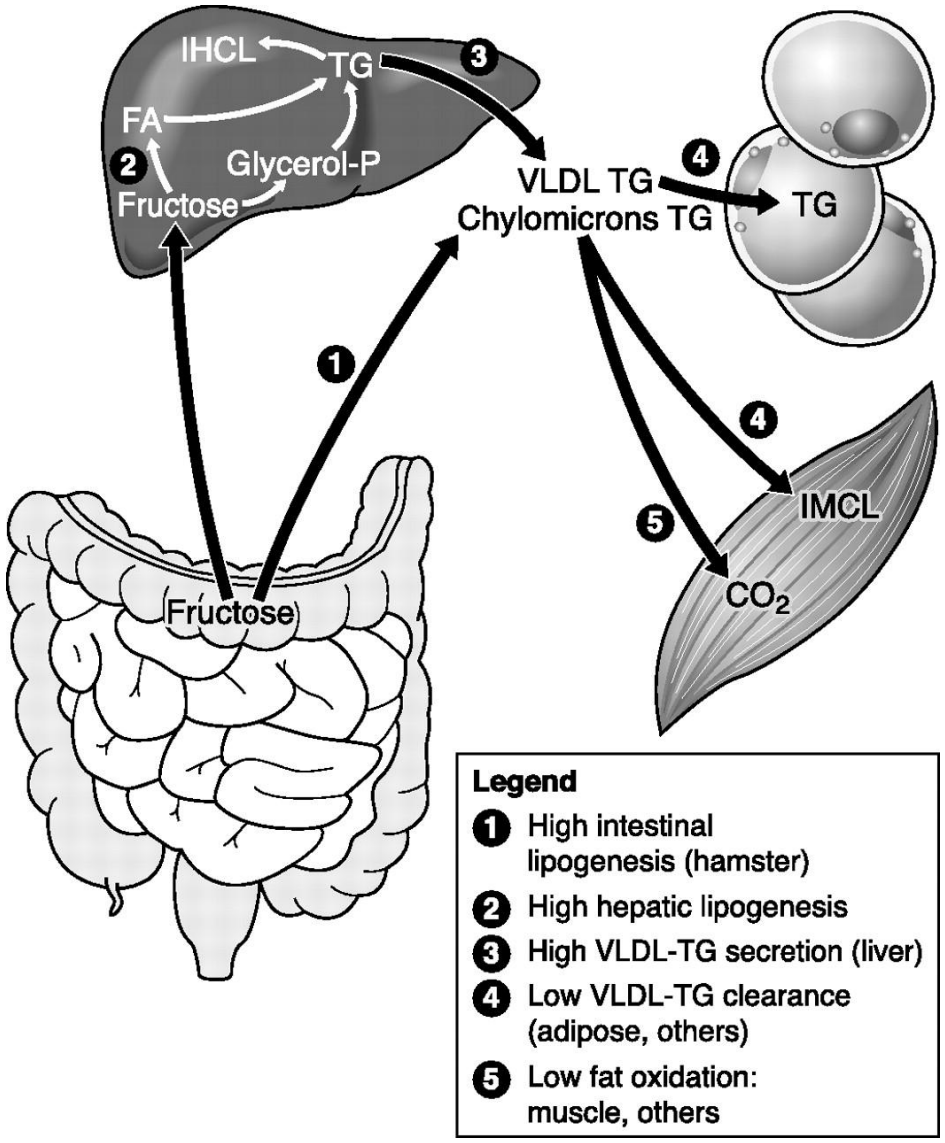
Beverages providing 25% of energy requirements for 10 weeks



J Clin Invest 2009;119:1322

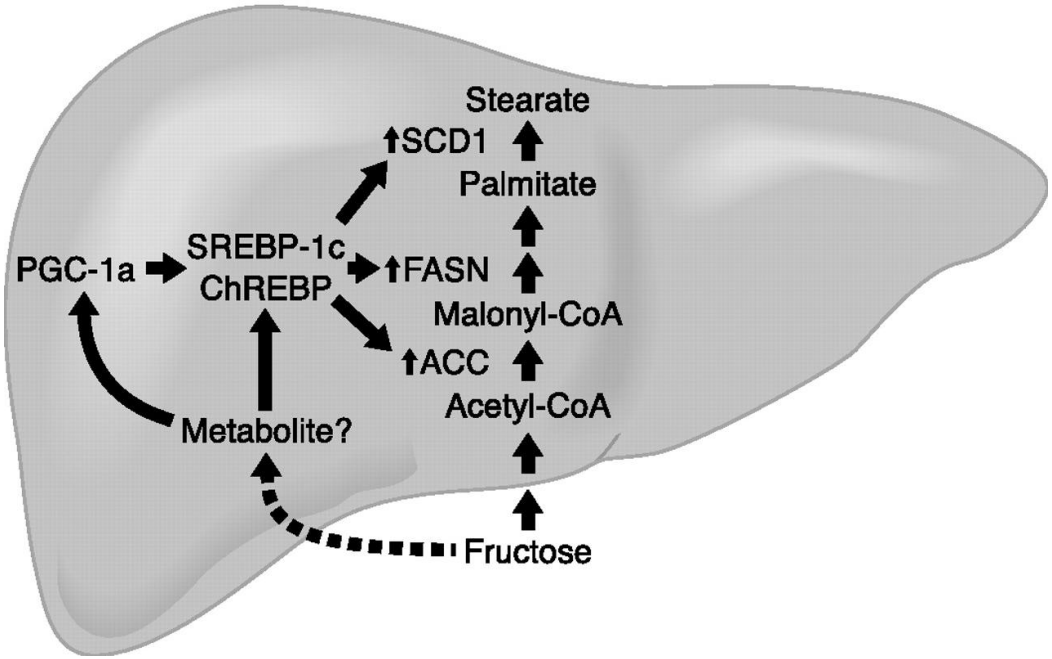

A
Fasting apoB (mg/dl)
120
100
80
60
40
20
0
0
2
8
10
Glucose beverage intervention wk
B
+++
**
****
Fasting apoB (mg/dl)
Fructose beverage intervention wk
C
++
*
Fasting sdLDL (mg/dl)
40
35
30
25
20
15
10
5
Glucose beverage intervention wk
D
+++
****
Fructose beverage intervention wk
E
Postprandial RLP-TG (mg/dl)
175
150
125
100
75
50
25
Glucose beverage intervention wk
F
++++
*
***
Fructose beverage intervention wk

Possible mechanisms involved in fructose-induced dyslipidemia



Tappy L , and Lê K Physiol Rev 2010;90:23-46

Mechanisms for fructose-induced de novo lipogenesis

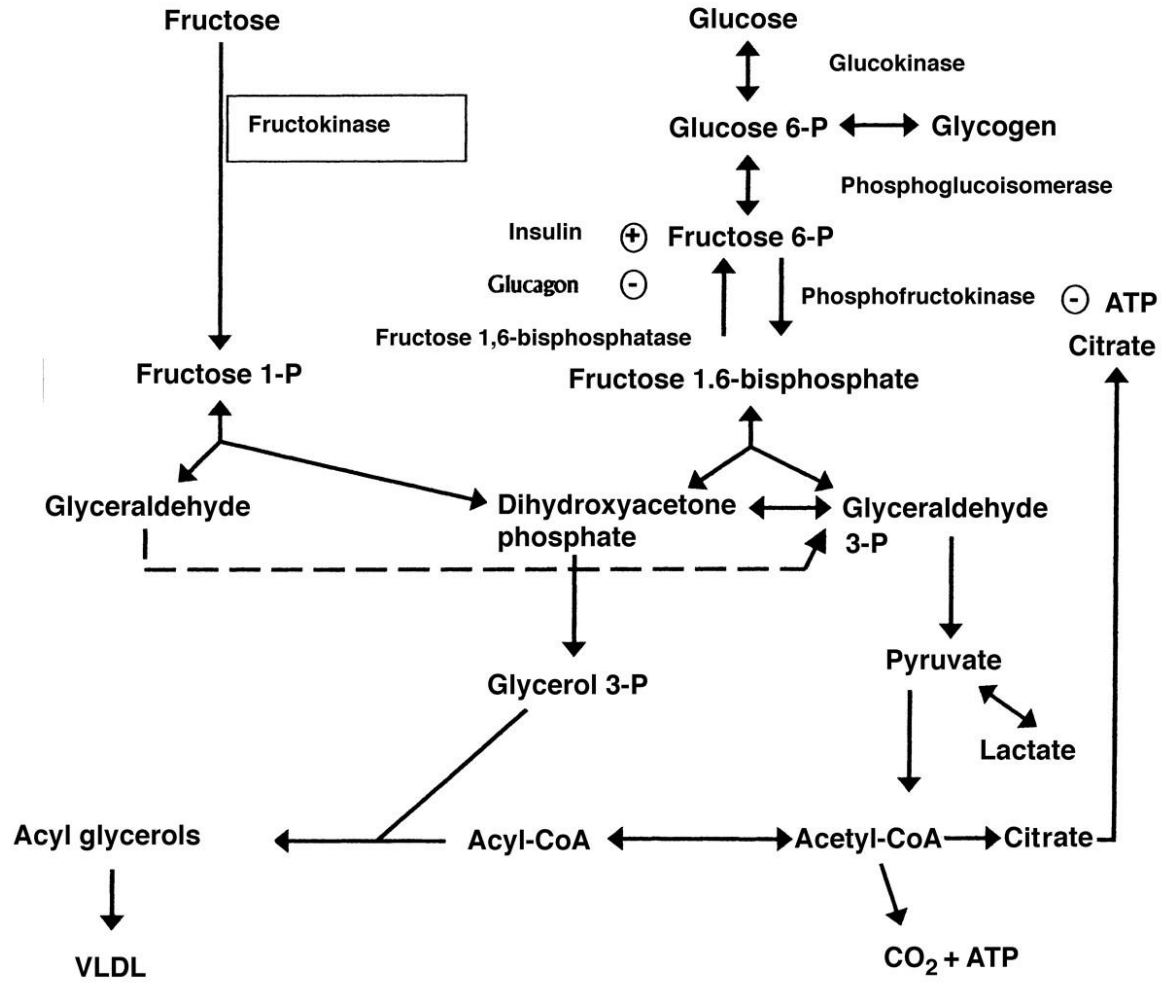


Stimulation of FA synthesis

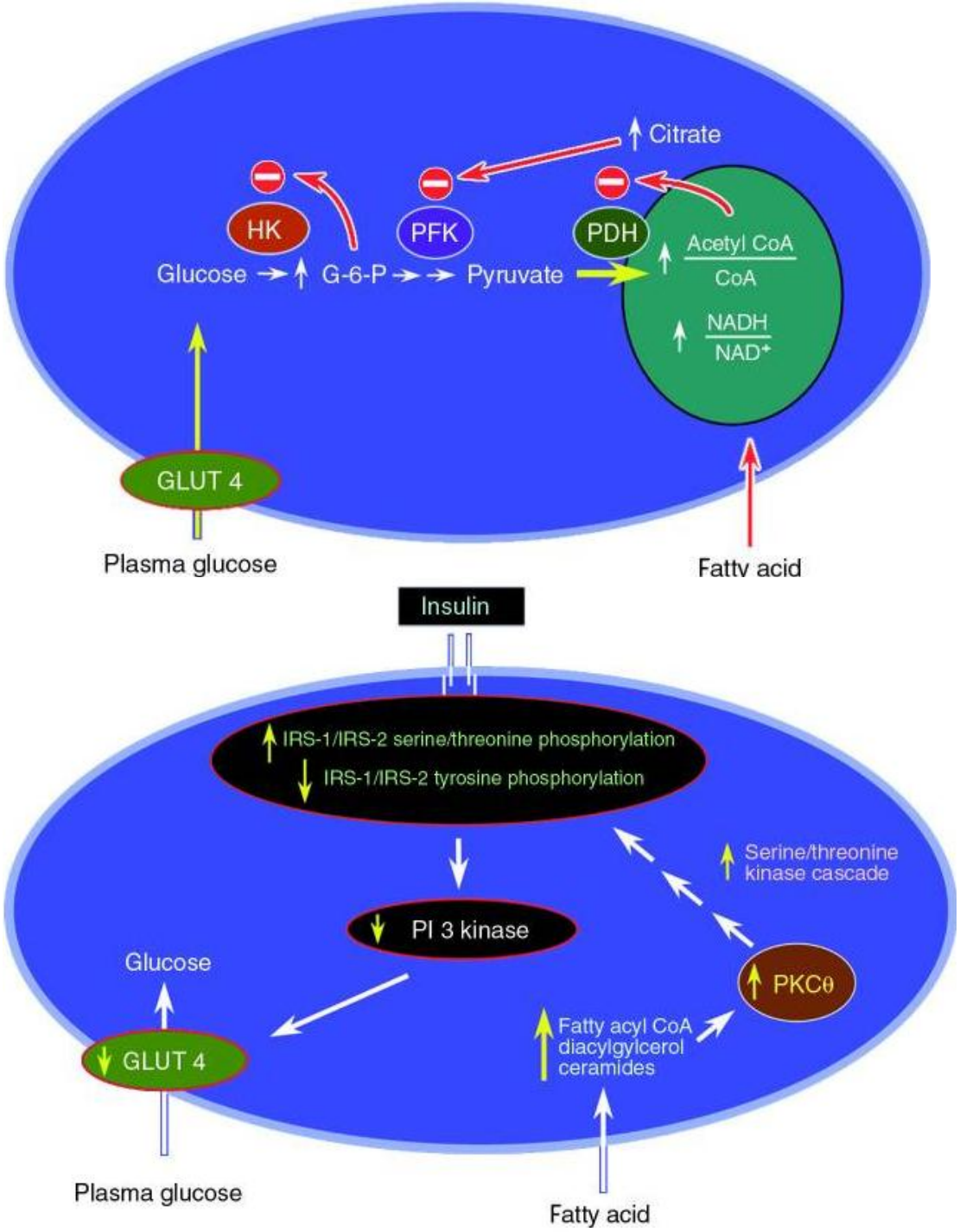
1) Unregulated provision of triose-P and acetyl-CoA
2) Increased expression of key lipogenic genes

Physiol Rev 2010:90:23

Unique metabolic disturbances underlie the induction of insulin resistance



Elliott S S et al. Am J Clin Nutr 2002;76:911-922



Mechanism of fatty acid induced IR in skeletal muscle as proposed by Randle et al.

Proposed alternative mechanism for fatty acid-induced IR in human skeletal muscle

J Clin Invest 2000;106:171

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  - Fructose-induced dyslipidemia
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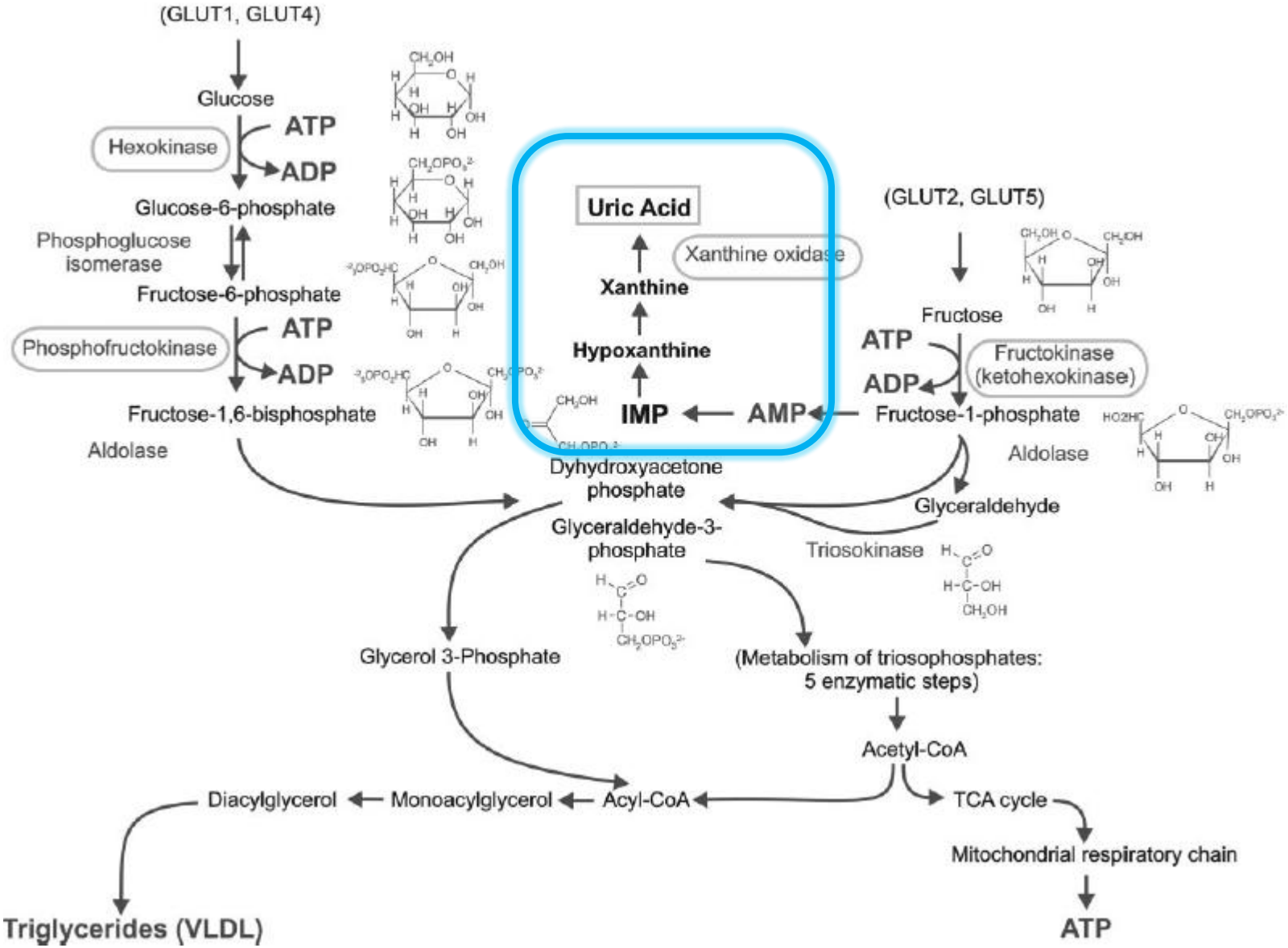
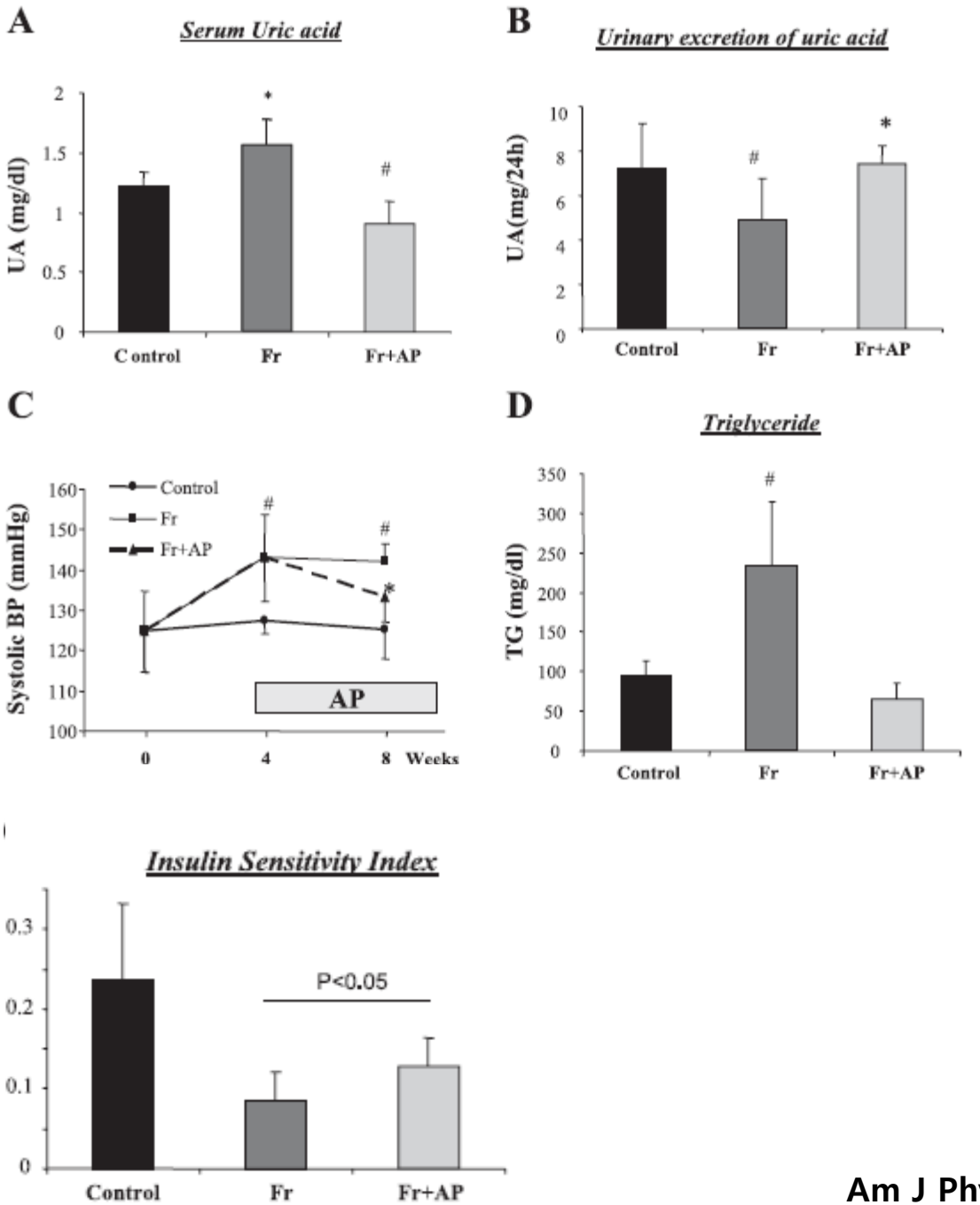
  - Fructose-induced leptin resistance
  - Endotoxin mediated inflammation, lipogenesis

Fructose, hyperuricemia, and insulin resistance



Endocr Rev 2009:30:96



Effects of allopurinol (AP) treatment for hyperuricemia on metabolic parameters in fructose-fed(Fr) rats

Am J Physiol Renal Physiol 2006;290:F625

Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study

Relative risk of incident gout in men according to levels of soft drink consumption

Variable	Frequency of intake (servings)						P for trend
	<1/month	1/month-1/week	2-4/week	5-6/week	1/day	≥2/day	
Sugar sweetened soft drinks:							
No of cases	279	251	82	88	39	16	—
Person years	158 891	151 173	53 086	47 433	20 485	7392	—
Age, BMI, alcohol, and energy adjusted relative risk (95% CI)	1.0*	1.00 (0.84 to 1.19)	1.00 (0.78 to 1.29)	1.30 (1.01 to 1.67)	1.44 (1.02 to 2.04)	1.78 (1.06 to 2.98)	0.002
Multivariate relative risk (95% CI)†	1.0*	1.00 (0.84 to 1.20)	0.99 (0.77 to 1.29)	1.29 (1.00 to 1.68)	1.45 (1.02 to 2.08)	1.85 (1.08 to 3.16)	0.002

RR of incident gout in men according to fructose intake

Variable	Fifths of fructose intake					P for trend
	1st	2nd	3rd	4th	5th	
Free fructose (% of energy):	<3.5	3.5-4.4	4.5-5.3	5.4-6.6	>6.6	
No of cases	152	154	146	160	143	—
Person years	87 136	87 618	87 818	88 050	87 839	—
Age, BMI, alcohol, and energy adjusted relative risk (95% CI)	1.0	1.19 (0.95 to 1.49)	1.21 (0.96 to 1.53)	1.45 (1.15 to 1.83)	1.43 (1.12 to 1.83)	0.001
Multivariate relative risk* (95% CI)	1.0	1.26 (1.00 to 1.59)	1.33 (1.04 to 1.70)	1.68 (1.30 to 2.16)	1.81 (1.38 to 2.38)	<0.001
Multivariate relative risk† (95% CI)	1.0	1.29 (1.02 to 1.64)	1.41 (1.09 to 1.82)	1.84 (1.40 to 2.41)	2.02 (1.49 to 2.75)	<0.001
Total fructose‡ (% of energy):	<6.9	6.9-8.5	8.6-10.0	10.1-11.8	>11.8	
No of cases	186	139	153	137	140	—
Person years	87050	87761	87815	88087	87748	—
Age, BMI, alcohol, and energy adjusted relative risk (95% CI)	1.0	0.90 (0.72 to 1.13)	1.11 (0.88 to 1.39)	1.08 (0.85 to 1.37)	1.24 (0.97 to 1.57)	0.04
Multivariate relative risk* (95% CI)	1.0	0.96 (0.76 to 1.21)	1.20 (0.95 to 1.53)	1.25 (0.96 to 1.61)	1.52 (1.15 to 2.01)	0.001
Multivariate relative risk† (95% CI)	1.0	0.98 (0.77 to 1.25)	1.29 (1.00 to 1.67)	1.41 (1.06 to 1.88)	1.81 (1.31 to 2.50)	<0.001

BMJ 2008;336:309

High serum uric acid as a novel risk factor for Type 2 DM

HR for incident of T2DM according to levels of uric acid

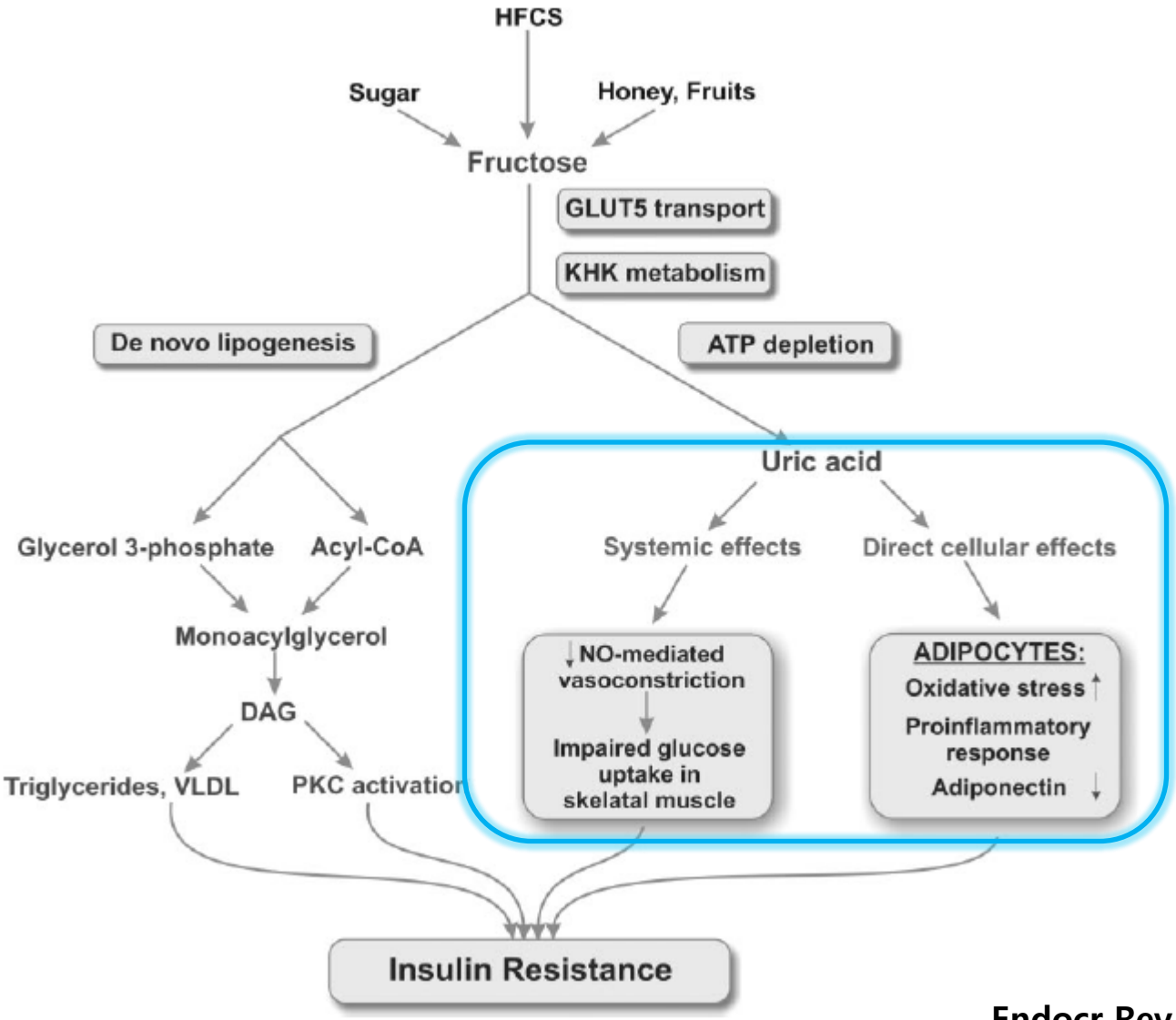
4516 population, 10 years of f/u

		HR (95% CI)		
Serum uric acid quartile	Participants (cases)	Model 1	Model 2	Model 3
1 (≤267 μmol/l)	1,153 (77)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
2 (268–310 μmol/l)	1,141 (94)	1.30 (0.96–1.76)	1.14 (0.83–1.57)	1.08 (0.78–1.49)
3 (311–370 μmol/l)	1,175 (120)	1.63 (1.21–2.19)	1.23 (0.89–1.67)	1.12 (0.81–1.53)
4 (>370 μmol/l)	1,067 (171)	2.83 (2.13–3.76)	1.92 (1.41–2.62)	1.68 (1.22–2.30)
P for trend		<0.001	<0.001	<0.001
1 SD increment	4,536 (462)	1.53 (1.39–1.67)	1.37 (1.23–1.52)	1.31 (1.18–1.46)

Model 1: age, sex, Model 2: model 1 +BMI, WC, Model 3: model 2+BP, HDL-C

Diabetes Care 2008;31:361

Potential mechanisms by which fructose and uric acid may induce insulin resistance



Endocr Rev 2009:30:96

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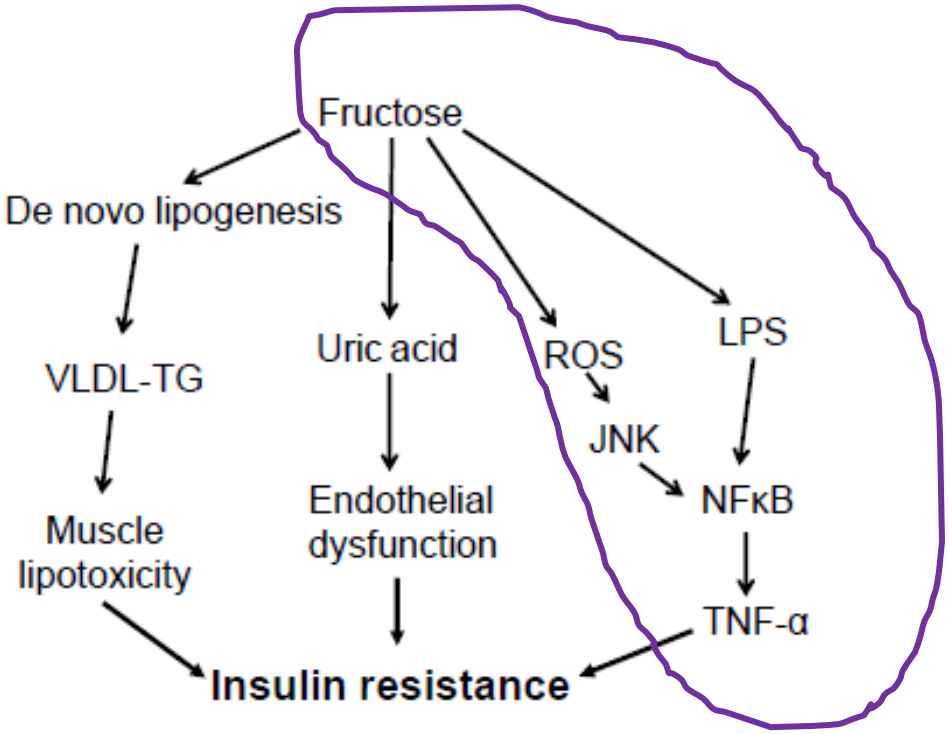
  - Endotoxin mediated inflammation, lipogenesis
  - Fructose-induced leptin resistance

Fructose induced oxidative stress and inflammation



BMC Biology 2012;10:42

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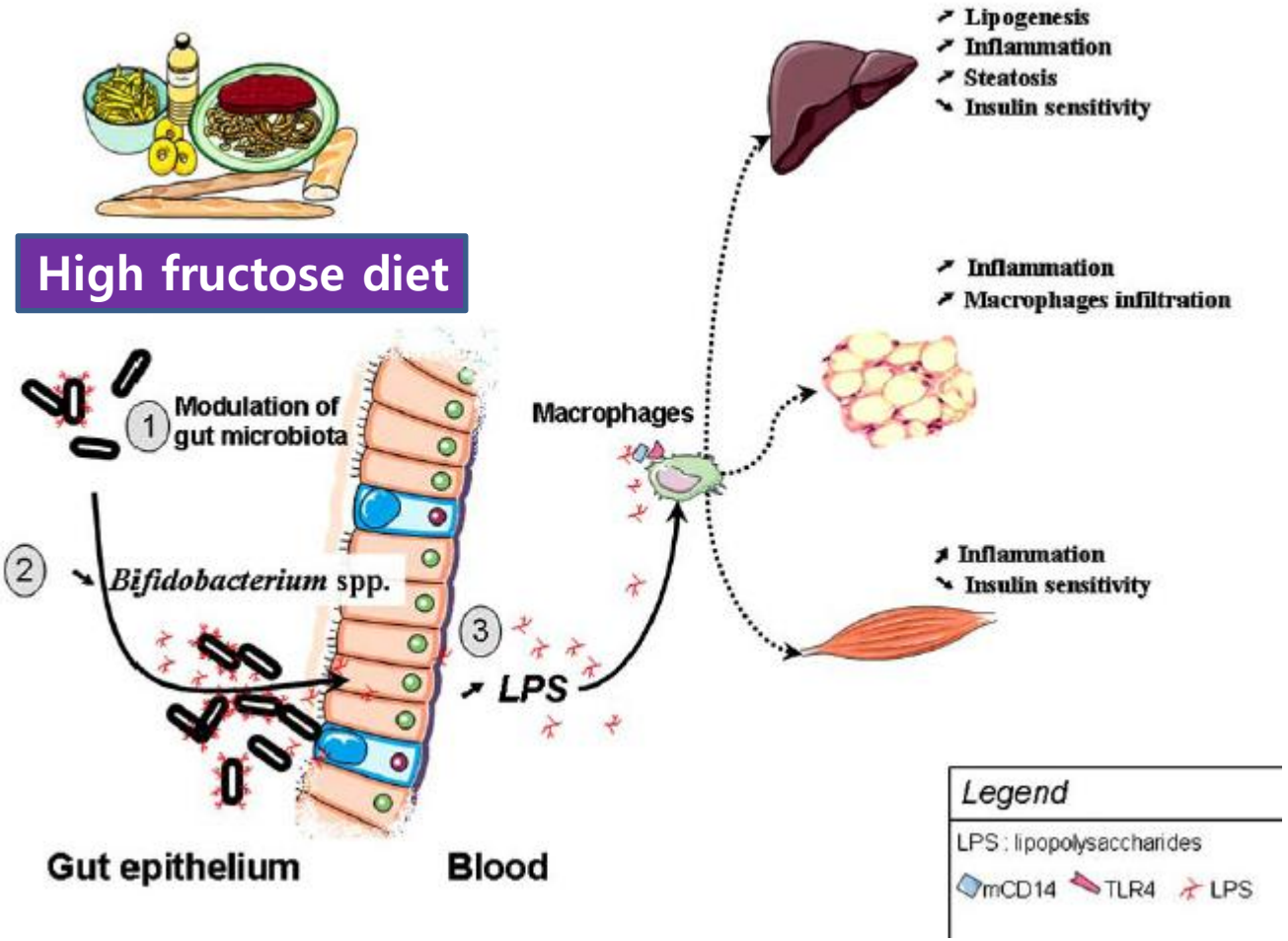
The role of the Gut microbiota in energy metabolism and metabolic disease



High fructose diet feeding changes gut microbiota, promotes endotoxemia and triggers the development of metabolic disorders via a CD14/TLR4 dependent mechanism

Nonalcoholic Fatty Liver Disease in Humans Is Associated with Increased Plasma Endotoxin and Plasminogen Activator Inhibitor 1 Concentrations and with Fructose Intake[1]

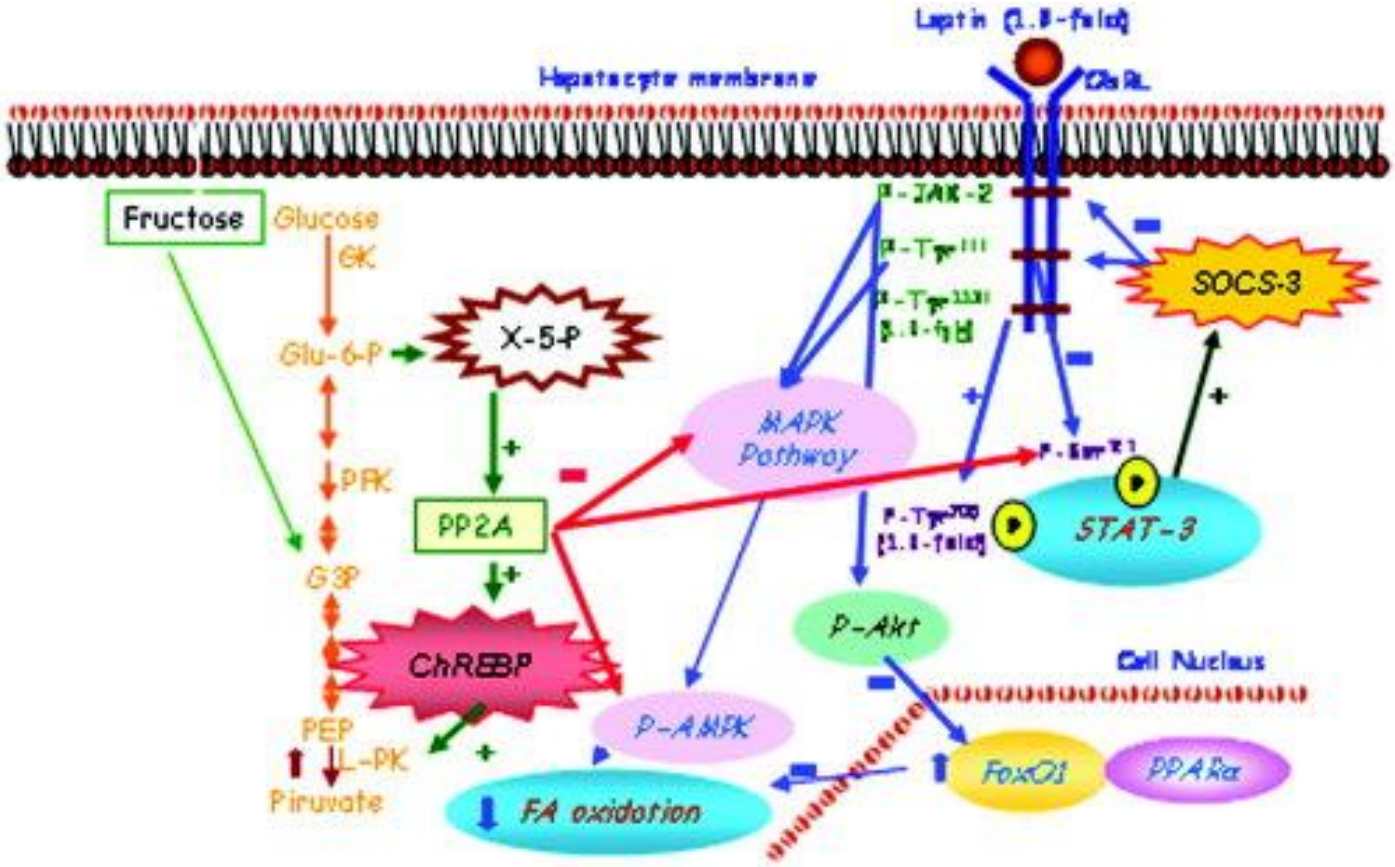
Abstract

Results of animal experiments suggest that consumption of refined carbohydrates (e.g. fructose) can result in small intestinal bacterial overgrowth and increased intestinal permeability, thereby contributing to the development of nonalcoholic fatty liver disease (NAFLD). Furthermore, increased plasminogen activator inhibitor (PAI)-1 has been linked to liver damage of various etiologies (e.g. alcohol, endotoxin, nonalcoholic). The aim of the present pilot study was to compare dietary factors, endotoxin, and PAI-1 concentrations between NAFLD patients and controls. We assessed the dietary intake of 12 patients with NAFLD and 6 control subjects. Plasma endotoxin and PAI-1 concentrations as well as hepatic expression of PAI-1 and toll-like receptor (TLR) 4 mRNA were determined. Despite similar total energy, fat, protein, and carbohydrate intakes, patients with NAFLD consumed significantly more fructose than controls. Endotoxin and PAI-1 plasma concentrations as well as hepatic TLR4 and PAI-1 mRNA expression of NAFLD patients were significantly higher than in controls. The plasma PAI-1 concentration was positively correlated with the plasma endotoxin concentration (Spearman $r = 0.83$; $P < 0.005$) and hepatic TLR4 mRNA expression (Spearman $r = 0.54$; $P < 0.05$). Hepatic mRNA expression of PAI-1 was positively associated with dietary intakes of carbohydrates (Spearman $r = 0.67$; $P < 0.01$), glucose (Spearman $r = 0.58$; $P < 0.01$), fructose (Spearman $r = 0.58$; $P < 0.01$), and sucrose (Spearman $r = 0.70$; $P < 0.01$). In conclusion, our results suggest that dietary fructose intake, increased intestinal translocation of bacterial endotoxin, and PAI-1 may contribute to the development of NAFLD in humans. J. Nutr. 138: 1452–1455, 2008.

Fructose-Induced Insulin Resistance

- Classic obesity-associated mechanisms
  - Fructose ingestion and satiety responses
- Independent of weight gain or differences in energy intake
  - Fructose-induced dyslipidemia
  - Fructose-induced hyperuricemia
  - Fructose-induced oxidative stress and inflammation
  - Endotoxin mediated inflammation, lipogenesis
  - Fructose-induced leptin resistance

Proposed effects of fructose ingestion on liver leptin signal transduction pathway



Suppressor of cytokine signaling-3 (SOCS-3) and a deficit of serine/threonine (Ser/Thr) phosp hoproteins involved in leptin transduction mediate the effect of fructose on rat liver lipid met abolism

Hepatology 2008;48:1506

Introduction

Unique characteristics of Fructose Metabolism

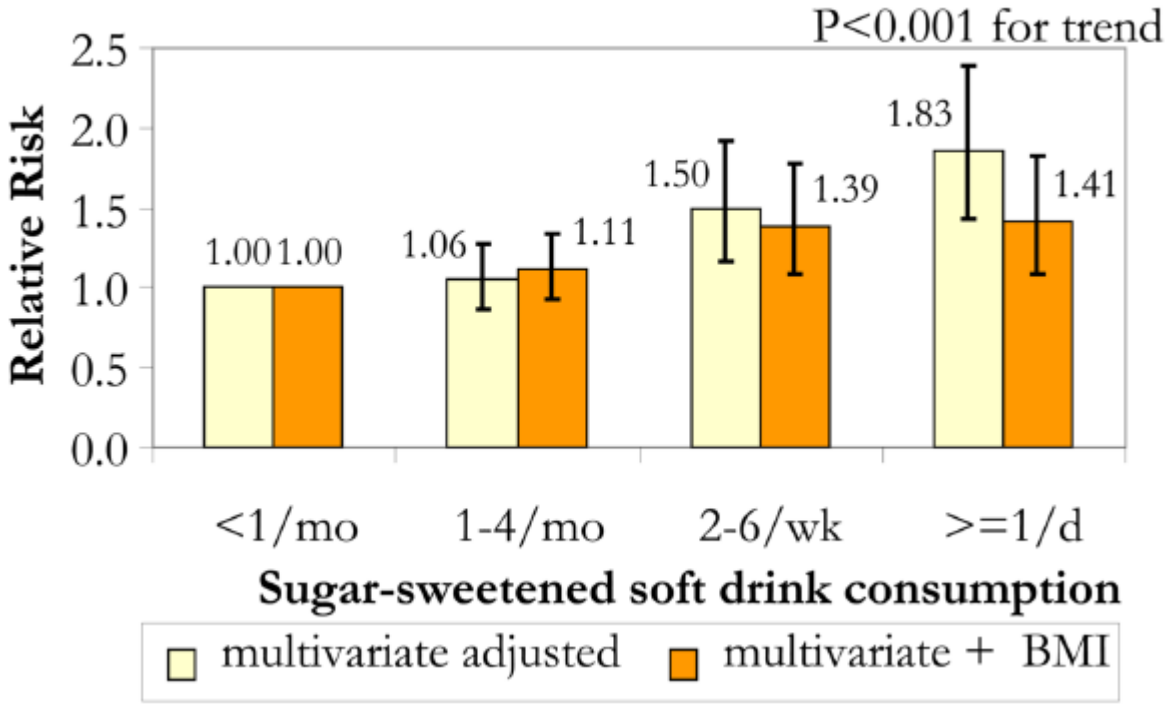
Mechanism for Fructose-Induced Insulin Resistance

Epidemiological Studies
: Fructose intake and Type 2 diabetes

Summary

Sugar-sweetened beverages, incidence of T2DM in young and middle-aged women

From 1991 to 1999 among women in Nurses' Health Study II.
N=91249 women



Physiol Behav 2010:10:47JAMA 2004;292:927-934

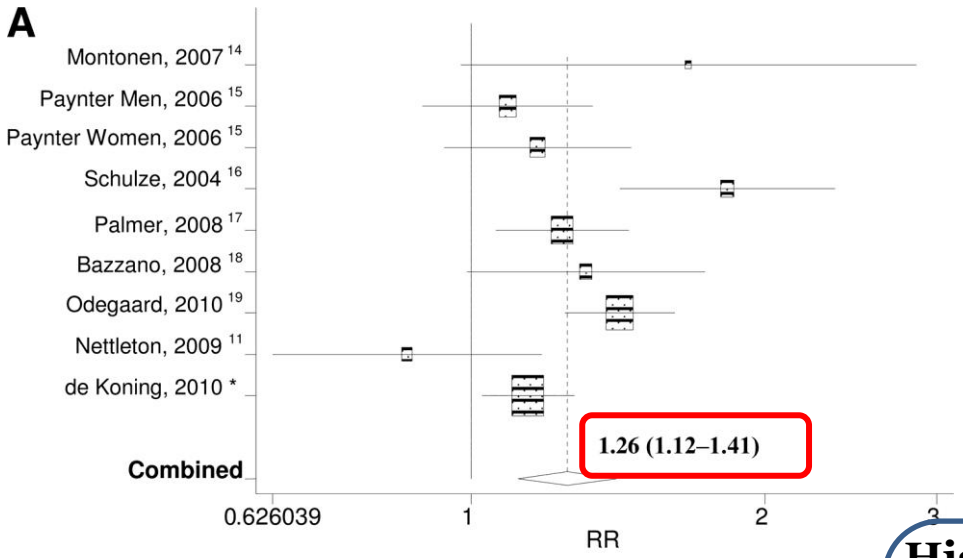
Relative risk of Type 2 diabetes according to frequencies of Sugar-Sweentened soft drink consumption by obesity status, physical activity level, family history of diabetes, and intake levels of cereal fiber, trans-fat, and P:S ratio in 91249 women

	No. of Cases	Sugar-Sweetened Soft Drink Intake, RR (95% CI)				*P* Value for Trend
		<1/mo	1-4/mo	2-6/wk	≥1/d	
Nonobese (BMI <30)†	143	1.00	1.14 (0.74-1.76)	1.60 (0.91-2.79)	1.78 (0.97-3.26)	.06
Obese (BMI ≥30)	579	1.00	1.08 (0.87-1.35)	1.31 (0.98-1.74)	1.35 (1.01-1.80)	.04
P value for interaction						.47
High physical activity‡	308	1.00	0.96 (0.71-1.30)	1.46 (0.99-2.15)	1.54 (1.01-2.33)	.02
Low physical activity‡	433	1.00	1.08 (0.84-1.38)	1.39 (1.01-1.91)	1.68 (1.21-2.32)	.001
P value for interaction						.83
Without family history	459	1.00	1.14 (0.89-1.45)	1.49 (1.09-2.04)	1.86 (1.34-2.56)	<.001
With family history	282	1.00	0.86 (0.62-1.20)	1.32 (0.89-1.96)	1.30 (0.85-1.99)	.12
P value for interaction						.52
High cereal fiber intake§	319	1.00	0.94 (0.71-1.26)	1.33 (0.89-1.98)	1.44 (0.86-2.42)	.08
Low cereal fiber intake	422	1.00	1.15 (0.88-1.50)	1.52 (1.10-2.08)	1.79 (1.31-2.43)	<.001
P value for interaction						.58
High P:S ratio§	356	1.00	1.02 (0.77-1.35)	1.65 (1.16-2.36)	1.64 (1.11-2.43)	.005
Low P:S ratio	385	1.00	1.04 (0.80-1.37)	1.22 (0.87-1.72)	1.53 (1.09-2.15)	.01
P value for interaction						.44
Low *trans*-fat intake§	280	1.00	1.07 (0.78-1.48)	1.69 (1.14-2.50)	1.59 (1.03-2.44)	.02
High *trans*-fat intake	461	1.00	1.00 (0.79-1.28)	1.26 (0.92-1.72)	1.66 (1.21-2.27)	.001
P value for interaction						.87

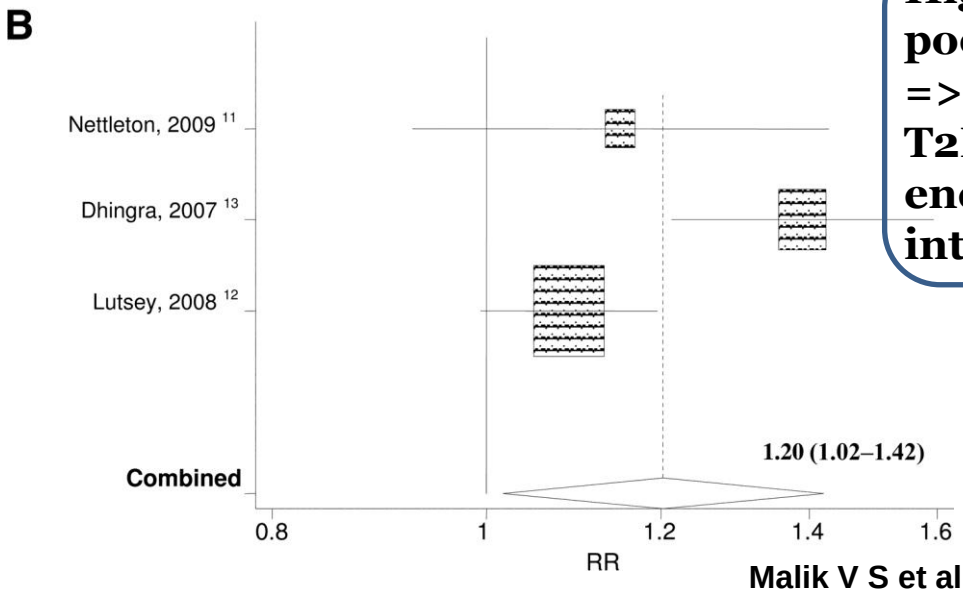
JAMA 2004;292:927

SSBs and Risk of T2DM and MS : A meta-analysis

T2DM



MS



High-calorie nutrient poor foods; SSBs =>individuals at risk for T2DM should be encouraged to limit their intake of SSBs

American Diabetes Association.

Malik V S et al. Diabetes Care 2010;33:2477-2483

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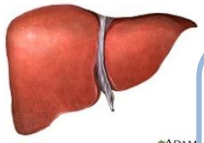
Summary

Effects of fructose on various organ

ctivates tatste centers
ddicting behaviors
ɒecrease malonyl CoA
Decrease satiety
Leptin resistance
Increase lactate



Fatty liver, IR
Elevated triglycerides
ATP depletion
Inflammation
Uric acid generation

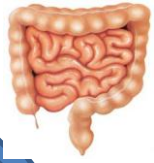
Sugar

HFCS

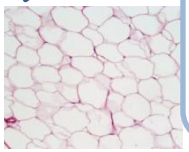
Honey
, fruits

fructose

Inflammation
Endothelial dysfunction



Impair gut integrity
Endotoxin-inflammation
Intestinal IR

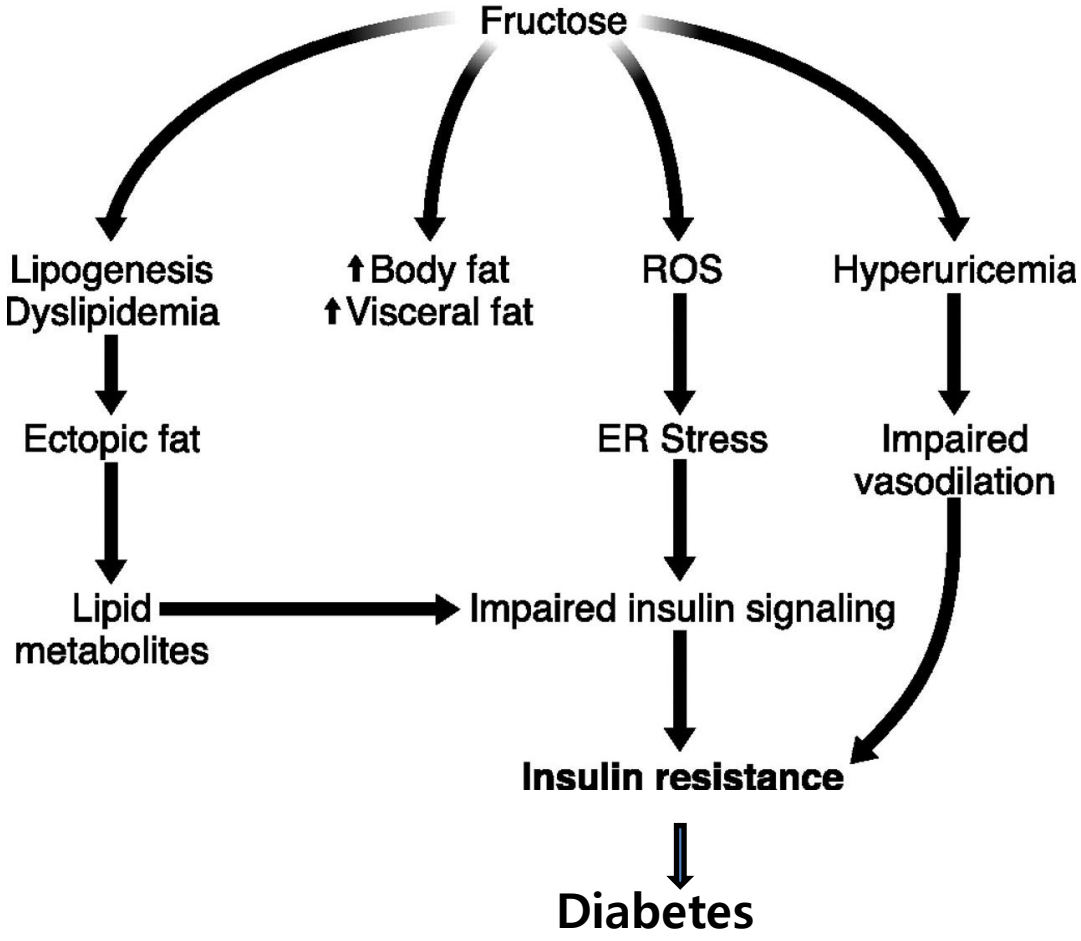


Oxidative stress
Inflammation
Reduced adiponectin

Metabolic syndrome
Insulin resistance
Elevated BP
Abdominal obesity
Dyslipidemia → **T2DM**
Fatty liver
Inflammation
Oxidative stress
Endothelial dysfunction
hyperuricemia

Endocr Rev 2009:30:96

Potential mechanisms on T2DM of Fructose



Physiol Rev 2010:90:23

Summary

- Fructose induce the deleterious effect on glucose metabolism and insulin sensitivity
- Insulin resistance is closely linked to lipid metabolism disorders ;

  higher ectopic lipid deposition, toxic lipid-derived metabolites reduce insulin signaling
- **Old hypothesis**

  Excessive intake of sugar, and in particular fructose, may be an important cause of T2DM.

  =>No old hypothesis : may be right!
- **Although more research is needed, sufficient evidence exists for public health strategies to discourage consumption of fructose as part of a healthy lifestyle**