PATHOGENESIS OF DIABETES MELLITUS

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Disclosures

- No conflicts of interest

Learning Objectives

- Review the pathogenesis of diabetes mellitus
- Describe and differentiate type 1 and type 2 diabetes
- State diagnostic criteria

Classification of Diabetes mellitus	Features
Type 1 diabetes **A. Immune mediated** **B. Idiopathic**	**β-cell destruction leading to absolute insulin deficiency**
Type 2 diabetes	**Insulin resistance +/- insulin deficiency**
Gestational diabetes mellitus (GDM)	
Other specific types	**A. Genetic defects of β-cell function** **B. Genetic defects in insulin action** **C. Diseases of exocrine pancreas** **D. Endocrinopathies** **E. Drug or chemical induced** **F. Infections** **G. Uncommon forms of immune-mediated diabetes** **H. Other genetic syndromes associated with diabetes**

Differential Diagnosis of Type 1 and Type 2 Diabetes

	Type 1 Diabetes	Type 2 Diabetes
Usual clinical course	Insulin-dependent	Initially non-insulin-dependent
Usual age of onset	<20 years (but ~50% over 20 years)	>40 years but increasingly earlier
Body weight	Often lean but ~50% overweight or obese	Usually obese
Onset	Often acute	Subtle, slow
Ketosis prone	Yes	No
Family history	≤15% with 1st-degree relative	Common
Frequency of HLA-DR3, DR4, DQB1*0201, *0302	Increased	Not increased
Islet autoantibodies (GADA, ICA, IA-2A, IAA, ZNT8A)	Present	Absent

GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IAA, autoantibodies to insulin; IA-2A, tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8.

*Needs to be refined for nonwhite population groups.

Rewers M. *Diabetes Metab J*. 2012;36:90-97.

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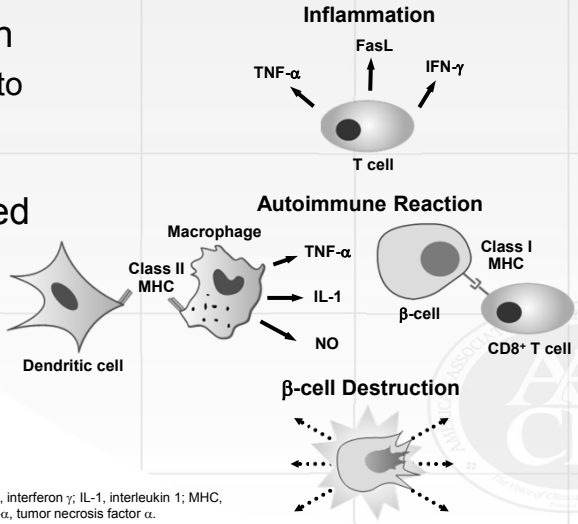
Type 1 Diabetes Pathophysiology

- β-cell destruction
  - Usually leading to absolute insulin deficiency
- Immune mediated
- Idiopathic



CD8, cluster of differentiation 8; FasL, Fas ligand; IFN-γ, interferon γ; IL-1, interleukin 1; MHC, major histocompatibility complex; NO, nitric oxide; TNF-α, tumor necrosis factor α.

Maahs DM, et al. *Endocrinol Metab Clin North Am*. 2010;39:481-497.

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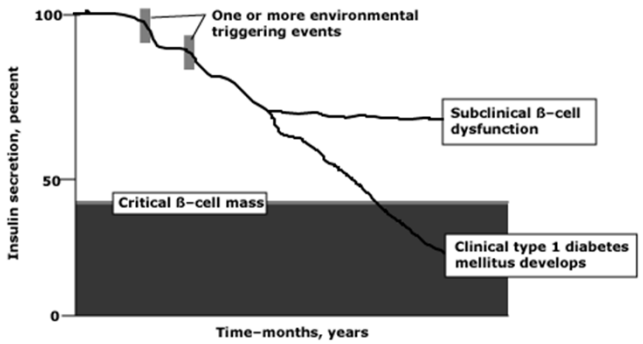
Time course of type 1 diabetes mellitus



Time course of the development of type 1 diabetes. Genetic markers are present from birth, immune markers first appear at the time of the environmental triggering events, and sensitive metabolic markers of deficient insulin secretion begin to appear soon after the onset of beta cell dysfunction. However, clinically evident type 1 diabetes does not occur until there has been a much greater loss of functioning beta cell mass. UpToDate®

Type 1 diabetes staging

Table 2.1—Staging of type 1 diabetes (4,5)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

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Immune-Mediated Diabetes (T1a Diabetes)

β-Cell Destruction

- Variable rate
  - Rapid in infants and children (primarily)
  - Slow in adults (primarily)

Immune Markers

- Islet cell autoantibodies
- Autoantibodies to insulin
- Autoantibodies to GAD (GAD65)
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2b

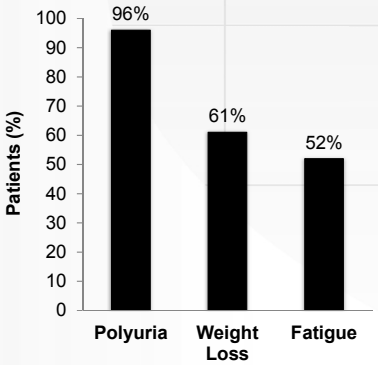
When fasting hyperglycemia is first detected, 85% – 90% of individuals have ≥1 autoantibody

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

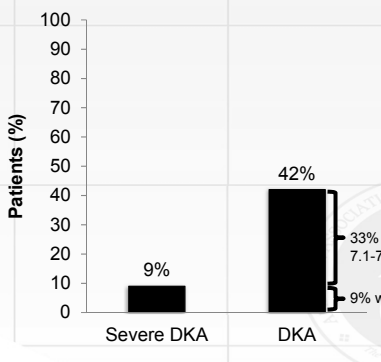
Symptoms and Severity of T1D at Presentation

EURODIAB (N=1260)

Presenting Symptoms



DKA at Presentation



DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

Levy-Marchal C, et al. *Diabetologia.* 2001;44 (Suppl 3):B75-B80.

Incidence and Prevalence of Type 1 Diabetes

- T1D is the major type of diabetes in youth
  - Accounts for ≥85% of all diabetes cases in patients <20 years of age
- Incidence is increasing by 2% to 5% worldwide
- U.S. prevalence is approximately 1 in 300

T1D, type 1 diabetes.

Maahs DM, et al. *Endocrinol Metab Clin North Am*. 2010;39:481-497. Menke A, et al. *Epidemiology*. 2013;24:773-774.

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Diabetes in Children and Young Adults

- In the past, diabetes in youth was almost always T1D, but more T2D is no longer "adult onset" diabetes only
- Nearly all children with diabetes diagnosed <10 years have T1D
  - Majority of non-Hispanic youth with diabetes diagnosed have T1D
- However, among US children 10-19 years at diagnosis
  - Half of African-American and Hispanic patients have T2D
  - More than half of Asian/Pacific Islanders and American Indians have T2D

T1D, type 1 diabetes; T2D, type 2 diabetes.

Dabelea D, et al. *JAMA*. 2007;297:2716-2724.

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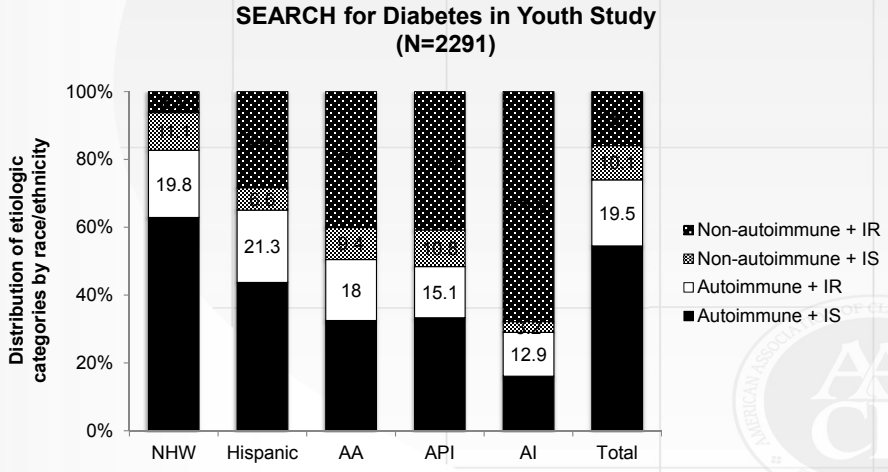
Type of Diabetes in Youth by Race/Ethnicity and Etiology



AA, African American; AI, American Indian; API, Asian/Pacific Islander; IR, insulin resistant; IS, insulin sensitive; NHW, non-Hispanic white.

Dabelea D, et al. *Diabetes Care*. 2011;34:1628-1633.

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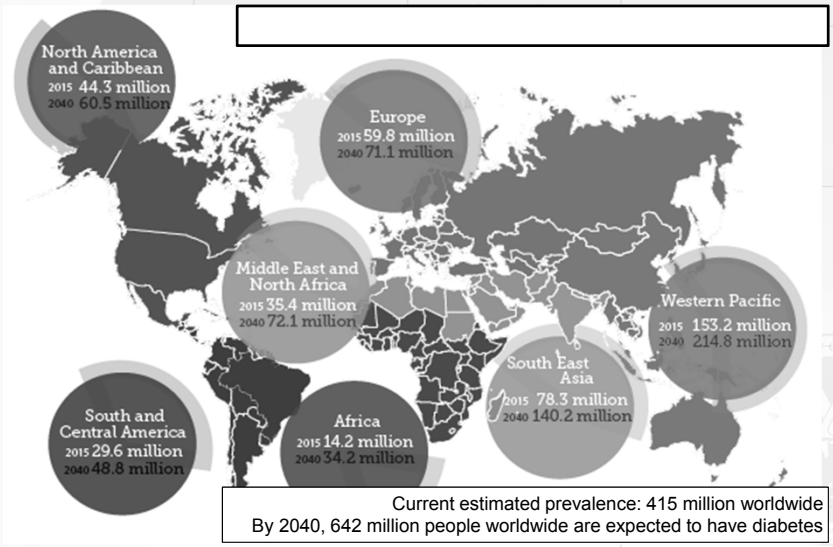
Worldwide Prevalence of Diabetes



Current estimated prevalence: 415 million worldwide
By 2040, 642 million people worldwide are expected to have diabetes

IDF. Diabetes Atlas Update 2015. Available at: http://www.idf.org/sites/default/files/Atlas7e-poster.pdf.

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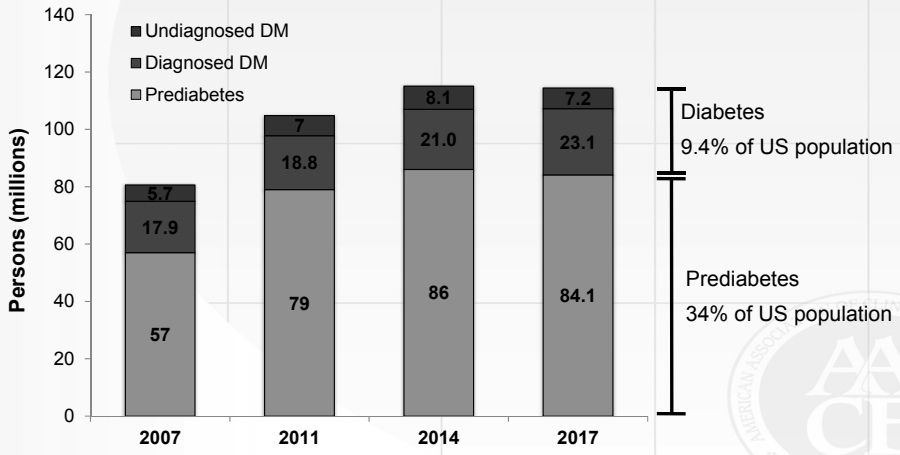
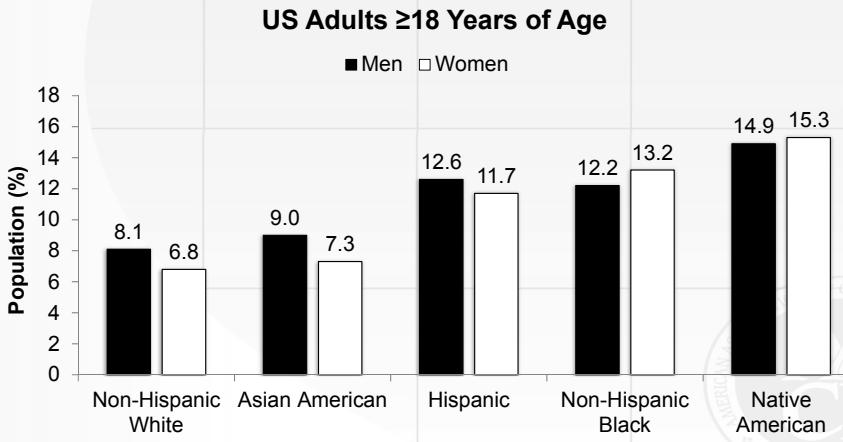
Prevalence of Diabetes and Prediabetes in the United States



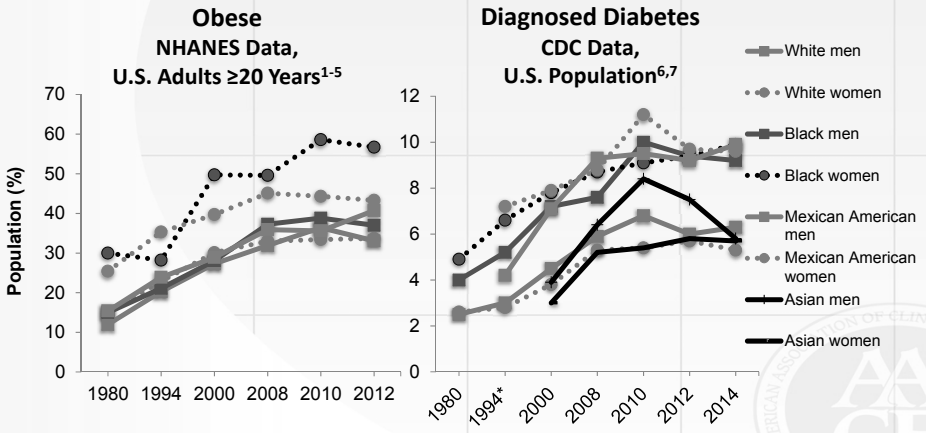
CDC. National diabetes fact sheet, 2008. CDC. National diabetes fact sheet, 2011. CDC. National diabetes statistics report, 2014. CDC. National diabetes statistics report, 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.

Prevalence of Diagnosed Diabetes in Different US Ethnic and Racial Groups



CDC. National diabetes statistics report, 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

T2D Prevalence Parallels Prevalence of Obesity



BMI, body mass index (in kg/m²); CDC, Centers for Disease Control and Prevention; NHANES, National Health and Nutrition Examination Survey (x-axis lists last year of each survey).
*NHANES 1994 data.
1. Flegal KM, et al. *Int J Obes Relat Metab Disord*. 1998;22:39-47. 2. Flegal KM, et al. *JAMA*. 2002 ;288:1723-1727. 3. Flegal KM, et al. *JAMA*. 2010;303:235-241. 4. Flegal KM, et al. *JAMA*. 2012;307:491-497. 5. Ogden CL, et al. *JAMA*. 2014;311:806-814. 6. Harris MI, et al. *Diabetes Care*. 1998;21:518-524. 7. CDC. Diabetes data & trends. Available at: https://www.cdc.gov/diabetes/statistics/prev/national/figraceethsex.htm and http://www.cdc.gov/diabetes/statistics/prev/national/fighispanicthsex.htm.

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Criteria for diagnosis of diabetes

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

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Natural History of Type 2 Diabetes

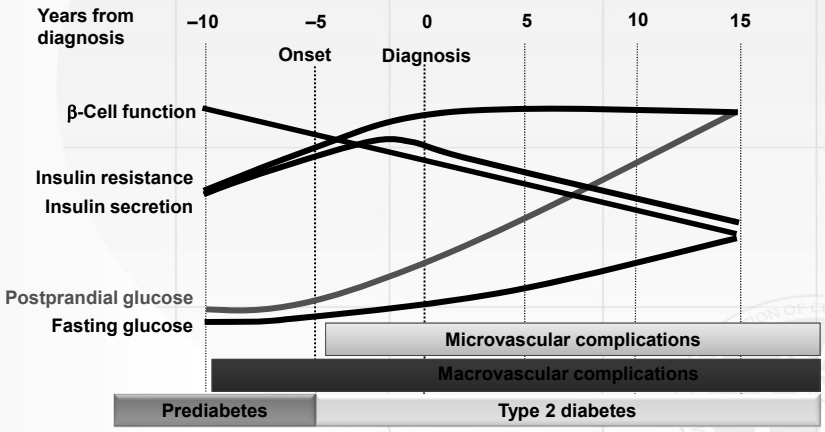

Figure courtesy of CADRE.

Adapted from Holman RR. *Diabetes Res Clin Pract*. 1998;40(suppl):S21-S25; Ramlo-Halsted BA, Edelman SV. *Prim Care*. 1999;26:771-789; Nathan DM. *N Engl J Med*. 2002;347:1342-1349; UKPDS Group. *Diabetes*. 1995;44:1249-1258

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Pathophysiology of Type 2 Diabetes

Organ System	Defect
Major Role	
Pancreatic beta cells	Decreased insulin secretion
Muscle	Inefficient glucose uptake
Liver	Increased endogenous glucose secretion
Contributing Role	
Adipose tissue	Increased FFA production
Digestive tract	Decreased incretin effect
Pancreatic alpha cells	Increased glucagon secretion
Kidney	Increased glucose reabsorption
Nervous system	Neurotransmitter dysfunction

DeFronzo RA. *Diabetes*. 2009;58:773-795

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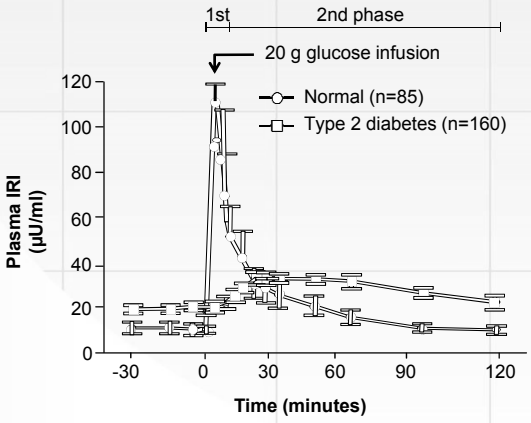
Acute Insulin Response Is Reduced in Type 2 Diabetes



IRI, immunoreactive insulin.

Pfeifer MA, et al. *Am J Med*. 1981;70:579-588.

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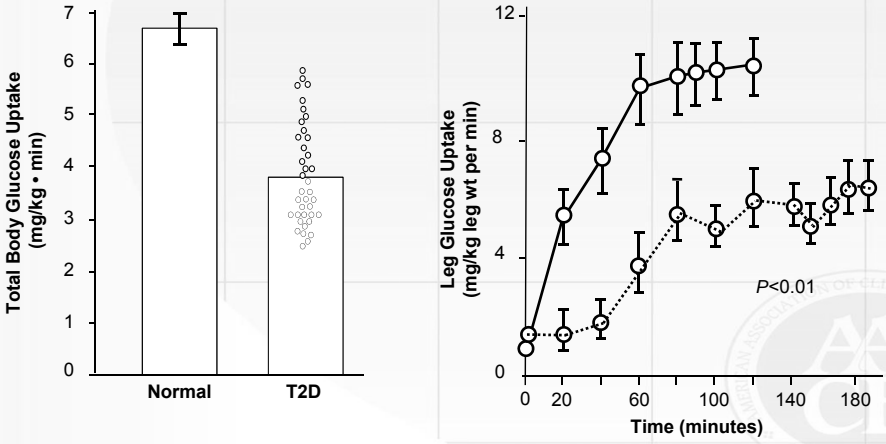
Defective Insulin Action in Type 2 Diabetes



T2D, type 2 diabetes.

DeFronzo RA. *Diabetes*. 2009;58:773-795; DeFronzo RA, et al. *J Clin Invest*. 1985;76:149-155.

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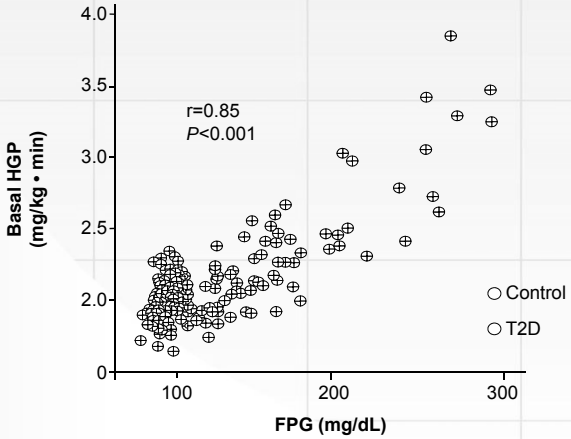
Elevated Fasting Glucose in Type 2 Diabetes Results From Increased HGP



FPG, fasting plasma glucose; HGP, hepatic glucose production; T2D, type 2 diabetes.

DeFronzo RA, et al. *Metabolism*. 1989;38:387-395.

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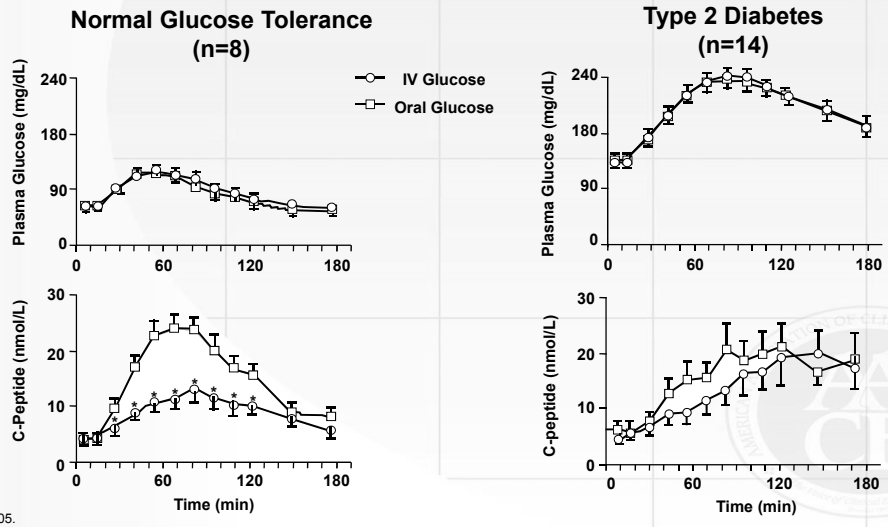
The Incretin Effect Is Diminished in Type 2 Diabetes



*$P \leq .05$.

Nauck M, et al. *Diabetologia*. 1986;29:46-52.

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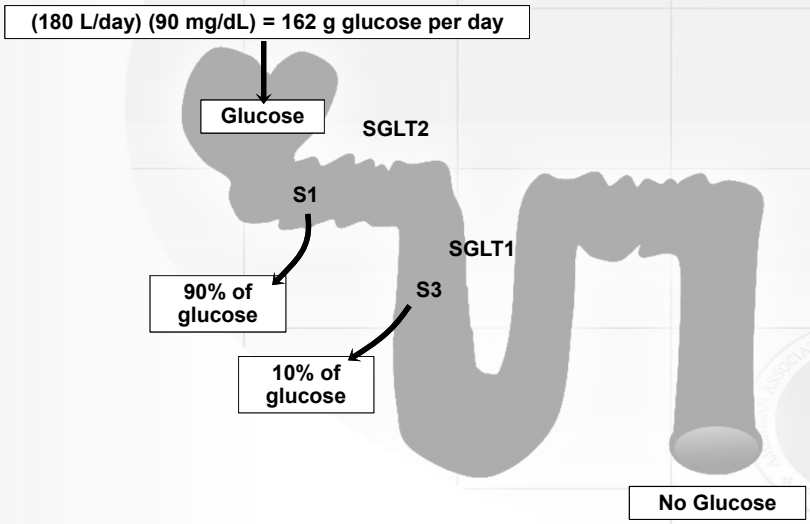
Normal Renal Handling of Glucose



Abdul-Ghani MA, et al. *Endocr Pract*. 2008;14:782-790.

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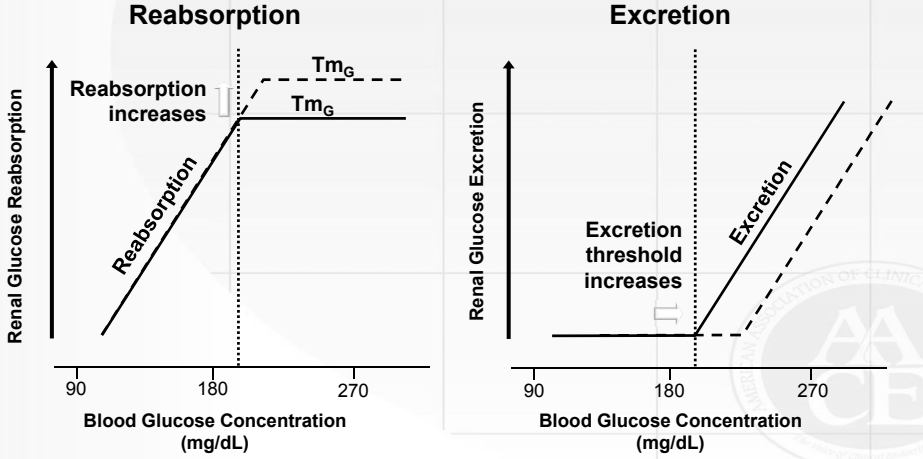
Increased SGLT2 Protein Levels Change Glucose Reabsorption and Excretion Thresholds



Tm_G, glucose transport maximum.

Abdul-Ghani MA, DeFronzo RA. Endocr Pract. 2008;14:782-790.

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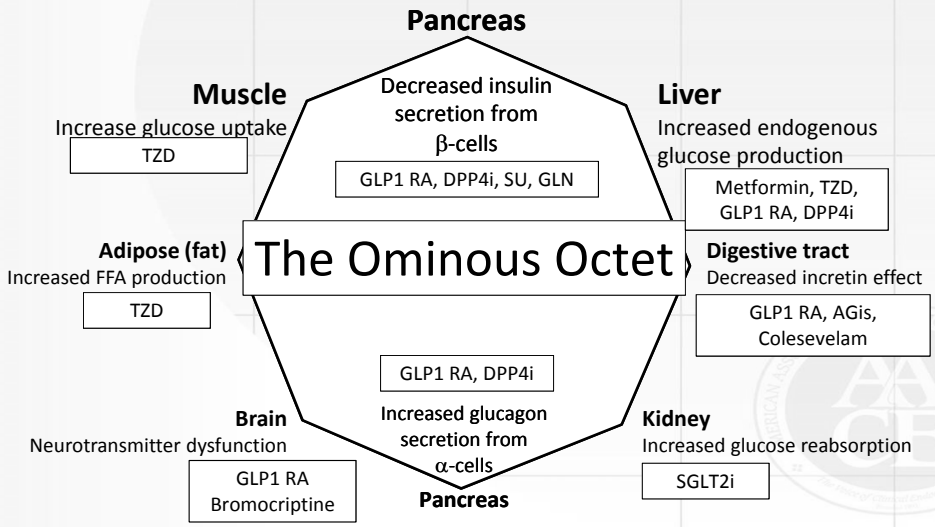
Mechanism of Action of Antihyperglycemic Agents



DeFronzo RA. *Diabetes*. 2009;58:773-795

- What about insulin secretion and action if born to DM/GDM mothers?

Maternal Diabetes and Impaired Offspring Insulin Action

Table 2. Indicies of Insulin Sensitivity and Insulin Secretion

	O-GDM	O-Type1	O-NoGDM	O-BP	*P* value[a]
n	167	153	139	128	(total 587)
Insulin sensitivity					
BIGTT-$S_{I0-30-120}$	7.97 (3.57)[b]	8.27 (3.36)[b]	8.18 (3.08)[b]	9.79 (3.39)	**<.0001**
Matsuda index[c]	20.80 (18.98–22.80)[b]	23.28 (21.37–25.36)	21.73 (19.96–23.66)[b]	27.00 (24.77–29.45)	**<.0001**
Insulin resistance					
HOMA-IR[c]	10.53 (9.58–11.57)[b]	9.28 (8.49–10.15)	10.57 (9.65–11.57)[b]	8.47 (7.71–9.31)	**.002**
Insulin secretion					
BIGTT-$AIR_{0-30-120}$[c]	2060 (1871–2265)	2270 (2096–2459)	2239 (2073–2417)	2177 (1991–2381)	.37
Insulinogenic index[c]	86.90 (76.58–96.36)	84.70 (76.44–93.86)	97.19 (85.27–110.76)	90.34 (80.13–101.86)	.35
CIR[c]	765 (688–850)	831 (749–922)	928 (825–1044)	919 (818–1033)	.04
Disposition index					
DI_1 (BIGTT-$S_{I0-30-120}$ × BIGTT-$AIR_{0-30-120}$)	16 101 (7694)[b]	18 148 (7482)	17 867 (6701)[b]	21 454 (13697)	**<.0001**
DI_2 (CIR × Matsuda index)[c]	15 743 (13 877–17 861)[b,d]	20 059 (17 334–21 587)[b]	19 346 (17 750–22 667)[b]	24 820 (22 197–27 752)	**<.0001**
DI_3 (CIR/HOMA-IR)[c]	72.53 (63.50–82.81)[b]	89.15 (78.92–100.69)	87.74 (77.37–99.52)	108.47 (96.14–122.35)	**.028**

Includes offspring with normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance and screen detected, and treatment-naive type 2 diabetes. Data are mean (SD) unless otherwise indicated.

[a] Analyses between proportions in the 4 groups were performed by 1-way-ANOVA.

[b] Compared with O-BP, $P < .05$ (post hoc test: independent samples *t* test and Bonferroni).

[c] Data are given as geometric mean and CIs because of log transformation to obtain normal distribution.

[d] Compared with O-NoGDM, $P < .05$ (post hoc test: independent samples *t* test and Bonferroni).

Kelstrup. J Clin Endocrinol Metab, September 2013, 98(9):3793–3801

◦ What about a past history of GDM?

History of GDM increases risk of DM

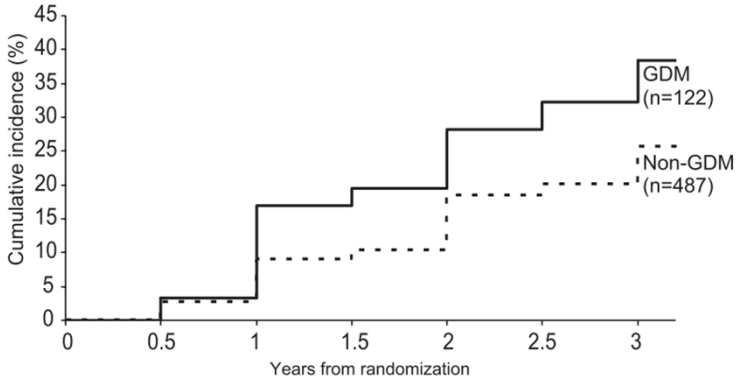
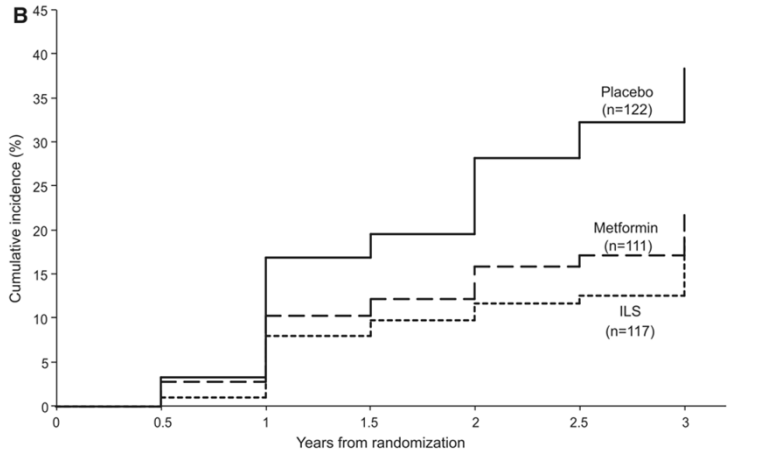


FIG. 2. Cumulative incidence of diabetes mellitus among the placebo group by history of GDM.

Ratner *et al.* Diabetes in Women with a History of GDM J Clin Endocrinol Metab, December 2008, 93(12):4774–4779

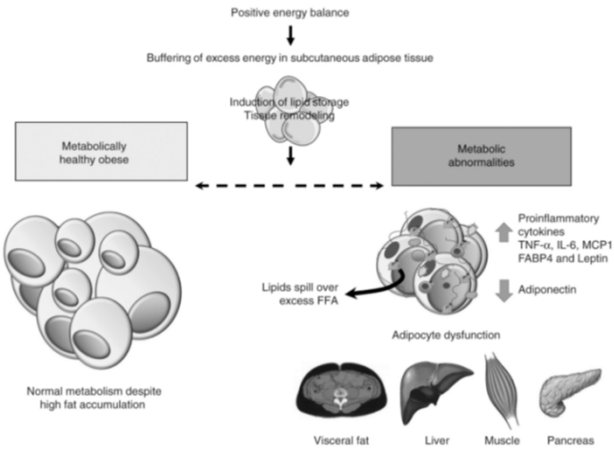
Diabetes prevention in women with history of GDM: Intensive life style change and Metformin give hope!!



Ratner *et al.* Diabetes in Women with a History of GDM J Clin Endocrinol Metab, December 2008, 93(12):4774–4779

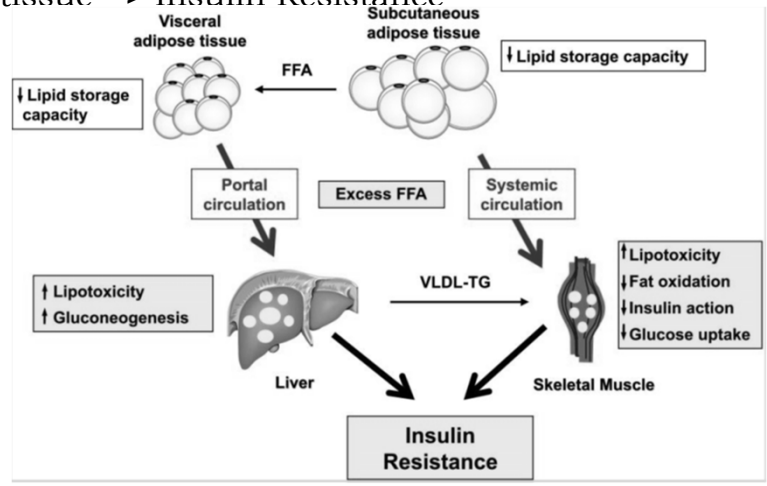
- Adiposopathy? ADIPO-SO-what?

Adiposopathy in metabolic syndrome: adipocyte hypertrophy as opposed to adipocyte hyperplasia



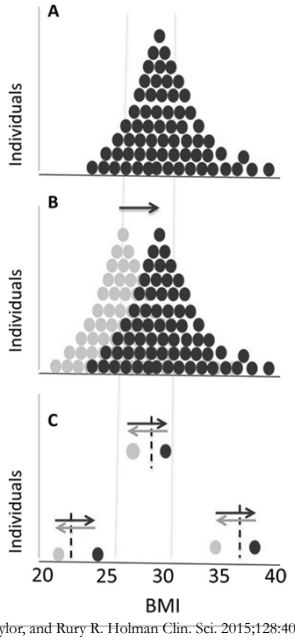
Gaggini M, Horm Mol Biol Clin Investig. 2017 Sep 25;31(1).

Adiposopathy: decreased plasticity and abnormal distribution of adipose tissue --> Insulin Resistance



Galgani JE, Am J Physiol Endocrinol Metab. 2008 Nov; 295(5): E1009–E1017.

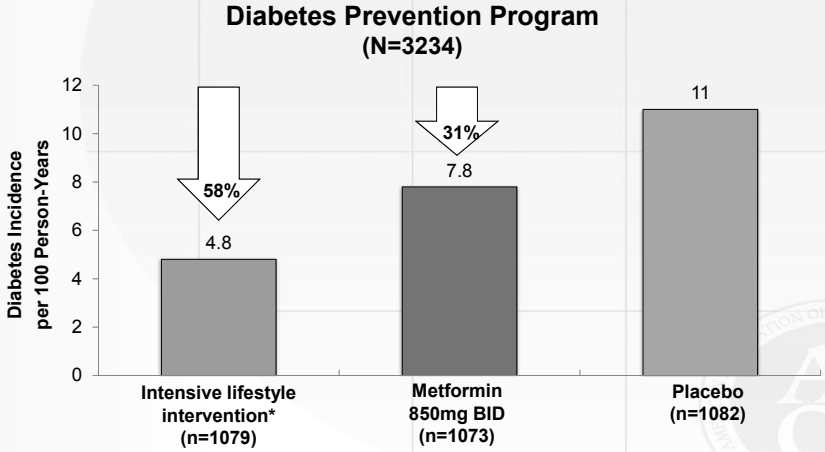
What is the personal fat threshold?



Roy Taylor, and Rury R. Holman Clin. Sci. 2015;128:405-410

PORTLAND PRESS

Intensive Lifestyle Intervention Effectively Prevents Progression From IGT to T2D



*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

IGT, impaired glucose tolerance; T2D, type 2 diabetes.

DPP Research Group. *N Engl J Med*. 2002;346:393-403.

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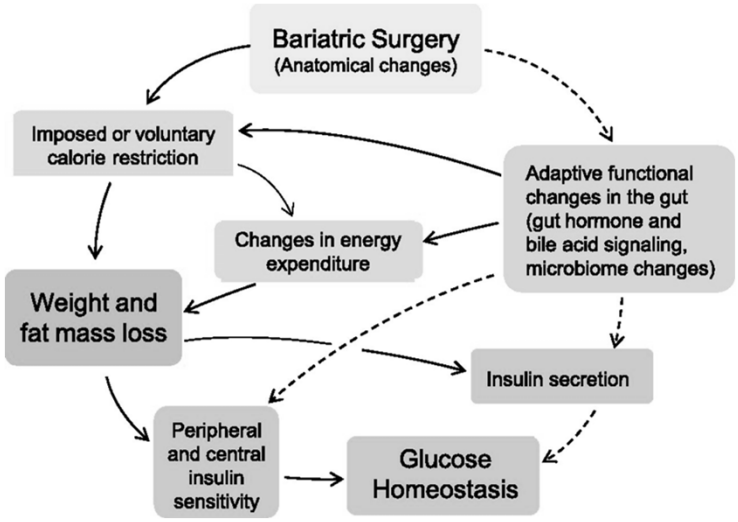
What can we learn about the pathogenesis of type 2 diabetes mellitus from bariatric surgery outcomes?

- Bariatric surgery is an effective intervention for treating type 2 diabetes
- Improvement in metabolic control is often evident within days to weeks (weight loss independent)
- What are the underlying mechanisms?

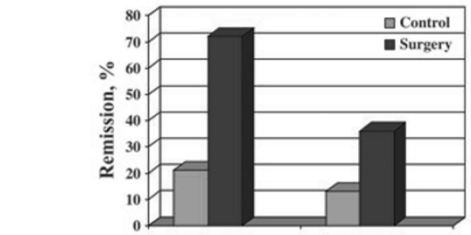
Schematic diagram showing the major factors and pathways involved in the beneficial effects of bariatric surgeries on body weight and glucose homeostasis, with emphasis on caloric restriction and weight loss–dependent (solid lines) and –independent (broken lines) factors.



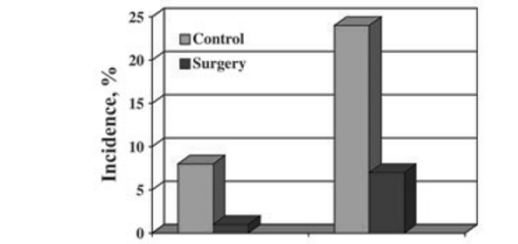
John P. Kirwan et al. Diabetes 2018;67:1043-1044

American Diabetes Association.

What can we learn about the pathogenesis of type 2 diabetes mellitus from bariatric surgery outcomes?



Number of subjects:	2 year	10 year
Control	248	84
Surgery	342	118
Adjusted Odds ratio	8.42	3.45
95% CI	5.68 - 12.5	1.64 - 7.28
P value	<0.001	<0.001

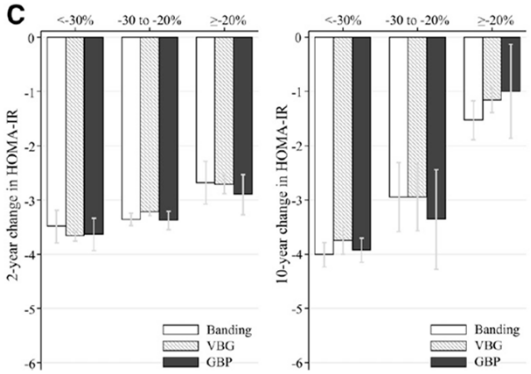


Number of subjects:	2 year	10 year
Control	1402	539
Surgery	1489	517
Adjusted Odds ratio	0.14	0.25
95% CI	0.08 - 0.24	0.17 - 0.38
P value	<0.001	<0.001

Sjostrom L, J Int Med, 2013

What do we know about the long term effects of bariatric surgery on metabolic improvement?

- Long term improvement in glucose, insulin and insulin resistance --> weight loss dependent
- Degree of weight loss is more important for long term reductions in fasting insulin and glucose than choice of bariatric surgery



Sjoholm K, Diabetes Care, 2016

- I'm sure I don't have diabetes?? Do I??

- Can we predict T2DM earlier than detection of pre-diabetes by current criteria?

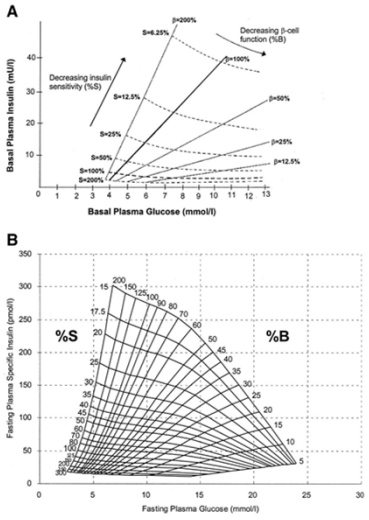
Can we predict T2DM earlier than detection of pre-diabetes by current criteria?

Table 2.5—Criteria defining prediabetes*
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Diabetes Care Volume 42, Supplement 1, January 2019

1985 HOMA Model



Tara M. Wallace et al. Dia Care 2004;27:1487-1495

American Diabetes Association.

OGTT insulin patterns: strong independent predictor of type 2 diabetes over 10 year follow up

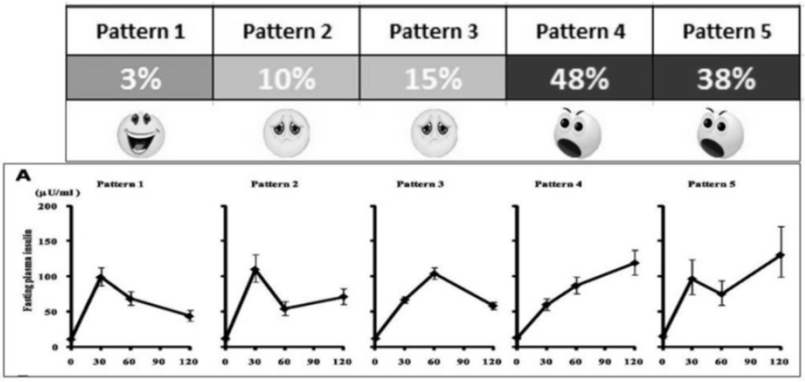
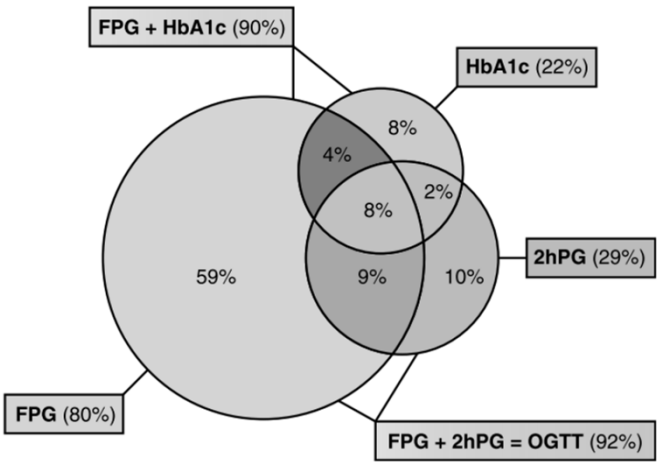


Figure 1—A: Insulin concentration patterns during an OGTT (geometric means [95% CI]): pattern 1, peak of insulin during an OGTT at 30 min and insulin levels at 60 min greater than those at 120 min; pattern 2, peak of insulin at 30 min and insulin levels at 60 min less or equal to those at 120 min; pattern 3, peak of insulin at 60 min; pattern 4, peak of insulin at 120 min and insulin levels at 30 min lower than those at 60 min; and pattern 5, peak of insulin at 120 min and insulin levels at 30 min greater or equal to those at 60 min. B: Plasma glucose pattern during an OGTT for each of these insulin patterns (means [95% CI]).

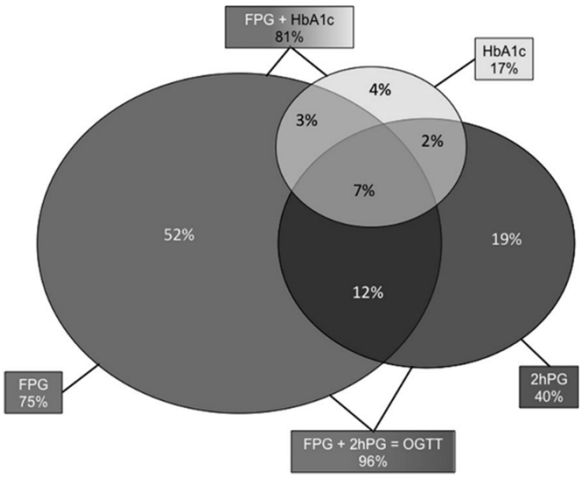
Hayashi T, Diabetes Care. 2013 May;36(5):1229-35

40 % of patients with HTN and Dyslipidemia have either pre-diabetes or diabetes
Best test to screen: OGTT



Shahim B, Cardiovasc Diabetol. 2018 Jan 24;17(1):21.

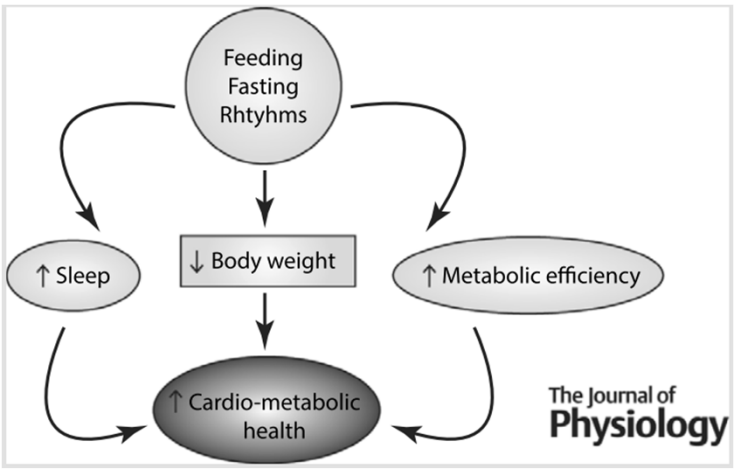
90% of patients with CAD have either pre-diabetes or diabetes
Best test to screen: OGTT



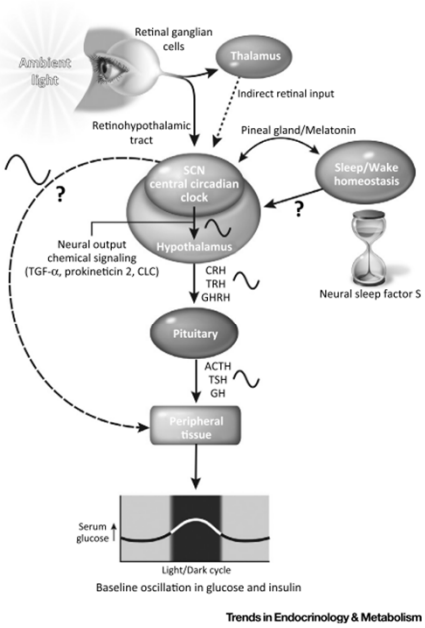
Gyberg V, European Heart Journal (2015) 36, 1171–1177

◦ Are your clocks in SYNC?

Synchronizing feeding-fasting with light-dark cycle

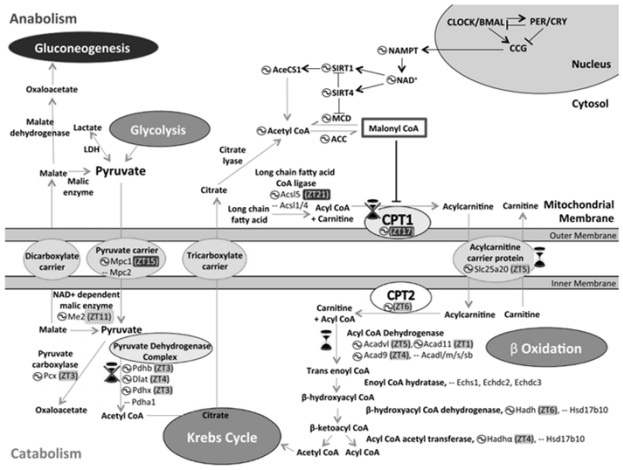


Melkani GC, J Physiol 000.00 (2017) pp 1–10



Zarrinpar A, Trends Endocrinol Metab. 2016 Feb; 27(2): 69–83.

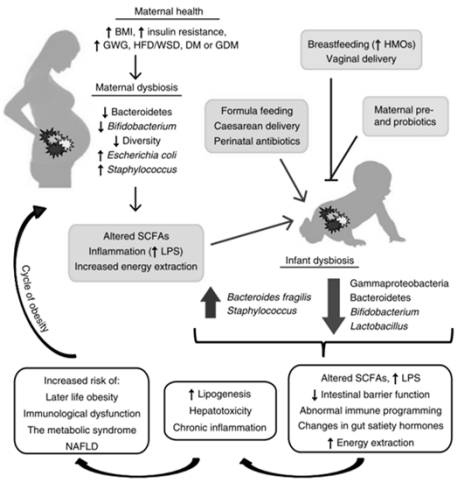
Circadian rhythm of glucose/lipid metabolism



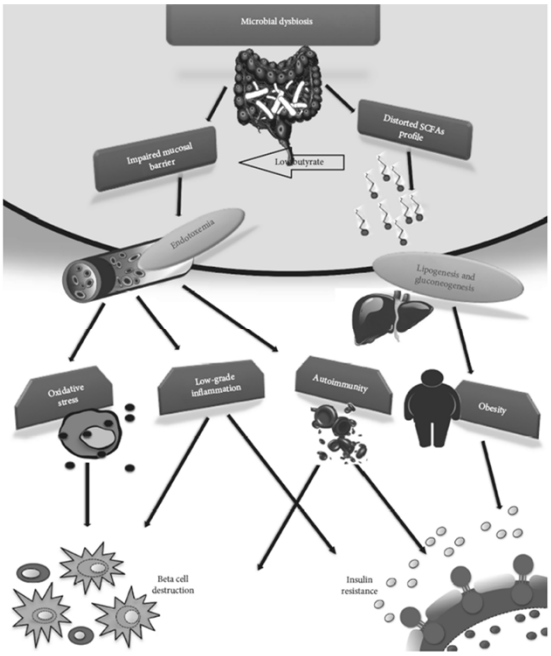
Manoogian EN, Proc Natl Acad Sci U S A. 2016 Mar 22; 113(12): 3127–3129.

- What about the bugs in the room?

Dysbiosis and childhood obesity



Soderborg TK, Diabetologia.2016 May; 59(5):895-906



Microbial dysbiosis can lead to

- Oxidative stress
- Inflammation
- Autoimmunity
- Obesity

Sohail MU, J Diabetes Research.2017

Summary

- Type 1 diabetes mellitus: beta cell destruction leading to absolute insulin deficiency
- Type 2 diabetes mellitus: beta cell dysfunction in the background of insulin resistance
- Useful to think in terms of antibody status and beta cell reserve for atypical diabetes (C-peptide less than 1 ng/mL indicating insulin dependence)
- Pathophysiology of diabetes mellitus is complex
- Pre-natal and post natal factors, circadian disruption, gut microbiome all play important role
- Pre-diabetes, history of GDM: potential for greatest impact in prevention of diabetes by lifestyle change

Learning Assessment Question #1

In contrast to type 1 diabetic patients, patients with type 2 diabetes:

a) Often experience an acute onset of diabetes
b) Have an increased frequency of HLA-DR3, DR4, DQB1*0201, *0302
c) Do not have islet autoantibodies
d) Are often lean

Learning Assessment Question #2

Which of the following would **NOT** be considered diagnostic for diabetes?

a) FPG 130 mg/dL
b) A1C 6.7%
c) 2-h PG 250 mg/dL during OGTT
d) Random PG 180 mg/dL

Learning Assessment Question #3

Which of the following is involved in the pathogenesis of type 2 diabetes?

a) Decreased FFA production by adipose tissue
b) Increased incretin effect in the digestive tract
c) Increased glucose reabsorption by the kidney
d) Decreased glucagon secretion by pancreatic alpha cells

◦ THANK YOU

References

- http://outpatient.aace.com/slide-library
- ADA Standards of Medical Care in Diabetes – 2019, Diabetes Care 2019 Jan; 42 (Supplement 1)