UCSF Benioff Children's Hospitals

Type 2 diabetes in Children and Adolescents

2025 PES Board Review Course in Pediatric Endocrinology

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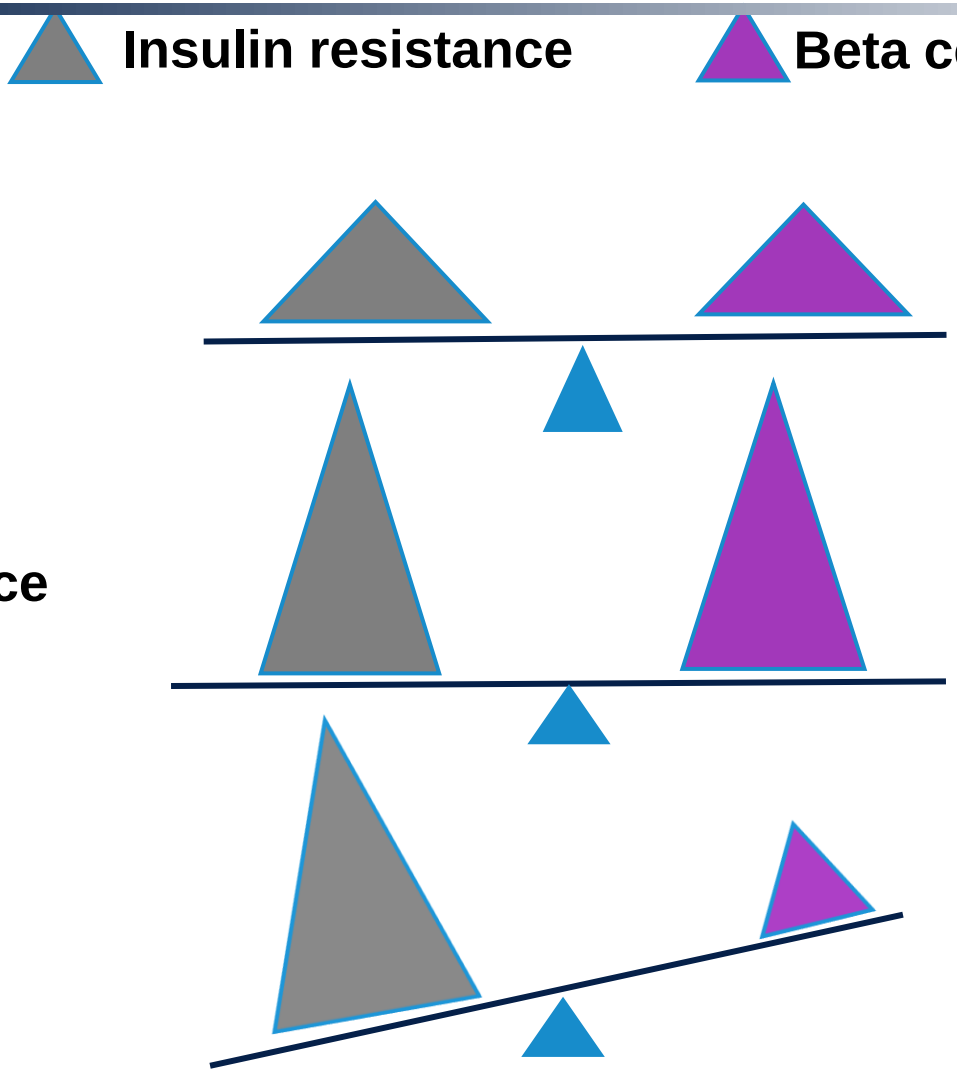
- Lecture content updated and modified from Dr. Philip Zeitler's 2021 slides

Content Domain	Exam Weights
1. Normal Physiology and Structural Development of Endocrine Systems	6%
2. Pharmacology	2%
3. Diabetes Mellitus	11%
4. Disorders of Growth	10%
5. Disorders of the Thyroid Gland	9%
6. Disorders of Puberty	8%
7. Disorders of the Adrenal Gland	7%
8. Disorders of the Hypothalamic-Pituitary Axis	6%
9. Hypoglycemia	5%
10. Disorders of Sex Development	5%
11. The Posterior Pituitary Gland and Disorders of Vasopressin and Water Metabolism	5%
12. Disorders of Weight Homeostasis	5%
13. Disorders of Mineral and Bone Metabolism	5%
14. Combined Endocrine Disorders and Enteric Neuroendocrine Tumors	3%
15. Lipid Disorders	3%
16. Gender Medicine	2%
17. Population Health and Screening	2%
18. Systems-Based Practice	2%
19. Core Knowledge in Scholarly Activities	4%
	100%

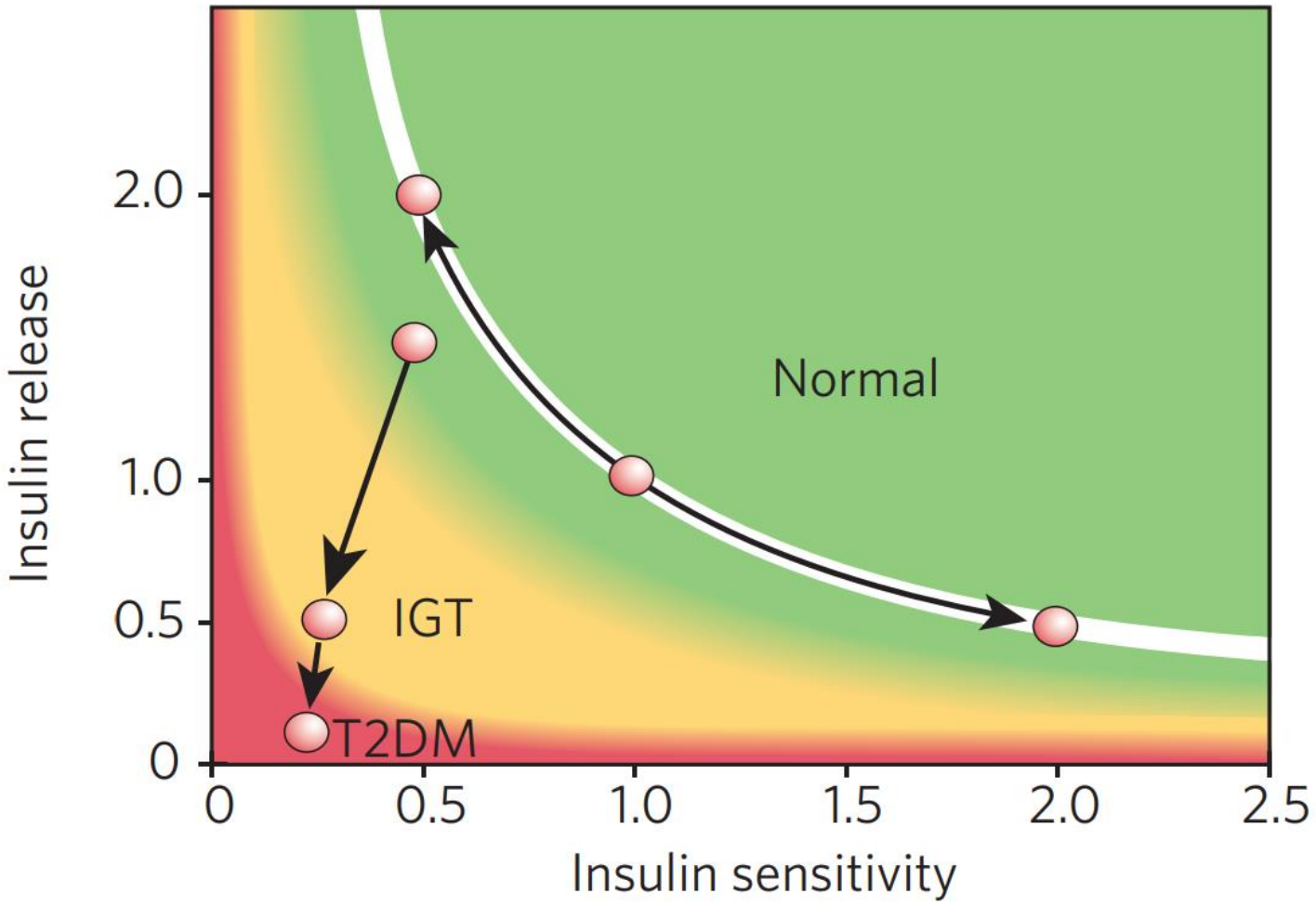
Know the roles of insulin resistance, obesity, and insulin deficiency in the pathophysiology of type 2 diabetes

Glucose homeostasis is a balance between insulin action and secretion



Diabetes occurs when this balance is lost

The relationship between insulin secretion and insulin action is a hyperbolic function



Kahn SE et al: *Nature* 2006

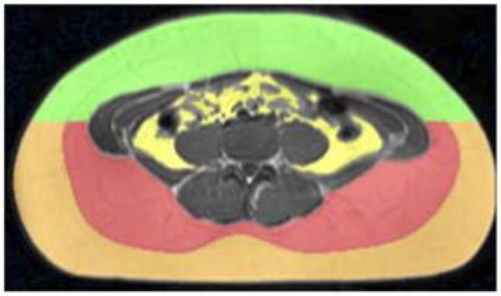
Causes of insulin resistance

- **Inherited**
  - Rare mutations: insulin receptor, glucose transporter, signaling proteins
  - Insulin receptor antibodies
- **Acquired**
  - Obesity
  - Inactivity
  - Inflammation
  - Fatty acids
  - Medications

Central obesity is “central” to the development of insulin resistance in T2D

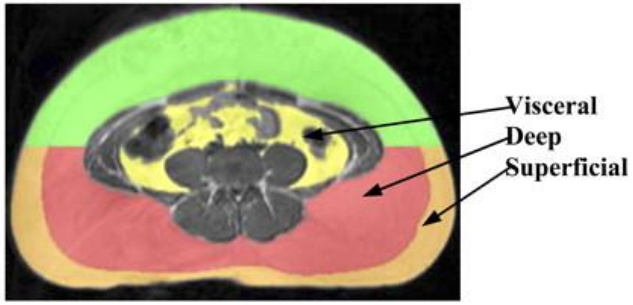
Males

Tertile 1
Age: 14
BMI: 35.3
Percent Fat: 41.7%



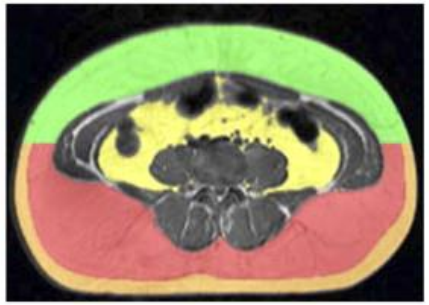
Proportion of Visceral Fat: 0.08
Visceral Fat: 56 cm^2
Subcutaneous Fat: 628 cm^2
Deep-to-Superficial Ratio: 0.84
Matsuda Index: 2.60
Fasting Insulin: 23 µU/ml
2-hr Glucose: 80 mg/dl
TG: 100 mg/dl
HDL: 39 mg/dl

Tertile 2
Age: 14
BMI: 34.0
Percent Fat: 39.3%



Proportion of Visceral Fat: 0.10
Visceral Fat: 68 cm^2
Subcutaneous Fat: 616 cm^2
Deep-to-Superficial Ratio: 2.08
Matsuda Index: 1.17
Fasting Insulin: 33 µU/ml
2-hr Glucose: 118 mg/dl
TG: 109 mg/dl
HDL: 34 mg/dl

Tertile 3
Age: 14
BMI: 33.1
Percent Fat: 38.4%



Proportion of Visceral Fat: 0.15
Visceral Fat: 89 cm^2
Subcutaneous Fat: 519 cm^2
Deep-to-Superficial Ratio: 2.84
Matsuda Index: 0.82
Fasting Insulin: 43 µU/ml
2-hr Glucose: 124 mg/dl
TG: 140 mg/dl
HDL: 40 mg/dl

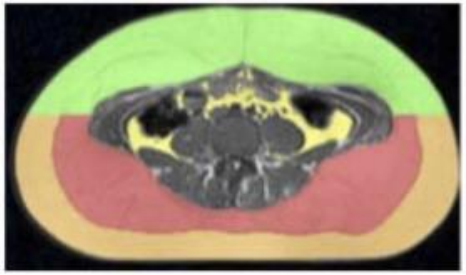
Insulin sensitivity ↓ as visceral fat ↑

Taksali et al., Diabetes., 2008

Increase in visceral fat and decrease in subcutaneous fat leads to decreased in insulin sensitivity

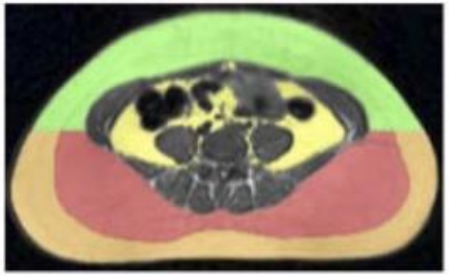
Females

Tertile 1
Age: 12
BMI: 33.3
Percent Fat: 40.4%



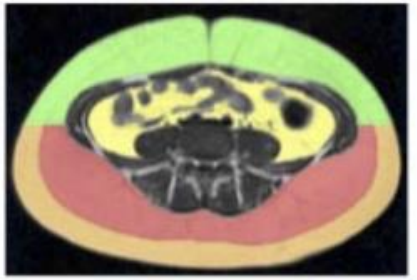
Proportion of Visceral Fat: 0.05
Visceral Fat: 28 cm^2
Subcutaneous Fat: 518 cm^2
Deep-to-Superficial Ratio: 1.15
Matsuda Index: 1.90
Fasting Insulin: 33 µU/ml
2-hr Glucose: 95 mg/dl
TG: 15 mg/dl
HDL: 44 mg/dl

Tertile 2
Age: 13
BMI: 27.7
Percent Fat: 38.2%



Proportion of Visceral Fat: 0.11
Visceral Fat: 50 cm^2
Subcutaneous Fat: 409 cm^2
Deep-to-Superficial Ratio: 1.26
Matsuda Index: 1.15
Fasting Insulin: 32 µU/ml
2-hr Glucose: 165 mg/dl
TG: 82 mg/dl
HDL: 61 mg/dl

Tertile 3
Age: 11
BMI: 27.6
Percent Fat: 37.7%

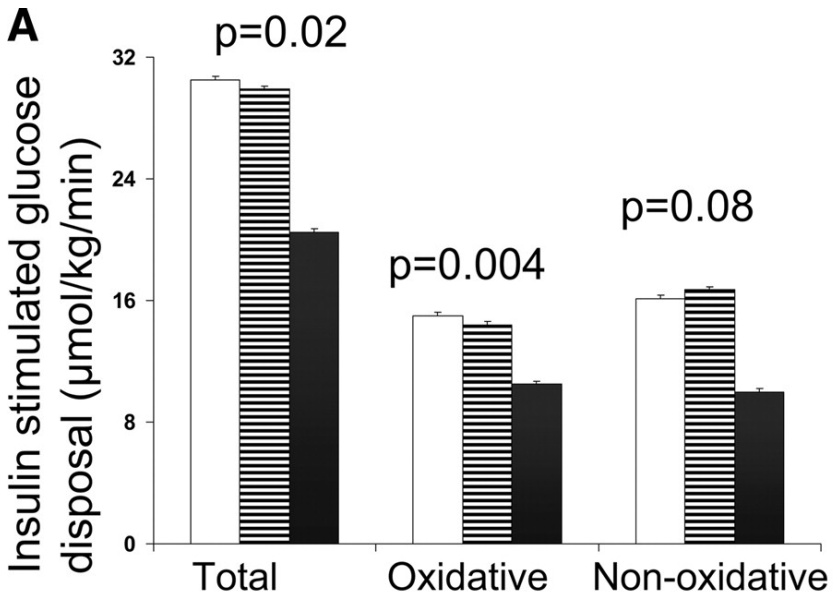


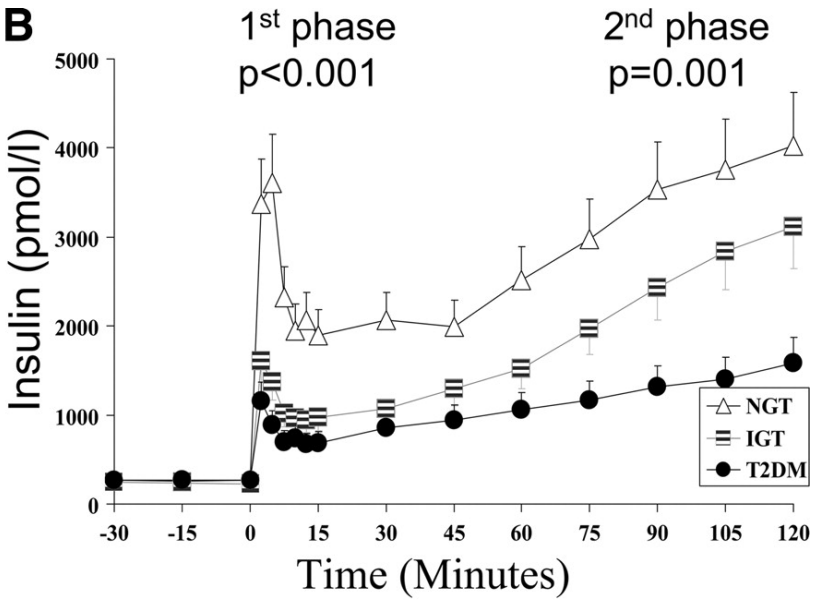
Proportion of Visceral Fat: 0.15
Visceral Fat: 58 cm^2
Subcutaneous Fat: 338 cm^2
Deep-to-Superficial Ratio: 1.39
Matsuda Index: 0.27
Fasting Insulin: 77 µU/ml
2-hr Glucose: 185 mg/dl
TG: 143 mg/dl
HDL: 33 mg/dl

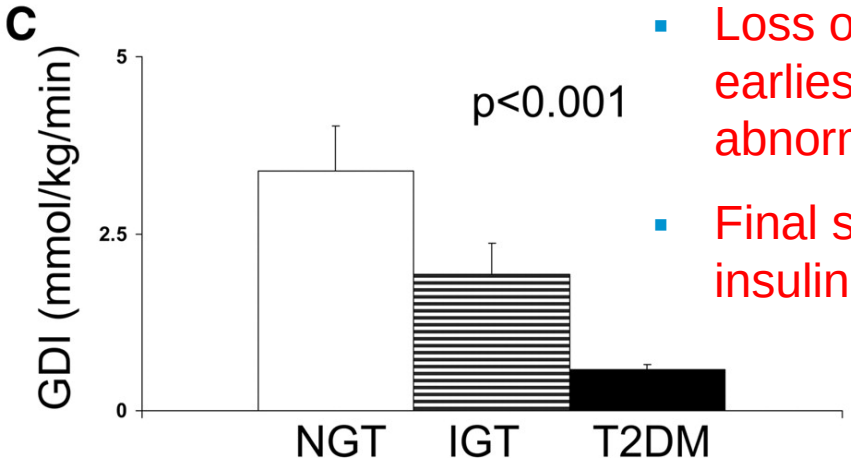
Insulin sensitivity ↓ as visceral fat ↑

Taksali et al., Diabetes., 2008

Insulin sensitivity and insulin secretion in the development of T2D



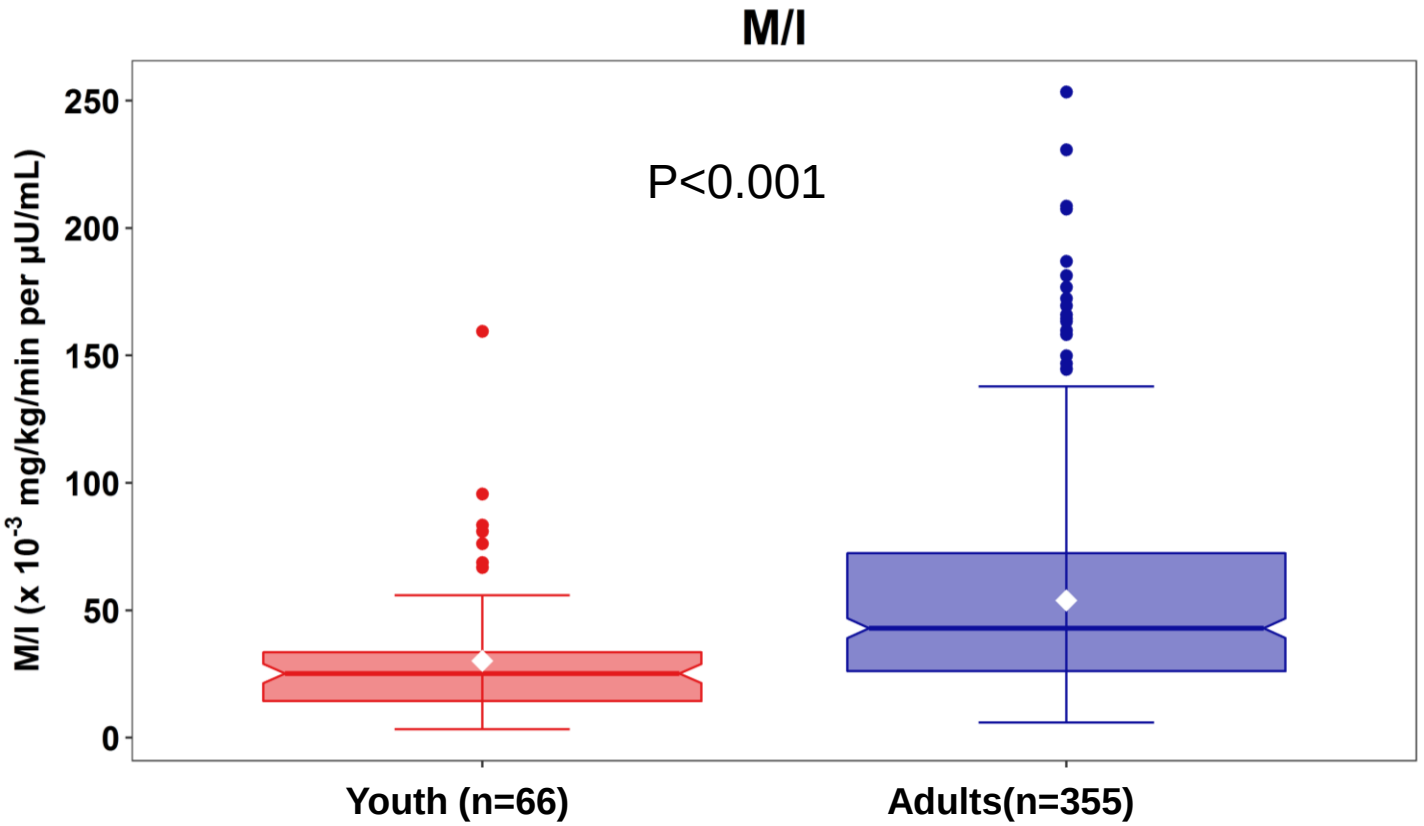




- Loss of 1st phase response is the earliest identifiable β-cell abnormality
- Final step is loss of 2nd phase insulin response

Bacha et al., *Diabetes*., 2009

Youth have greater insulin resistance for any degree of adiposity compared to adults



RISE consortium., *Diabetes Care*., 2018

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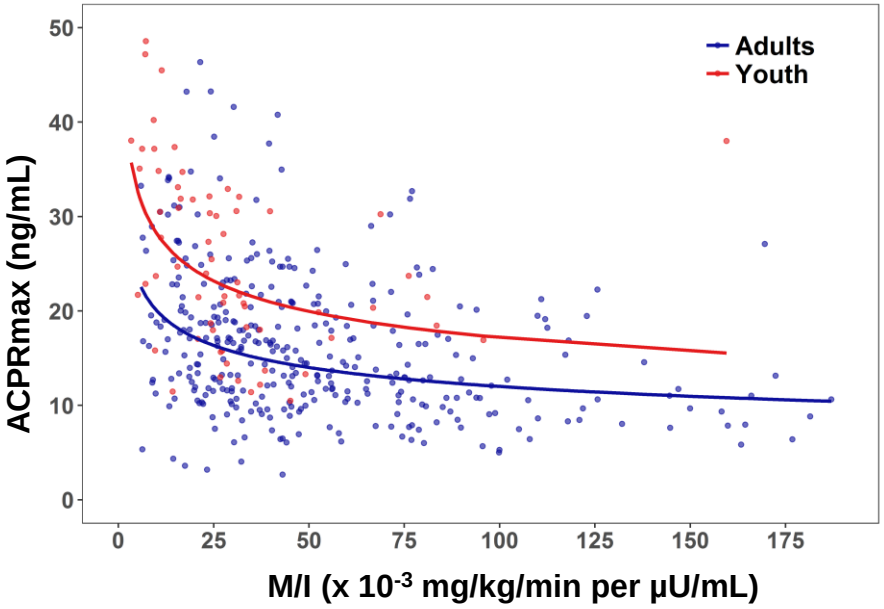
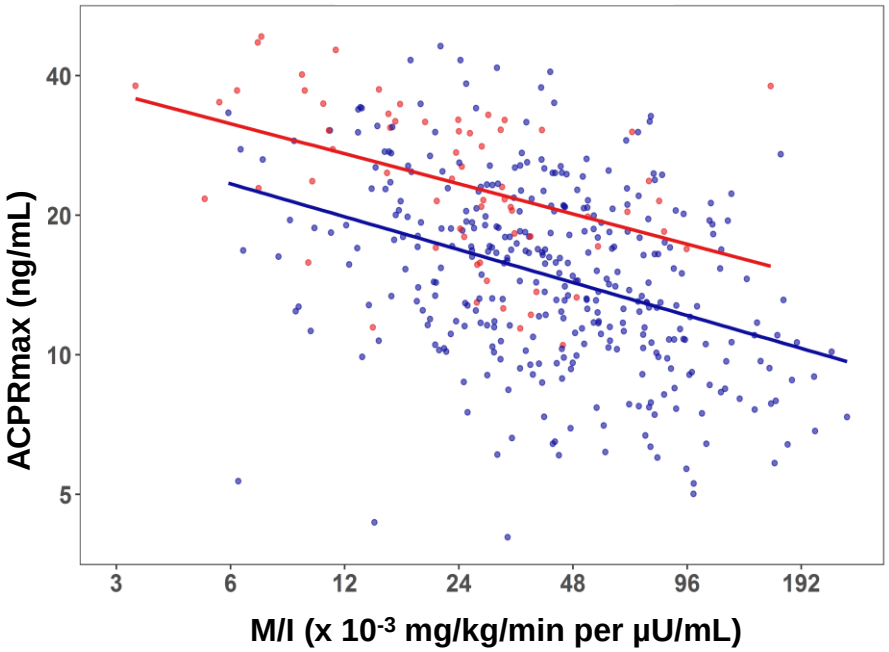
Youth have greater insulin secretion for any degree of insulin resistance compared with adults

ACPRmax



Log ACPRmax



Slope p<0.001 Group*Slope p=ns

RISE consortium., *Diabetes Care*., 2018

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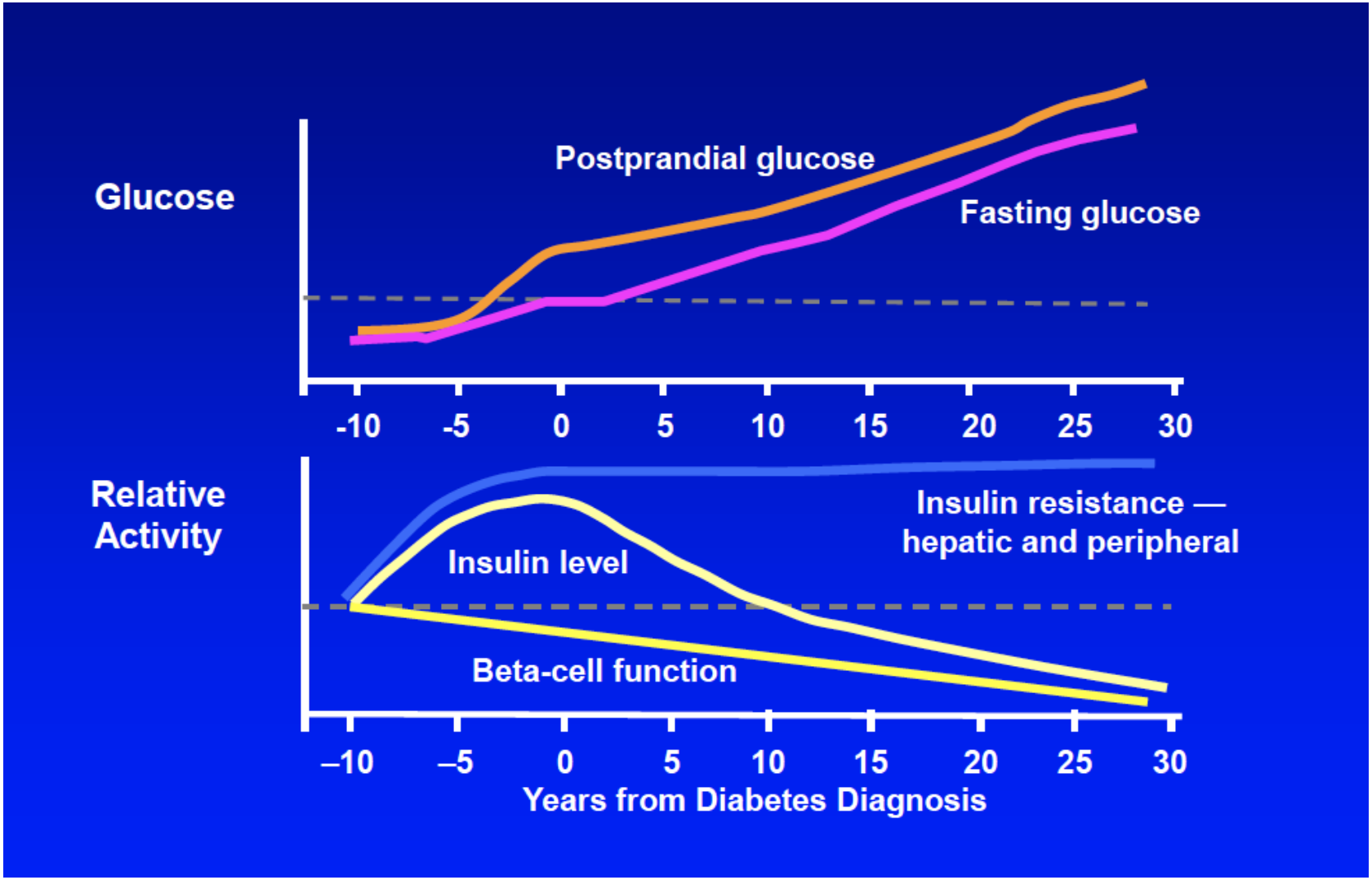
Development and Progression of T2D



Adapted from Ramlo-Halsted et al., *Primary Care: Clinics in Office Practice*., 1999

Summary of pathophysiology of youth T2D

- T2D occurs when β-cells cannot secrete sufficient insulin to compensate for insulin resistance
- Overweight and obesity are major contributors to the development of insulin resistance
- Youth with T2D have
  - Severe peripheral and hepatic insulin resistance
  - Increased fasting hepatic glucose production
  - Inadequate first- and second-phase insulin secretion
  - Greater insulin resistance for any degree of adiposity compared to adults
  - Greater insulin secretion for any degree of insulin resistance compared with adults.
- Upregulation of α-cell function with hyperglucagonemia has been implicated in the adult T2D but data are mixed in youth

Know the effect of adiponectin, leptin, IL-6, and TNF-alpha on insulin sensitivity and markers of insulin resistance

Know the cellular origin of adiponectin, ghrelin, amylin, glucagon- like peptide-1 (GLP-1) and leptin

Understand the actions of glucagon-like peptide-1 (GLP-1) on the GI system, pancreas, and brain

Adiponectin

- Synthesized by adipose tissue and serum concentration inversely correlated to body fat percentage
- Lower in diabetes
- Function
  - Increased insulin sensitivity
    - Improved markers of insulin resistance
  - Decreased gluconeogenesis
  - Increased glucose uptake
  - Increased beta oxidation of fatty acids

Leptin

- Synthesized in white adipose tissue
- Serum concentration is directly correlated with total body fat
- It signals the hypothalamus about the quantity of stored fat
- Inhibits appetite
- Obesity is associated with ↑ leptin levels
- Leptic signaling dysfunction in T2D

IL 6

- Synthesized and secreted by the adipose tissue
  - Adipose contributes up to 35 % of circulating IL6
- Stimulates recruitment and activation of macrophages in adipose tissue
- In the liver, IL-6 promotes STAT3-SOCS-3 pathway mediated impairment of insulin action
- In muscle, IL-6 promotes insulin-regulated glucose metabolism

TNF- α

- Secretion increased in adipose tissue from obese humans
- Induces insulin resistance by downregulating the tyrosine kinase activity of the insulin receptor and decreasing the expression of GLUT-4- reduces lipoprotein lipase activity in white adipocytes
- Stimulates hepatic lipolysis

Ghrelin

- Synthesized from cells lining the fundus of the stomach and in epsilon cells of the pancreas
- Rises before meals and falls after
- Stimulates appetite

Amylin

- Co-secreted from beta cells with insulin
- Contributes to glucose regulation
  - Decreased appetite
  - Slowed gastric emptying
  - Reduction in gastric enzymes
  - Suppression of glucagon
- ↑ in obesity (downregulation of receptor)
- Deficient in T2D

GLP-1

- Secreted by the L cells of the intestine in response to nutrients
- Rapidly metabolized by DPP-4
- Decreases serum glucose
  - Pancreas
    - Stimulates insulin secretion
    - Inhibits glucagon secretion
    - Increases beta cell mass
  - GI tract
    - Slows gastric emptying, leading to lower post-prandial glucose excursion
  - CNS
    - Decreased appetite through central actions on the hypothalamus
- GLP-1r (and GIPr) agonists available as Rx options for T2D and obesity
- DPP-4 inhibitors decrease metabolism of endogenous GLP-1

Know the effects of exogenous obesity on adiponectin and leptin levels

Obesity is associated with …..

- ↓ adiponectin levels
- ↑ leptin levels (development of resistance)

Know the association between insulin resistance and amylin levels

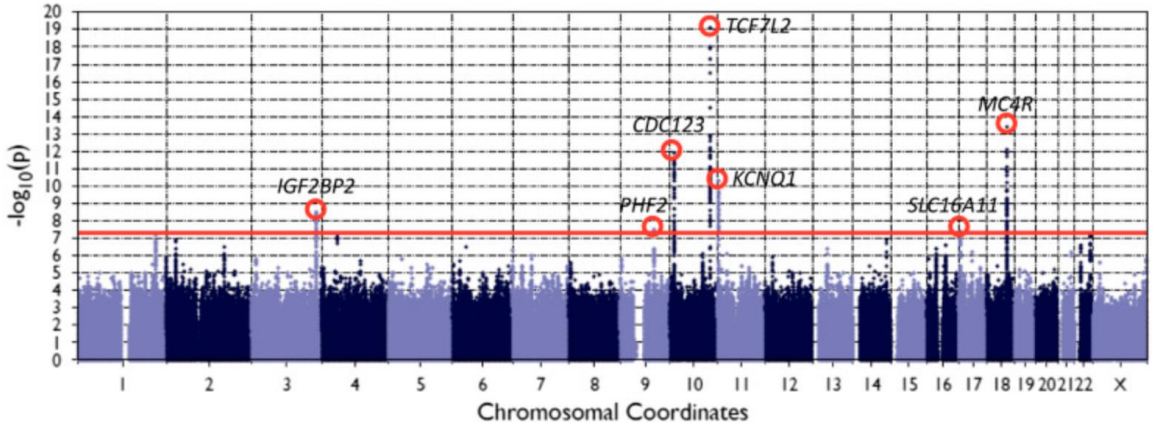
Amylin

- Amylin levels are ↑ in obesity with normal glucose tolerance (downregulation of receptor)
- But ↓ in insulin resistance and T2D

Understand the inheritance of type 2 diabetes and its implications for testing and counseling of family members

T2D is a complex disease

- Caused by complex interplay of environmental and numerous genetic variants of small and moderate effect sizes
- Monogenic diabetes- MODY- caused by single gene mutations
- Adults ~ 1000 genetic variants identified
- Youth- Similar genetic architecture but effect sizes are larger
- Strong family history of type 2 diabetes in first- or second-degree relatives
- High risk for T2D in offspring of a pregnancy complicated by gestational diabetes mellitus



GWAS of T2D in youth

Srinivasan et al., *Diabetes*., 2021

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Know screening criteria for type 2 diabetes in youth

ADA recommendations for screening for T2D in youth

- After the onset of puberty or Age ≥ 10 years (whichever is earlier)
- Overweight (BMI >85th) or Obese(BMI >95th percentile)
- **AND** who have one or more risk factors:
- Maternal history of diabetes or GDM during the child's gestation
- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs or conditions associated with insulin resistance
  - acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational age birth weight

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

More on Screening for T2D in youth

- If tests are normal, repeat testing at a minimum of 2-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating)
- Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1C can be used to test for prediabetes or diabetes in children and adolescents
- Children and adolescents with overweight or obesity in whom the diagnosis of T2D is being considered should have pancreatic autoantibodies tested to exclude autoimmune T1D

Recognize the clinical and laboratory findings in type 2 diabetes and differentiate from other types of diabetes

Clinical features of T2D

- Overweight or obese
- Mid-to late puberty
- Overrepresentation of youth of color and females
- Family history of T2D
- Maternal diabetes or gestational diabetes or T2D
- Signs or conditions associated with insulin resistance
  - acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational age birth weight

Laboratory diagnosis of T2D

FPG ≥126 mg/dL . Fasting is defined as no caloric intake for at least 8 h
OR
2-h PG ≥200 mg/dL during 75 g OGTT
OR
A1C ≥6.5%.
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL

- In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
- Pancreatic autoantibodies should be measured to exclude the possibility of autoimmune type 1 diabetes
- Genetic testing for MODY should be considered based on clinical characteristics and presentation

ADA, Standards of Care., 2025

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Prediabetes

- Impaired fasting glucose (100-125 mg/ dL) and impaired glucose tolerance (IGT) (2-hour glucose of 140-199 mg/dL on an OGTT)
- HbA1c 5.7%-6.4%.
  - HbA1c 6.0%-6.4% are at particularly high risk for developing diabetes
- Impaired fasting glucose and IGT are considered risk factors for both the development of diabetes and for cardiovascular disease
- Can occur with pubertal decrease in insulin sensitivity
- High rate of spontaneous remission of prediabetes in youth with obesity when puberty ends

- Magge et al., *J Pediatrics*., 2019

T1D vs T2D

Distinguishing between T1D and T2D can be difficult in adolescents

- Age
  - T2D exceedingly rare before puberty
- Weight and BMI
  - All cases of T2D > 85%ile
  - ~ 30%+ of T1D cases > 85%ile
- Pancreatic auto-antibodies
  - 15%+ of clinically defined adolescents with T2D may have antibodies
- Presentation
  - Casual diagnosis uncommon, but not impossible in T1D
- Ketosis
  - 25% of T2D may present with ketosis
- Family history
  - Family history of T2D common

Characteristic	Type 1 Diabetes	Type 2 Diabetes	Classic MODY
Age at onset	Peaks at 5 and 15 years of age	Teenage years, young adults	<25 years of age
Predominant ethnic groups affected	White	Hispanic, African American, Native American	Occurs in all ethnic groups
Male-to-female ratio	1.1:1	1:1.5	1:1
Severity at onset	Acute, severe, insulin required	Subtle, insulin not required	Subtle, insulin not required
Islet autoimmunity	Present	Absent	Absent
HLA-DR3, -DR4	Very common	No increased frequency	No increased frequency
Ketosis, DKA	Common	Uncommon	Rare
Long-term course	Insulin-dependent	Noninsulin-dependent	Noninsulin-dependent
Prevalence of obesity	Uncommon	≥90%	Uncommon
Proportion of cases of 100% youth-onset diabetes	Most common form of youth-onset diabetes	Rising in frequency; ± as common as type 1 diabetes in specific populations	≤5% of youth-onset diabetes in whites
Percentage of probands with an affected first-degree relative	≤15%	Variable but common	100%
Mode of inheritance	Nonmendelian, generally sporadic	Nonmendelian but strongly familial	Autosomal dominant
Number of genes controlling inheritance	Polygenic	Polygenic	Monogenic
Pathogenesis	Autoimmune beta cell destruction: insulinopenia	Insulin resistance plus relative insulinopenia	Insulinopenia

Recognize the various presentations of type 2 diabetes

Clinical presentations of T2D

- Varies widely
  - Asymptomatic or minimally symptomatic, diagnosed incidentally during routine laboratory testing
  - Severe presentation with symptomatic hyperglycemia, weight loss, metabolic decompensation, DKA, or HHNK syndrome
- Pediatric Diabetes Consortium study
  - The majority of participants (n = 282, 67%) presented with symptoms of diabetes and confirming laboratory data
  - A third of the participants (n= 139) were identified by high-risk screening
  - Diabetic ketoacidosis (DKA) was present in 11% during diagnosis
  - 2% had hyperglycemic, hyperosmolar state

Kligensmith et al., *Pediatric Diabetes*., 2016

DKA and HHS in T2D

- **Diabetic ketoacidosis**
  - Hyperglycemia, ketosis and acidosis
- **Hyperglycemic hyperosmolar state**
  - Severe hyperglycemia, marked increase in serum osmolality and severe dehydration *without* significant ketoacidosis
  - Enough circulating insulin to prevent excessive lipolysis and subsequent ketogenesis

Differences in treatment strategy between HHS and DKA include the volume of fluid administered, the timing of administration of insulin, and monitoring of the corrected sodium decline

Glaser et al., ISPAD 2022 guidelines

Know the implications of large, pivotal diabetes trials

Lessons learned from adult trials

UKPDS

- Tight control matters in T2D
- Sulfonylureas associated with increased CV risk and earlier β-cell failure

DPP

- In adults at risk for T2D, lifestyle intervention and metformin can reduce incidence of type 2 diabetes

ACCORD

- Tight control associated with mortality in those with elevated CV risk

GRADE

- Comparison of 4 medications when added to metformin
- Rates of HbA1C lowering > for glargine and liraglutide compared to glimepiride and sitagliptin

SEARCH for Diabetes in Youth

- Population based observational study to characterize the descriptive epidemiology of diabetes in youth < 20 years in the US
- 5 centers across US
- T2D rare in children < 10 years regardless of race and ethnicity
- Incidence
  - Unadjusted incidence rates of T2D ↑ by 7.1% annually (9.0 vs 12.5 cases per 100,000 youths per year in 2002-2003 and 2011-2012)
  - Increases in all subgroups except Non-Hispanic White
- Prevalence of T2D ↑ by 0.34 per 1000 youths to 0.67 per 1000 youths
- Future projections- By 2050, at current incidence rates, numbers may double, and may increase by more than fourfold if incidence rates increase as data suggest

The TODAY Cohort- Medication trial of T2D

Age	14.0 (12,16)
Duration of T2D (months)	5 (4,9)
BMI Z score	2.21 (1.89, 2.47)
Tanner 4/5	83.9%
Female	64.9%
Ethnicity	
White	19.9%
Hispanic	42.2%
Black	31.6%
American Indian	6.2%
Family Hx diabetes	
Nuclear	59.6%
Nuclear + GP	89.4%
GDM	33.3%
Acanthosis	97.0%

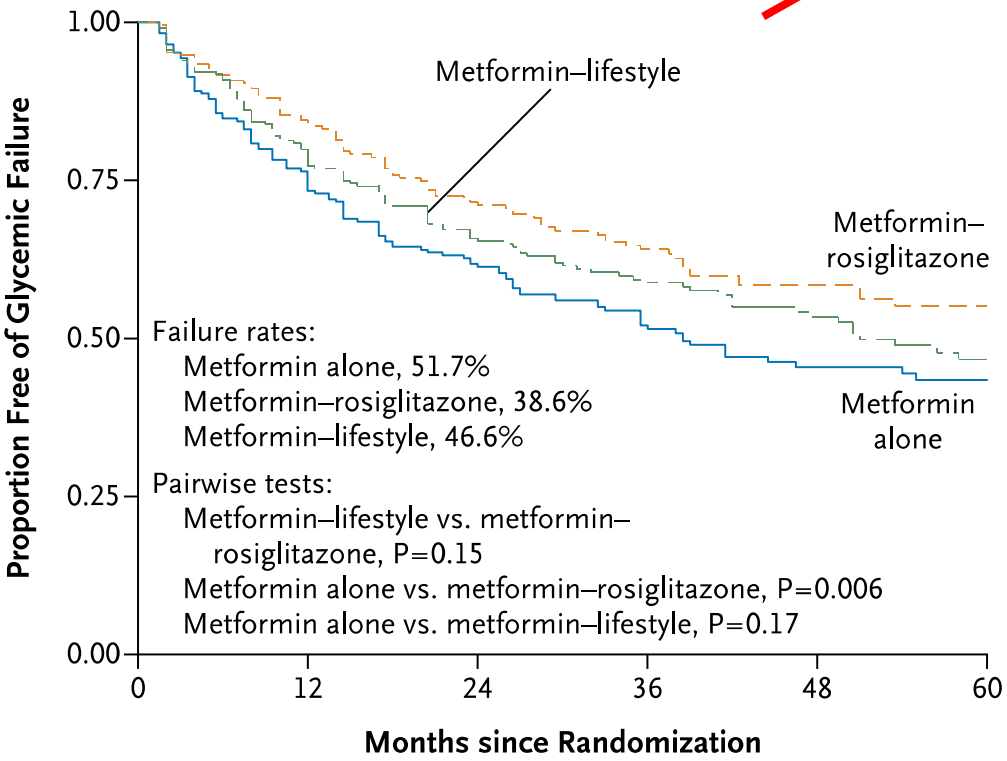
Lives with	
Both parents	38.7%
Mother only	47.0%
Father only	5.1%
Neither	9.2%
Parental Education	
Less than 12th grade	26.5%
High school	25.1%
Some college	31.8%
Bachelor's degree and above	16.6%
Income	
<$25K	21.5%
$25K-$50K	33.7%
$50K-$75K	24.8%
>$75K	20%

Median (25th, 75th %tiles)

Adapted from Copeland et al, *J Clin Endocrinol Metab*., 2010

TODAY Study: Results

n= 699



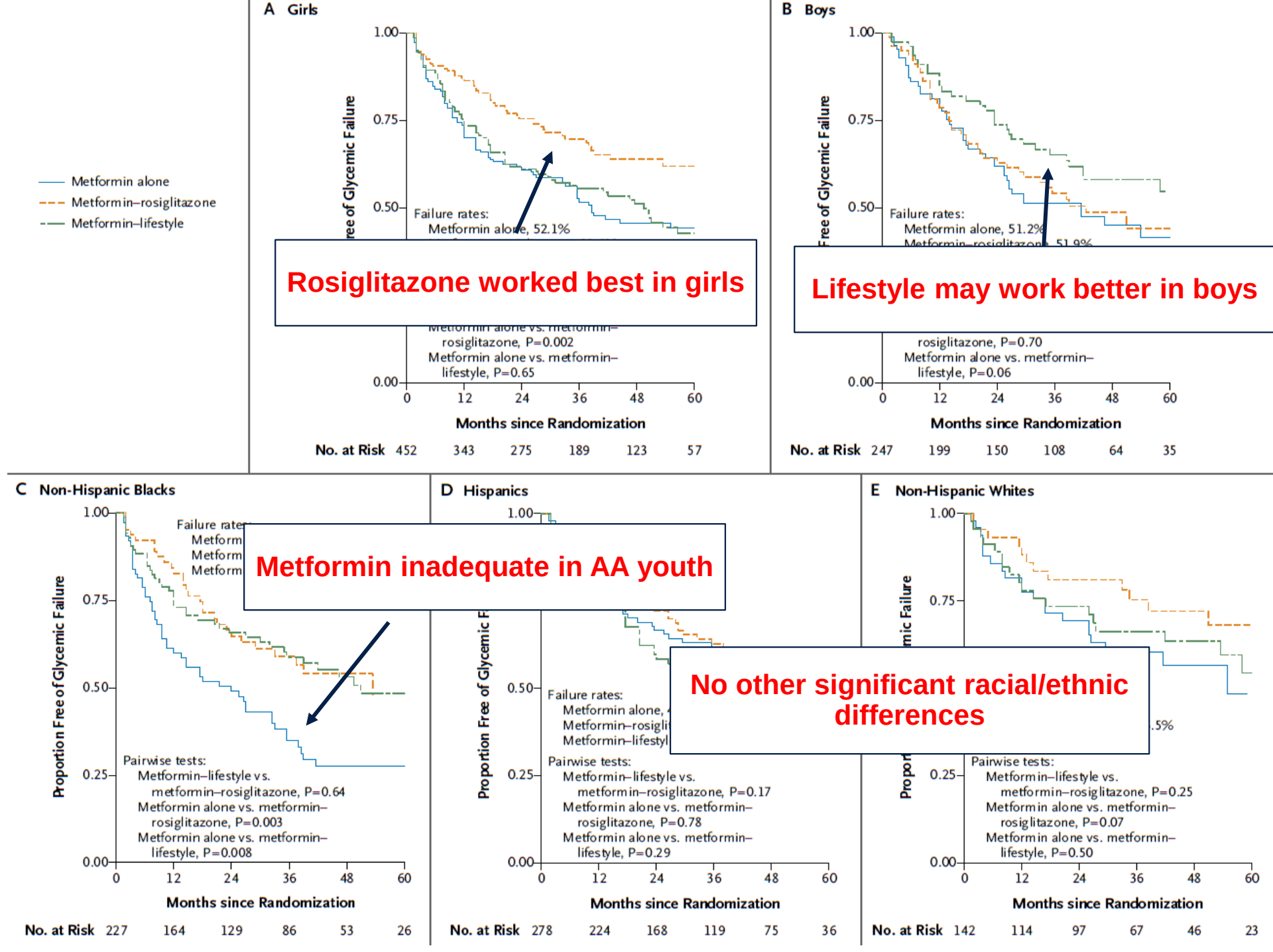
No significant difference with addition of lifestyle intervention

Small but significant improvement with rosiglitazone

High failure rate overall for metformin treatment

45.6% reached the primary outcome of loss of glycemic control despite combination therapy

Zeitler et al: A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes
TODAY Study Group: N Engl J Med 2012; 366:2247-2256


Metformin alone
Metformin–rosiglitazone
Metformin–lifestyle
A Girls
Proportion Free of Glycemic Failure
1.00
0.75
0.50
0.00
Failure rates:
Metformin alone, 52.1%
Metformin alone vs. metformin–rosiglitazone, P=0.002
Metformin alone vs. metformin–lifestyle, P=0.65
0
12
24
36
48
60
Months since Randomization
No. at Risk 452 343 275 189 123 57
Rosiglitazone worked best in girls
B Boys
Failure rates:
Metformin alone, 51.2%
rosiglitazone, P=0.70
Metformin alone vs. metformin–lifestyle, P=0.06
No. at Risk 247 199 150 108 64 35
Lifestyle may work better in boys
C Non-Hispanic Blacks
Pairwise tests:
Metformin–lifestyle vs. metformin–rosiglitazone, P=0.64
Metformin alone vs. metformin–rosiglitazone, P=0.003
Metformin alone vs. metformin–lifestyle, P=0.008
No. at Risk 227 164 129 86 53 26
Metformin inadequate in AA youth
D Hispanics
Failure rates:
Pairwise tests:
Metformin–lifestyle vs. metformin–rosiglitazone, P=0.17
Metformin alone vs. metformin–rosiglitazone, P=0.78
Metformin alone vs. metformin–lifestyle, P=0.29
No. at Risk 278 224 168 119 75 36
E Non-Hispanic Whites
Pairwise tests:
Metformin–lifestyle vs. metformin–rosiglitazone, P=0.25
Metformin alone vs. metformin–rosiglitazone, P=0.07
Metformin alone vs. metformin–lifestyle, P=0.50
No. at Risk 142 114 97 67 46 23
No other significant racial/ethnic differences

TODAY study summary

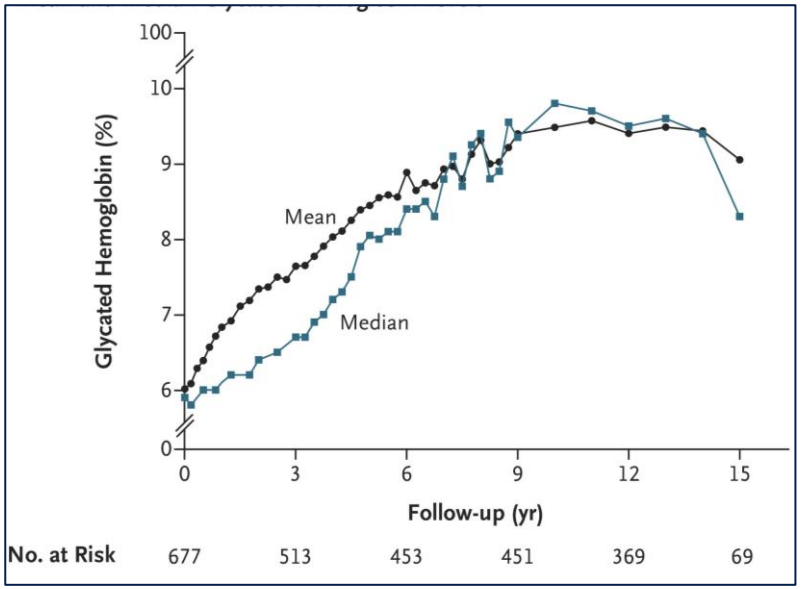
- Metformin monotherapy is inadequate for half of youth with T2D
- The role of intensive lifestyle interventions in youth T2D is uncertain
- There are important sex and race/ethnicity differences among youth with type 2 diabetes in the US
- Youth with type 2 diabetes have progressive loss of β-cell function that is rapid relative to adults and is irrespective of treatment

TODAY study summary contd…..

- Initial treatment with metformin is usually successful - even for participants on insulin
- Youth who cannot achieve HbA1c in the non-diabetes range on metformin are less likely to maintain glycemic control on oral meds and will require insulin
- Weight loss is associated with improved glycemic and non-glycemic measures
- Pregnancy outcomes in youth-onset T2D are troubling

TODAY long-term follow up- Increase in HbA1C trend over time

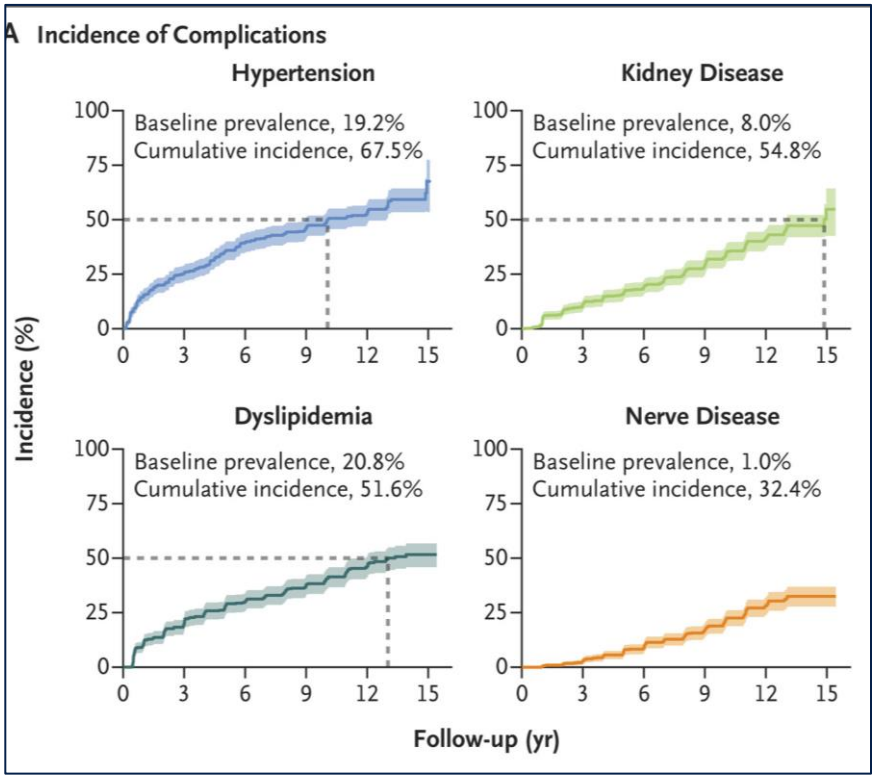
- Study end, mean age = 26.4 ± 2.8 y
- Mean time from diabetes Dx = 13.3± 1.8 y
- Median HbA1C ↑ over time
  - % of participants with HbA1C <6% ↓ from 75% at baseline to 19% at 15 years
  - % with HbA1C of at least 10% was 0% at baseline and 34% at 15 years

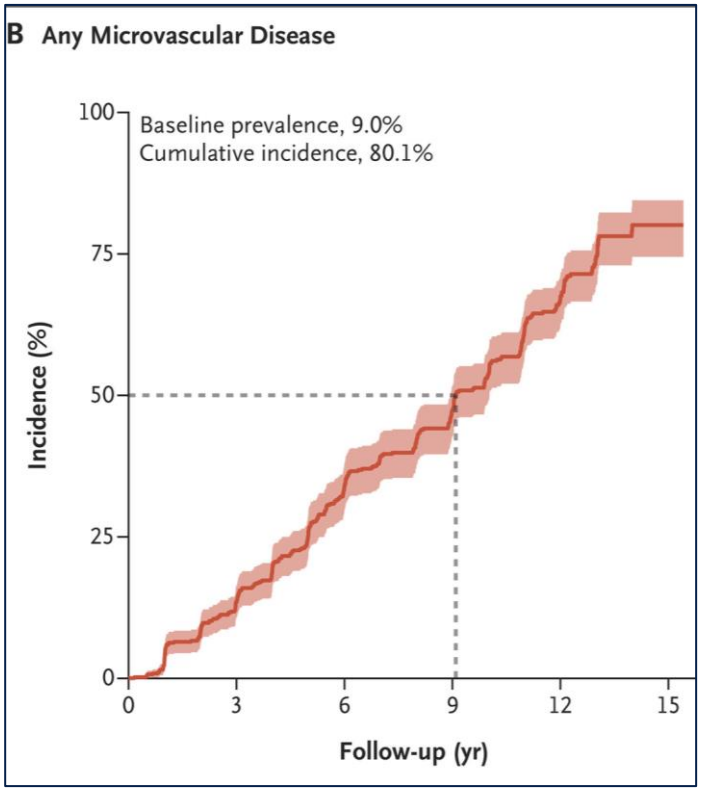


TODAY study group., *NEJM*., 2021

UCSF Benioff Children's Hospitals

Results: Complications appear early and accumulate rapidly





- Prevalence of retinal disease was 13.7% from 2010 to 2011 and 51.0% from 2017 to 2018
- **The cumulative incidence of any microvascular complication was 50.0% by 9 years and 80.1% by 15 years**

TODAY study group., *NEJM*., 2021

UCSF Benioff Children's Hospitals

Results: Predictors of complications

- Factors associated with an increased risk of the development of any microvascular complication:
  - youth of color
  - high baseline HbA1C
  - low insulin sensitivity
  - hypertension
  - dyslipidemia
- There were no differences according to the original treatment assignment.

TODAY study group., *NEJM*., 2021

RISE study

- 91 obese pubertal youth with pre-diabetes or early T2D
- Randomized to
  - 3 months insulin glargine + 9 months metformin
  - 12 months metformin
- β- cell function measured at 12 and 15 months
- Metformin alone/basal insulin followed by metformin did not halt the deterioration in β cell function
- Youth have greater insulin secretion for any degree of insulin resistance compared with adults
- Youth have greater insulin secretion for any degree of insulin resistance compared with adults

The Rise Consortium., *Diabetes Care*., 2018

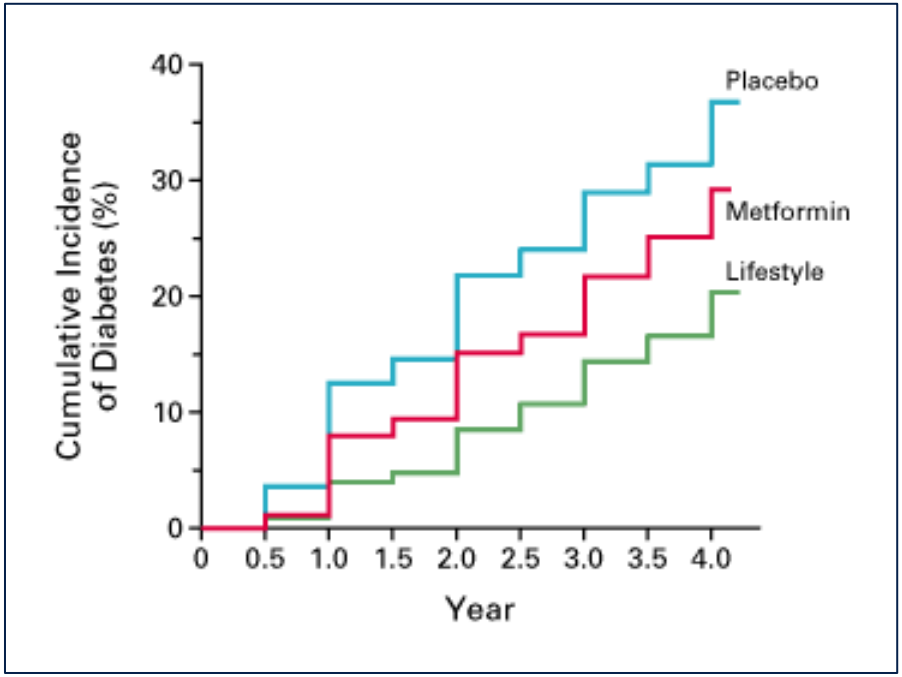
DISCOVERY study

- NIH funded multicenter observational study of youth at risk for diabetes
- Goal is to identify unique drivers of youth-onset type 2 diabetes
  - Biological, social and environmental factors
- Proposed n= 3600, ages 9-14 years

Understand that a reduced calorie diet and exercise are more effective than metformin in slowing the progression of type 2 diabetes

The Diabetes Prevention Program demonstrated that type 2 diabetes can be prevented in adults

- 3234 subjects with elevated fasting glucose levels and IGT
- Randomized to placebo, lifestyle or metformin
- Average age: 55 years
- Followed for 4 years



Risk reduction: 58% lifestyle
31% metformin

DPP Research Group *NEJM* 346:393-403, 2002

UCSF Benioff Children's Hospitals

Lifestyle education in T2D

- All youth with T2D and their families should receive comprehensive diabetes self-management education/support that is specific to youth and is culturally competent
- Lifestyle change must be part of any intervention
- Little evidence that this is effective on its own in children

Arslanian et al., *Diabetes Care*., 2018

Understand the treatment of type 2 diabetes, including the mechanisms of action of the medications used (See handout)

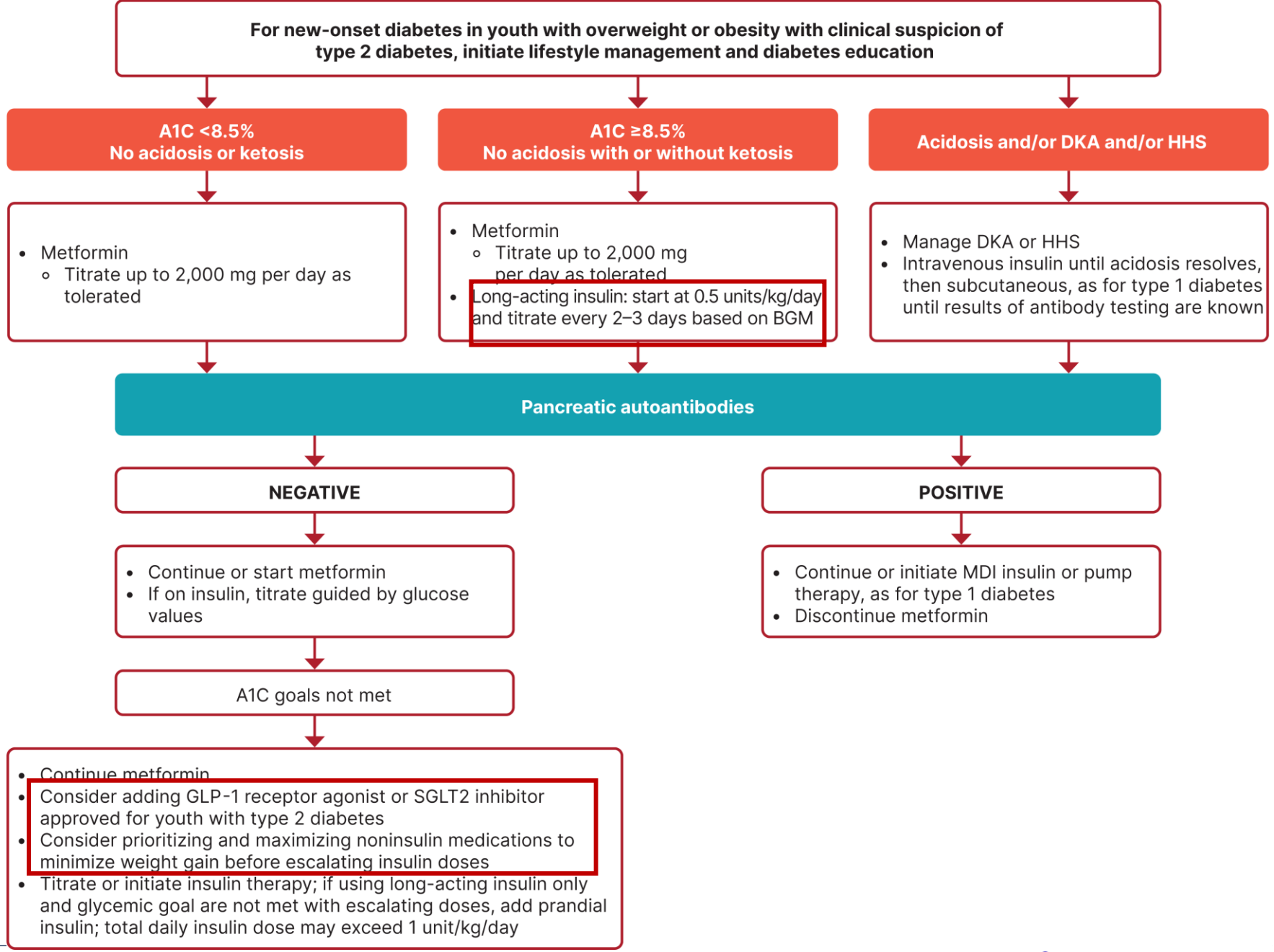
Treatment goals

- Diabetes defined by increased risk of complications
- UKPDS
  - Tight control leads to reduction in
    - Retinopathy
    - Nephropathy
    - Neuropathy
    - Cardiac events
  - There is a "legacy" effect of tight control leading to reduction in events even after intensive intervention is discontinued

Treatment goals: Aggressive management recommended

- Primary: Hemoglobin A1C <6.5 -7%
  - Revised in 2025 ADA and 2022 ISPAD guidelines
  - Taking into account low rate of hypoglycemia
- Home glucose monitoring should be individualized taking into account pharmacologic treatment
- Insufficient evidence regarding the frequency of fingerstick glucose measurements
- Monitoring (if not taking insulin)
  - Fingerstick blood glucose
  - Twice a day
  - 3 to 5 days a week
  - When ill
- Limited data on CGM use

Arslanian et al., *Diabetes Care*., 2018



American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Recognize the public health implications of type 2 diabetes in youth and possible public health interventions aimed at the prevention of type 2 diabetes

T2D prevention in youth

- Limited data in youth
- Some evidence that intensive lifestyle education based approaches are helpful for T2D prevention

Recognize that the co-morbid conditions associated with type 2 diabetes are the same as those associated with metabolic syndrome (eg, hypertension, hyperlipidemia, polycystic ovary syndrome, non- alcoholic fatty liver disease), and their treatment

Know when to monitor for lipids, blood pressure, and urine micro- albumin in patients with type 2 diabetes at diagnosis

Screening for co-morbidities

- Comorbidities more common at diagnosis than in T1D
- Co-morbidities increase more rapidly than in T1D
- Screening
  - Timing
    - At diagnosis
    - Yearly
  - Lipids
  - Urine albumin/creatinine ratio
  - Retinal screen
  - Evaluation for MASLD (AST and ALT)
  - Depression screening
  - BP at every visit
  - Screening for symptoms of obstructive sleep apnea at each visit

Arslanian et al., *Diabetes Care*., 2018

Know the treatment of co-morbid conditions associated with type 2 diabetes and metabolic syndrome

Dyslipidemia

- Testing when initial glycemic control has been achieved and annually thereafter
- Optimal cholesterol goals
  - LDL <100 mg/dL
  - HDL >35 mg/dL
  - Triglycerides <150 mg/dL
- If LDL cholesterol is >130 mg/dL, optimize glycemia and dietary counseling (7% sat fat, < 200 mg chol)
- If LDL cholesterol > goal after 6 months of dietary intervention, start statin, with goal of LDL <100 mg/dL
- If triglycerides are >400 mg/dL fasting or >1,000 mg/dL non-fasting, optimize glycemia and begin fibrate, with a goal of <400 mg/dL fasting (to reduce risk for pancreatitis).
- Adolescent girls on statins or fibrates should receive pregnancy counseling

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Hypertension

- Blood pressure should be measured at every visit
- For BP (BP≥ 90th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥120/80 mmHg) on 3 separate measurements, ambulatory blood pressure monitoring should be strongly considered
- After excluding secondary causes, if > 95%ile for age, sex, and height, intensify lifestyle intervention
- If BP remains > 95%ile for age after 6 months, initiate antihypertensive therapy
  - ACE inhibitors or angiotensin receptor blockers
  - Titrate to BP < 90th %ile or <130/80 if ≥13 years
  - Individuals of childbearing age should receive reproductive counseling

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Nephropathy

- Calculate eGFR at diagnosis and annually
- Random urine albumin/creatinine ratio at diagnosis and annually
- If ACR > 30 mg/g, repeat on first-morning urine
  - Should be confirmed on two of three samples
- Either an ACE inhibitor or an ARB recommended for modestly elevated UACR (30–299 mg/g creatinine)
- Strongly recommended for those with UACR >300 mg/g creatinine and/or eGFR <60 mL/min/1.73 m2
- Referral to nephrology recommended in case of uncertainty of etiology, worsening UACR, or decrease in eGFR

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Neuropathy

- At diagnosis and annually
- The examination should include
  - Inspection
  - Assessment of foot pulses
  - Pinprick and 10-g monofilament sensation tests
  - Testing of vibration sensation using a 128-Hz tuning fork
  - Ankle reflexes

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Retinopathy

- Dilated fundoscopy or retinal photography at diagnosis and annually
- Less frequent examination (every 2 years) may be considered if there is adequate glycemic control and a normal eye exam
- Retinal photography (with remote reading or use of a validated assessment tool) can be used for screening
- Such programs should provide pathways for timely referral for a comprehensive eye examination when indicated

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

MASLD

- Metabolic Dysfunction–Associated Steatotic Liver Disease–ALT and AST at diagnosis and annually
  - Biopsy only gold-standard diagnostic procedure
  - Treatment unclear
    - Reduction in weight and carbohydrate intake
    - Vitamin E 800 IU/day
    - Metformin
    - Incretin based therapies
- Referral to gastroenterology should be considered for persistently elevated or worsening transaminases

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Other screening

- Polycystic ovary syndrome - evaluate for symptoms and treat as indicated
- Sleep Apnea - screen for symptoms at every visit and refer as needed
- Depression and eating disorders - assess for depression, anxiety, and eating disorders at all visits
- Smoking assessment and cessation
- Preconception counseling

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Audience response questions

Question 1

Of the following, which is the last to occur in the sequence of events leading to clinically apparent T2D?

A) decrease in serum adiponectin

B) increased DPP-1 inhibition of GLP-1

C) loss of first-phase insulin secretion

D) loss of second-phase insulin secretion

E) worsening of pubertal insulin resistance

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Question 1

- The final step in the development of T2D is loss of 2nd phase insulin response following IV glucose challenge
- Loss of 1st phase response is the earliest identifiable β-cell abnormality and is present before clinically apparent diabetes
- A decrease in adiponectin is a marker of insulin resistance and occurs before any β-cell abnormalities are present
- DPP-4 is not an inhibitor of GLP-1
- Pubertal insulin resistance plays an important role in increasing risk for diabetes, but leads to hyperinsulinemia unless β-cell dysfunction is present

Question 2

A 14 year-old M is referred for evaluation of new-onset diabetes. He presented to his PCP for routine physical and was noted to be obese with BMI of 32 kg/m^2, acanthosis nigricans at his neck and in his axillae, and otherwise normal Tanner IV exam. Laboratory testing revealed a hemoglobin A1c of 6.8%, fasting glucose of 112 mg/dL, fasting insulin of 65 µU/ml

Of the following, the next best step in establishing the diagnosis of type 2 diabetes is:

A) Fasting C-peptide measurement

B) Fasting and 2-hour insulin measurement following 75 grams oral glucose

C) Fasting lipid panel

D) Pancreatic autoantibody determination

E) Repeat Hemoglobin A1c determination

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D) Pancreatic autoantibody determination

E) **Repeat Hemoglobin A1c determination**

Question 2

- The most important first step in this patient is establishing the diagnosis of diabetes
- The ADA criteria require repeat determination in the asymptomatic patient
- HbA1c must be performed in a certified chemistry laboratory; POC A1c are not acceptable for diagnosis
- Insulin and C-peptide measurements play no role in the diagnosis of diabetes. Elevated levels suggests T2D but are not diagnostic of diabetes or diabetes type
- Pancreatic autoantibodies distinguish T1D from T2D, but are not diagnostic of diabetes
- A fasting lipid panel is important to identify associated comorbidities but does not contribute to diagnosis of diabetes

Question 3

A 15 y/o F of Mexican descent presents with concerns of polyuria and polydipsia. Initial BG is 315 mg/dl. Her height and weight are at the 45th and 99th percentiles respectively. Her HbA1C is 9.1%. Serum electrolytes are normal. Urine analysis shows small ketones and 4+ glucose

Which one of the following statements reflects the best initial treatment choice?

A) Initial treatment should be with metformin, as long as liver and kidney function are normal

B) Insulin therapy should be initiated at diagnosis

C) Metformin plus a GLP-1 receptor agonist is likely more effective than metformin alone

D) The choice or insulin or metformin will depend on pancreatic autoantibody status

E) A combination of insulin plus metformin should be initiated regardless of whether the patient has type 1 or type 2 diabetes

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Question 3

- Insulin therapy should be initiated at diagnosis if HbA1C > 8.5%
- Insulin therapy is started before autoantibody results
- GLP-1 receptor agonists are currently not first line therapy
- Metformin can also be started at diagnosis but would not be initiated for suspected T1D