Pediatric type 2 diabetes: same as in adults?

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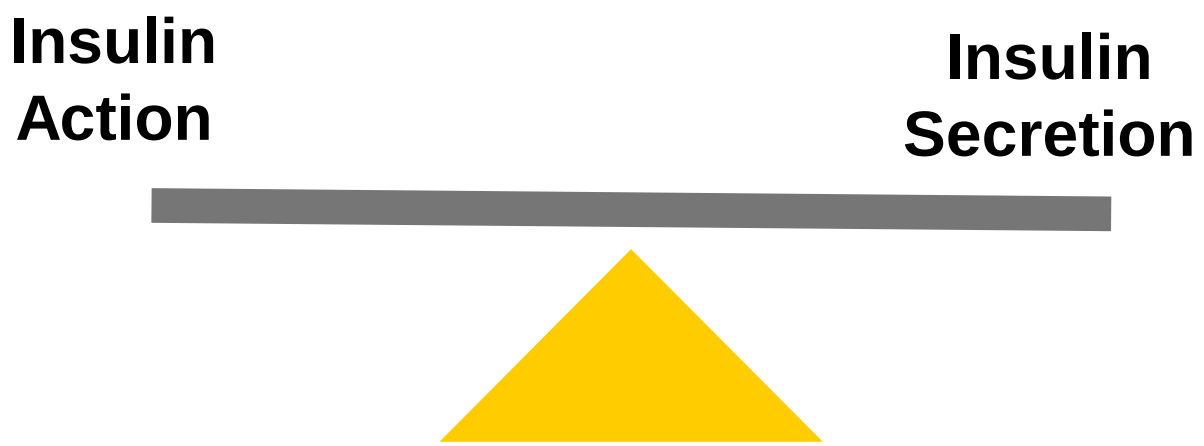
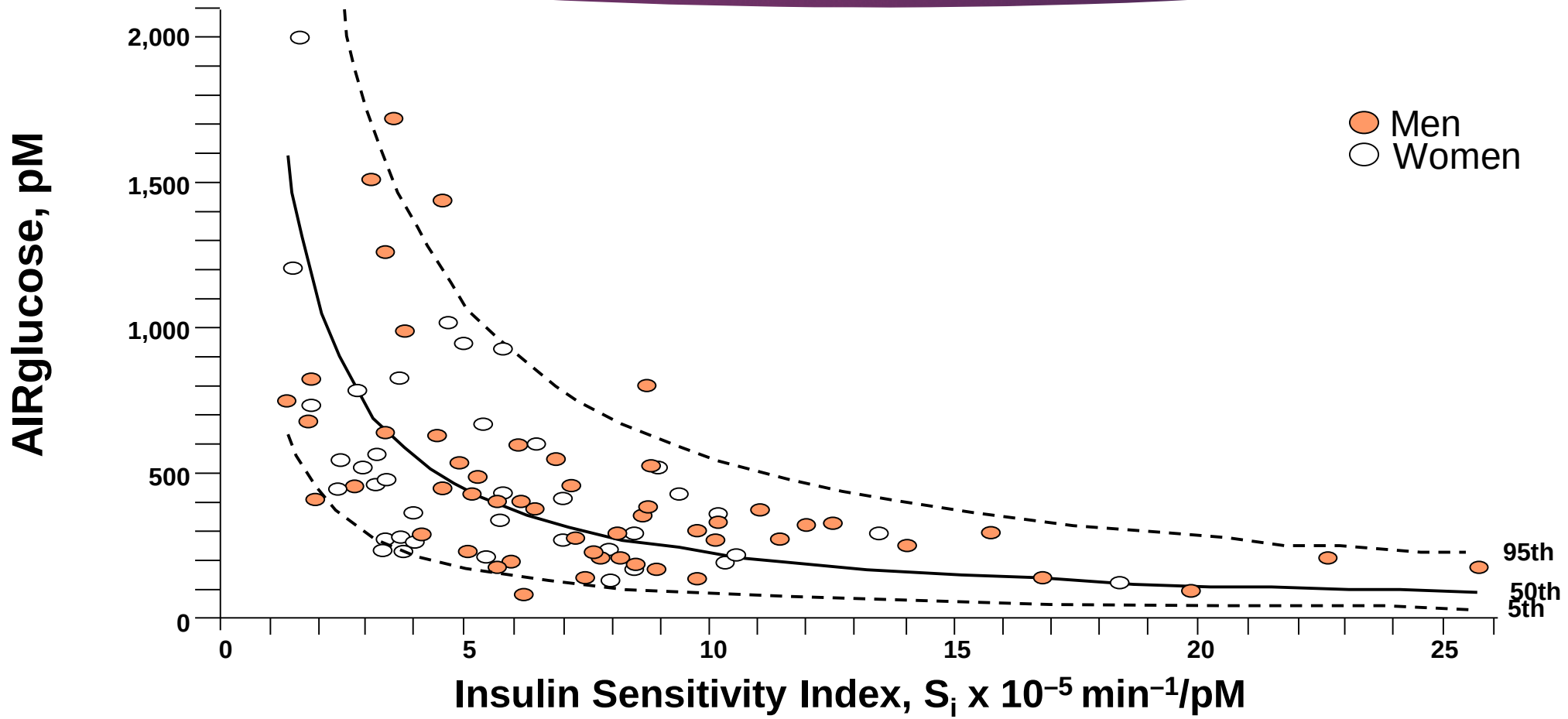
Glucose Homeostasis

- Balance Between Insulin action and secretion
- Diabetes occurs when this balance is lost

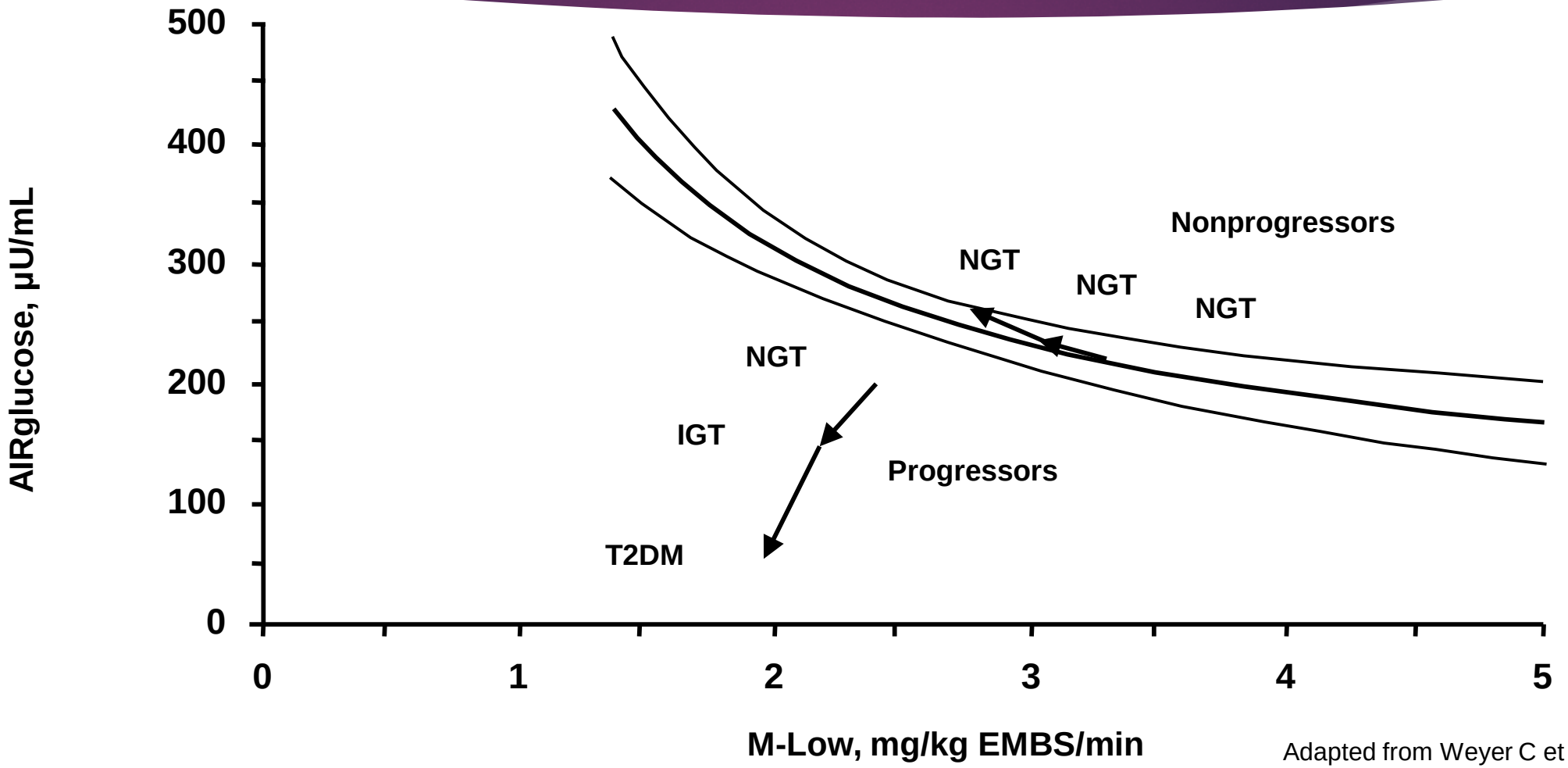


Insulin Sensitivity and Insulin Secretion in Healthy Subjects



Adapted from Vidal J, Kahn SE. In: Genetics of Diabetes Mellitus. 2001

Insulin Secretion and Insulin Action In the Development of Dysglycemia



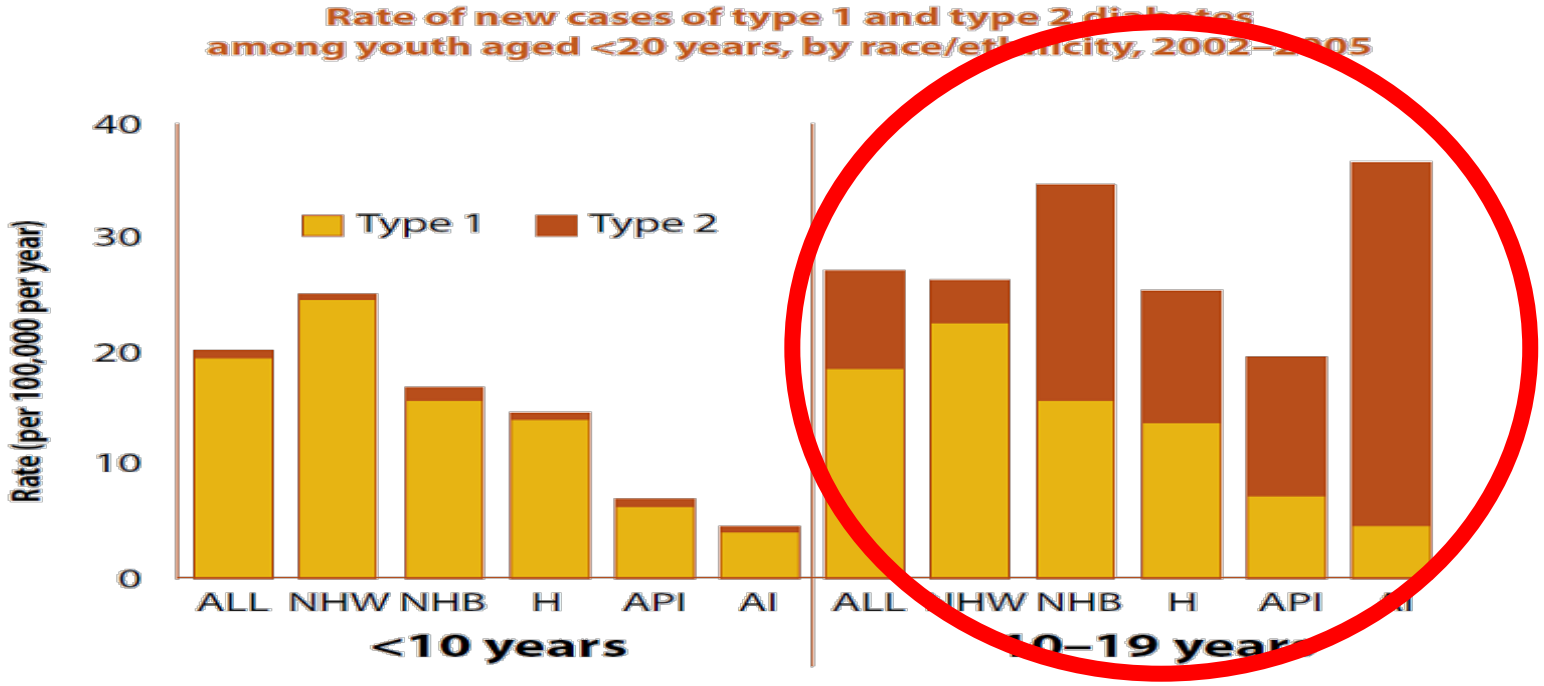
Adapted from Weyer C et al. J Clin Invest. 104, 1999.

US T2D Epidemiology: Adults versus Kids

	ADULTS	YOUTH (≤19 years)
Incidence (new cases/y)	**~1,469,000 per year**	**~5,100 per year**
Prevalence		
Overall	**12.3 per 100 *(12.3%)***	**0.5 per 1,000 *(~1 in 370 obese)***
10 - ≤14 years		**0.23 per 1,000 *(0.023%)***
15 - ≤19 years		**0.68 per 1,000 *(0.068%)***
20 - ≤44 years	**4.1 per 100 *(4.1%)***	
45 - ≤64 years	**16.2 per 100 *(16.2%)***	
65 and older	**25.9 per 100 *(25.9%)***	
Prevalence by Gender		
Male	**13.6 per 100 *(13.6%)***	**0.35 per 1,000 (0.035%)**
Female	**11.2 per 100 *(11.2%)***	**0.58 per 1,000 (0.058%)**

Nadeau et al Diabetes Care. 39:1635, 2016

Type 2 diabetes is rare in kids, but increases at puberty



Estimated prevalence in the US in 2009 – **20,000 to 40,000** under the age of 18

Liese et al. Pediatrics 2006

HEALTHY: the prevalence of undiagnosed diabetes is low

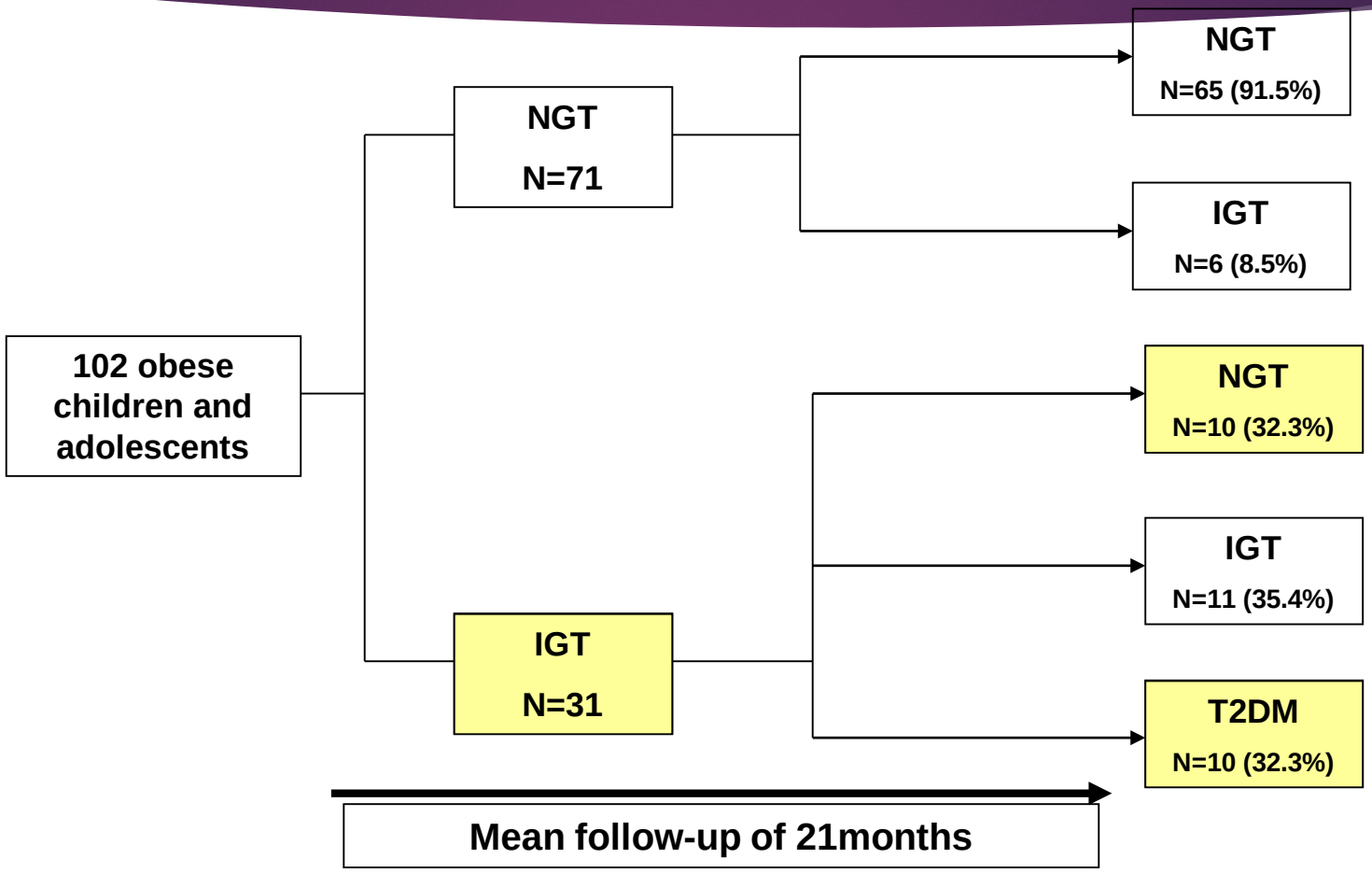
- 42 middle schools
  - ≥ 50% minority and/or
  - ≥ 50% eligible for free/reduced lunch

Measurement		6th grade N = 6367	8th grade N = 1740
BMI (kg/m^2)	Mean (SD)	22.4 (5.7)	24.3 (5.9)
BMI percentile (adjusted for age and gender)	< 85	50.5%	51.0%
	85-94	19.8%	19.8%
	≥ 95	29.7%	29.2%
Fasting glucose (mg/dL)	Mean (SD)	93.4 (6.7)	98.2 (8.5)
	< 100	84.0%	59.5%
	100-109	14.7%	34.3%
	110-125	1.2%	5.8%
	≥ 126	0.1%*	0.4%**
	*n=6 of which only 1 confirmed on follow-up testing; **n=7*		
Fasting insulin (μU/mL) ≥ 30		6.2%	36.2%

Diabetes Care 32:953;2009

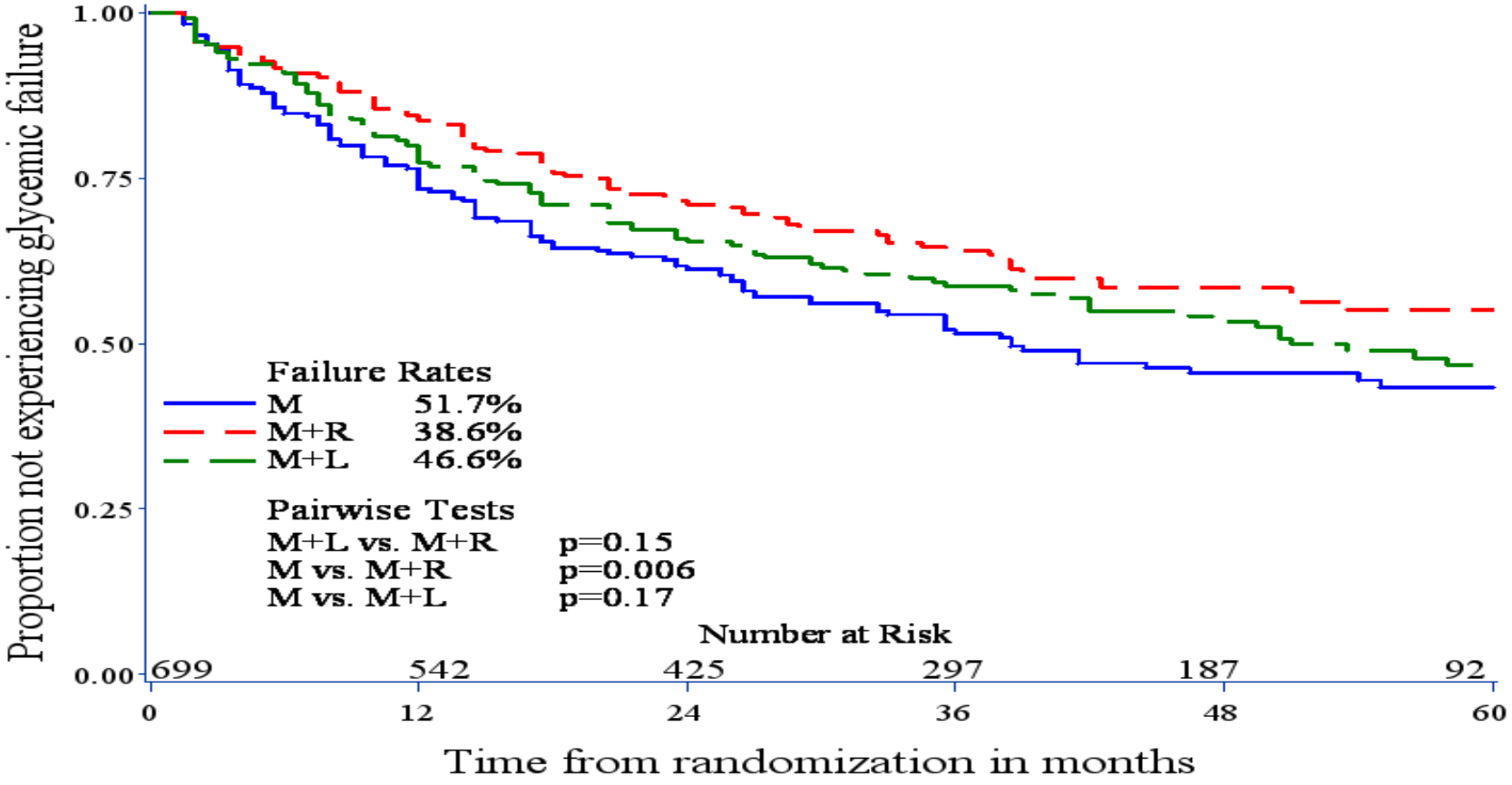
Diabetes Care 29;212;2006

Dysglycemia in youth has a high rate of spontaneous remission



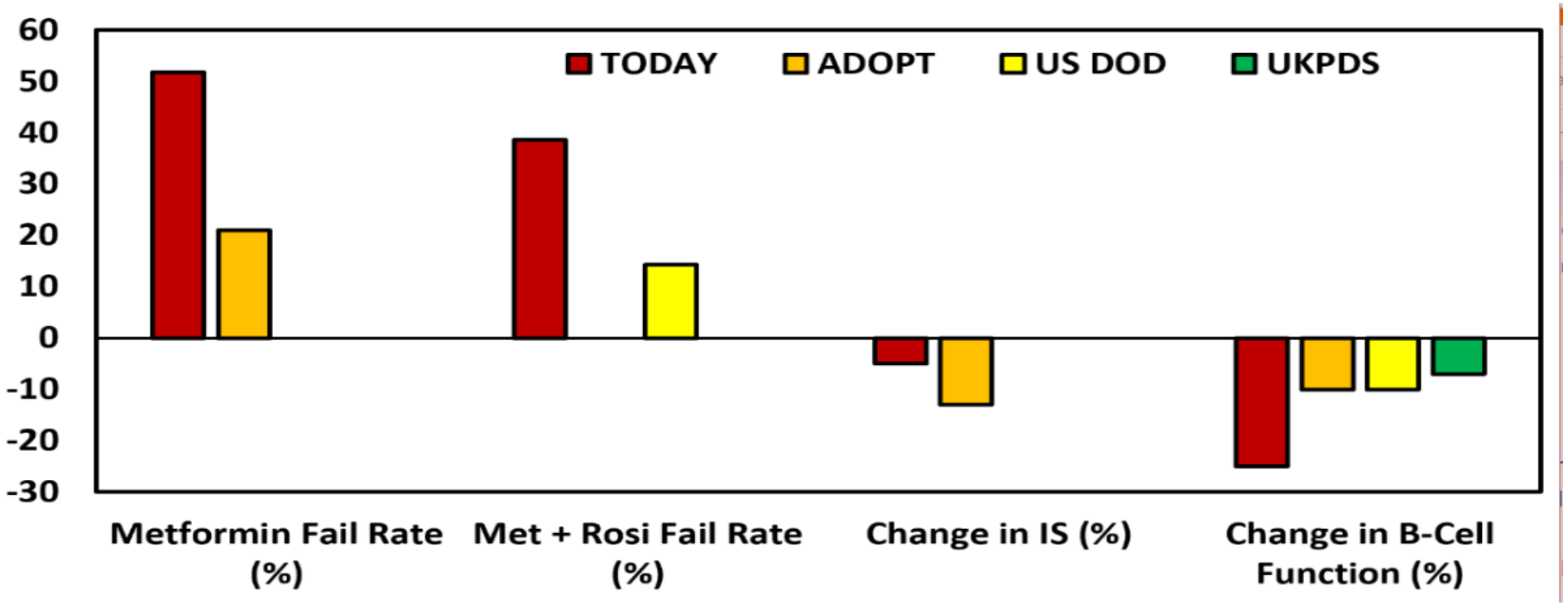
Weiss R. et al Diabetes Care 2005

Time to loss of glycemic control



TODAY N Engl J Med. 366:2247, 2012

Disease Progression With Treatment: *Kids versus Adults*



Nadeau et al Diabetes Care. 39:1635, 2016

Summary: pediatric type 2

- Lower prevalence
- Female preponderance
- Close association with puberty
- Higher rate of spontaneous improvement
- Faster loss of β-cell function
- Also:
  - 30-50% of youth with type 2 diabetes have renal hyperfiltration at diagnosis
  - Fatty liver disease is highly prevalent
  - More racially and socioeconomically challenged than adult type 2 populations

FDA

MOA Class	Drug	T2D Adult FDA Approval	T2D Children FDA Approval	T2D Children Clinical Evaluation*
Sulfonlyurea	Glyburide	1984, May	No	None
	Glipizide	1984, May	No	None
	Glimepiride	1995, November	No; included in USPI	Gottschalk et al. 2007
Biguanide	Metformin	1995, March	Yes, 2000, December	Jones et al. 2002
Alpha glucosidase inh	Acarbose	1995, September	No	None
Meglitinide	Repaglinide	1997, December	No	None
	Nateglinide	2000, December	No	None
Thiazolidinedione	Rosiglitazone	1999, May	No; included in USPI	Not published
	Pioglitazone	1999, July	No	Small; not published
Amylin analogue	Pramlintide	2005, March	No	None
GLP-1 analogue	Exenatide	2005, April	No	S/E study ongoing
	Liraglutide	2010, January	No	S/E study ongoing
	Exenatide LAR	2012, January	No	S/E study pending
	Albiglutide	2014, April	No	S/E study pending
	Dulaglutide	2014, September	No	S/E study pending
DPPIV inhibitor	Sitagliptin	2006, October	No	S/E study ongoing
	Saxagliptin	2009, July	No	S/E study ongoing
	Linagliptin	2011, May	No	S/E study ongoing
	Alogliptin	2013, January	No	S/E study ongoing
Bile acid sequestrant	Colesevelam	2009, October (diabetes)	No	S/E study ongoing
SGLT-2 inhibitor	Canagliflozin	2013, March	No	S/E study pending
	Dapagliflozin	2014, January	No	S/E study pending
	Empagliflozin	2014, August	No	PK ongoing
Dopamine agonist	Bromocriptine	2009, May (diabetes)	No	PK ongoing

FDA and Clinicaltrials.gov web sites

Completed studies to date

- **Rosiglitazone**: 24-week, randomized, double blinded, active control (no placebo).
  - At Week 24, the mean change from baseline in HbA1c was -0.14% with rosiglitazone and -0.49% with metformin
  - Insufficient power to demonstrate noninferiority
- **Glimepiride**: 24-week, randomized, double blinded, active control (no placebo).
  - At week 24, the mean change from baseline in HbA1c −0.95% with glimepiride and −1.39% with metformin.
  - Insufficient power to demonstrate noninferiority.
- **Glucovance (metformin/glyburide):** 26-week randomized, three arm-active controlled trial (glucovance vs. metformin vs. glyburide).
  - At week 26, the mean change from baseline in HbA1c was -0.80% with glucovance, -0.48% with metformin, and -0.96% with glyburide.
  - Glucovance not superior to either monotherapy.

http://wayback.archive-it.org/7993/20170722034802/https:/www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm328603.htm

EMA

Drug	Anticipated Completion Date
taspoglutide	March 2017
empagliflozin	February 2019
exenatide	July 2019
alogliptin	May 2020
insulin peglispro	June 2020
albiglutide	April 2021
omarigliptin	February 2022
dulaglutide	June 2022
lixisenatide	October 2022
sotagliflozin	February 2024
human recombinant interleukin-2	September 2024
ertugliflozin	March 2026
glucagon receptor antagonist	July 2027

Dilemma

- A total of ~ 5000 subjects are needed to complete current and planned trials
  - 12-15 % of all existing pediatric age type 2 diabetes patients in the US
- More mandated pediatric studies can be expected in the next few years.

Scarcity of eligible subjects for pediatric T2D trials

Total pediatric T2D population (~20-25,000 US*; 100%)

Socioeconomically challenged population, with many inherent barriers in daily living

Patients out of reach to study PIs

- Aggressive early treatment
- Receiving care at clinical care-only facilities
- Receiving care at research sites without dedicated pediatric T2D teams (e.g. T1D focused)

# of patients at sites active in T2D clinical trials (<20 %, a guesstimate)

"Pre-Screen" Failure

- Unlikely to be eligible – controlled on metformin, or insulin, A1c too high, high LFT, age >17 years old…
- Unlikely to adhere to research protocol, cannot be reached, no-show

# of patients approached for screening (<5 %, a guesstimate)

Screen Failure

- Unwilling to participate; cannot comply with study visits
- Inclusion/Exclusion criteria not met

Eligible subjects for pediatric T2D trials (1-2 %**) **cf: TODAY randomized 699 in 4.7 years**

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Thank you for your attention