Type 2 Diabetes in Youth (and other complications of obesity)

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Disclosures

- Dr. Styne will mention medications that are not approved for children
- Dr. Styne has no financial interest in any treatments mentioned

Objectives
At the Conclusion of This Session The Participant Will Be Able to :

- Understand the Etiology of Type 2 Diabetes Mellitus
- Understand the Epidemiology of Type 2 Diabetes
- Understand the Diagnosis of Type 2 Diabetes
- Understand the Treatment of Diabetes

Type 2 Diabetes in Youth (and other complications of obesity)

- The Problem
- The Cause
- The Diagnosis
- The Treatment
  - T2DM
  - Nephropathy
  - Hypertension
  - Dyslipidemia

First Notice?

7-14 Years Old

CLINICAL AND COMMUNITY STUDIES

ÉTUDES CLINIQUES ET COMMUNAUTAIRES

Non-insulin-dependent diabetes mellitus in Indian children in Manitoba

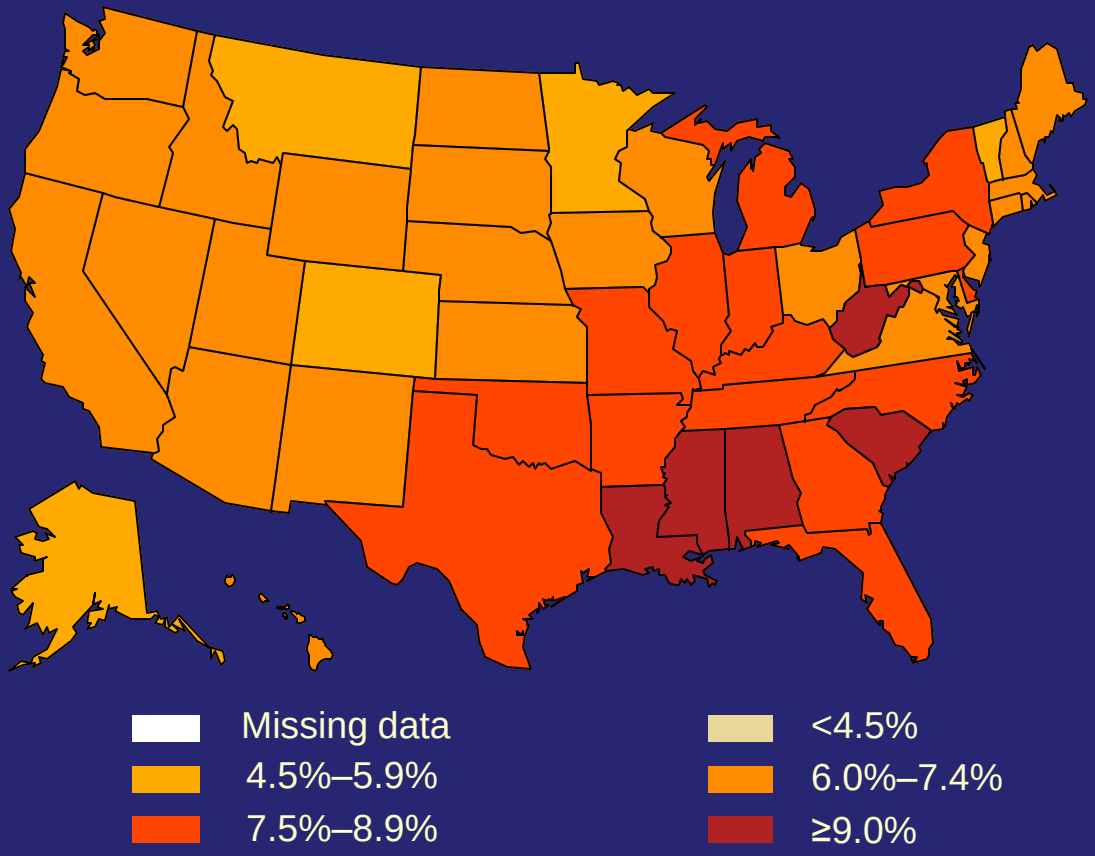
CAN MED ASSOC J 1992; 147 (1)

A Pending Epidemic? Type 2 (Adult Onset) Diabetes Mellitus During Childhood

- Recognized in Native American children in first
- A 10 fold increase noted by 1995 in Cincinnati
- Found internationally where obesity increases
- Presently 8-45% of new DM
- 2006: T2 DM prevalence estimates 1.54 / 1000
- By 2030, type 2 predicted to be more common than type 1 diabetes in youth
- Probably will cause early kidney, eye and cardiac disease based upon results of young adult onset

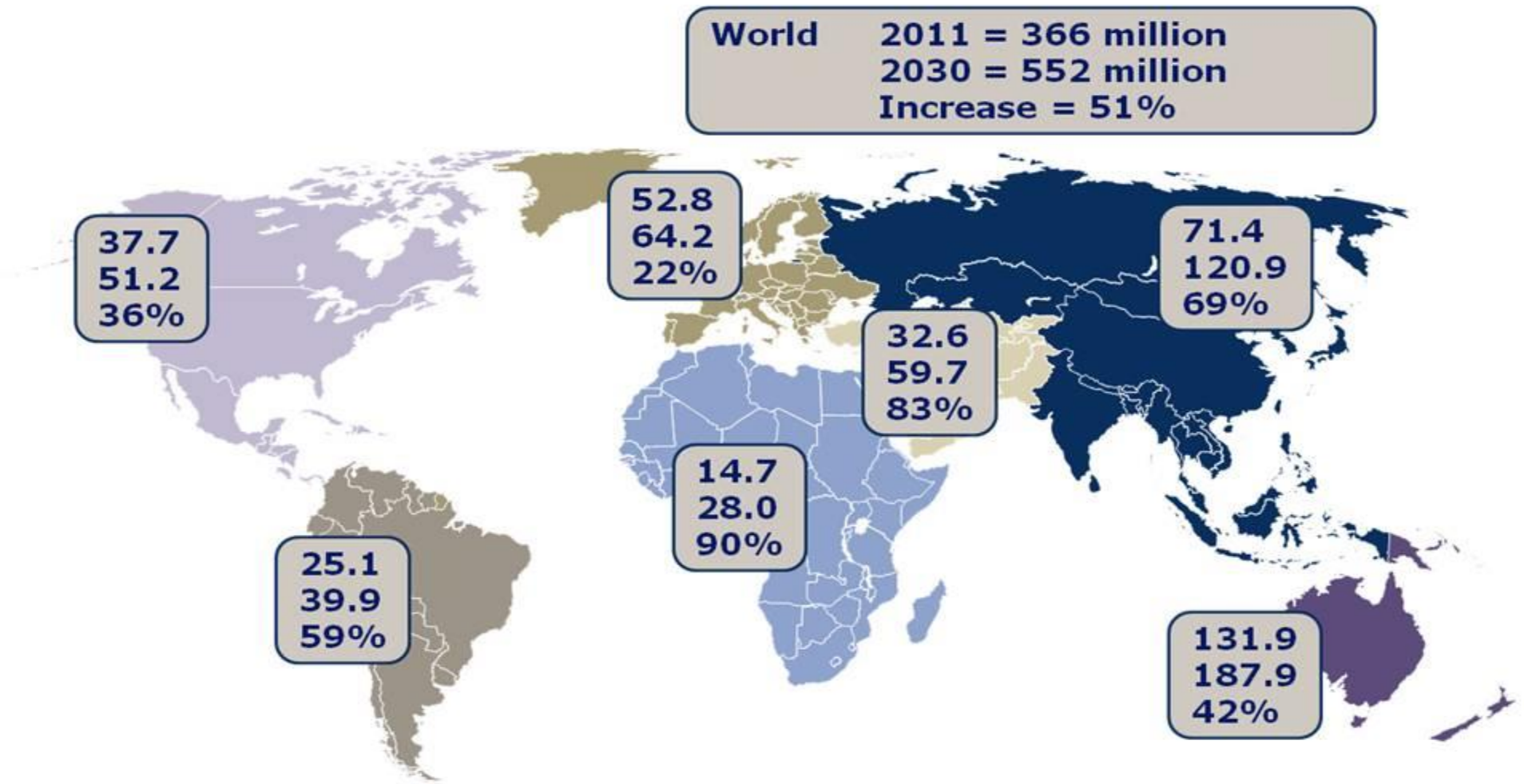
Age-Adjusted Prevalence of Diagnosed Diabetes Among U.S. Adults

2005



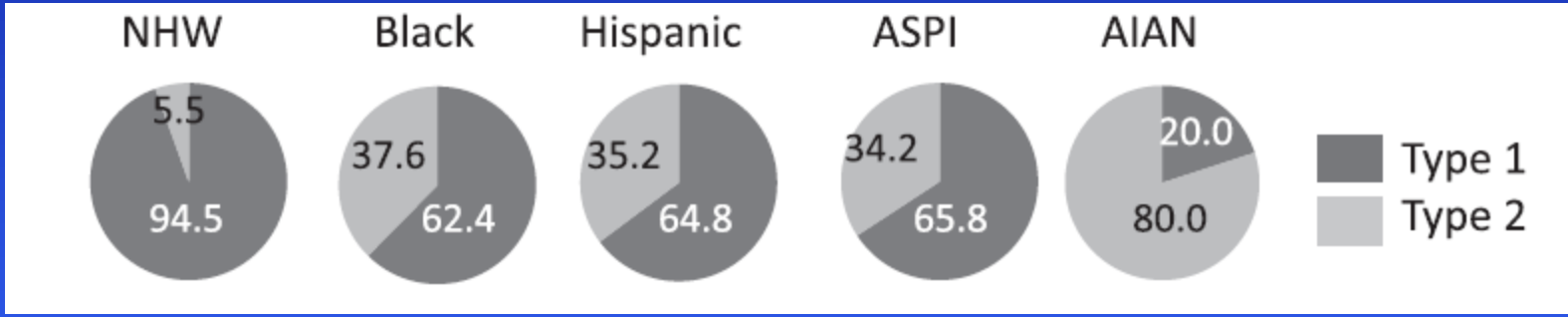
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

The Diabetes Epidemic: Global Projections, 2010–2030



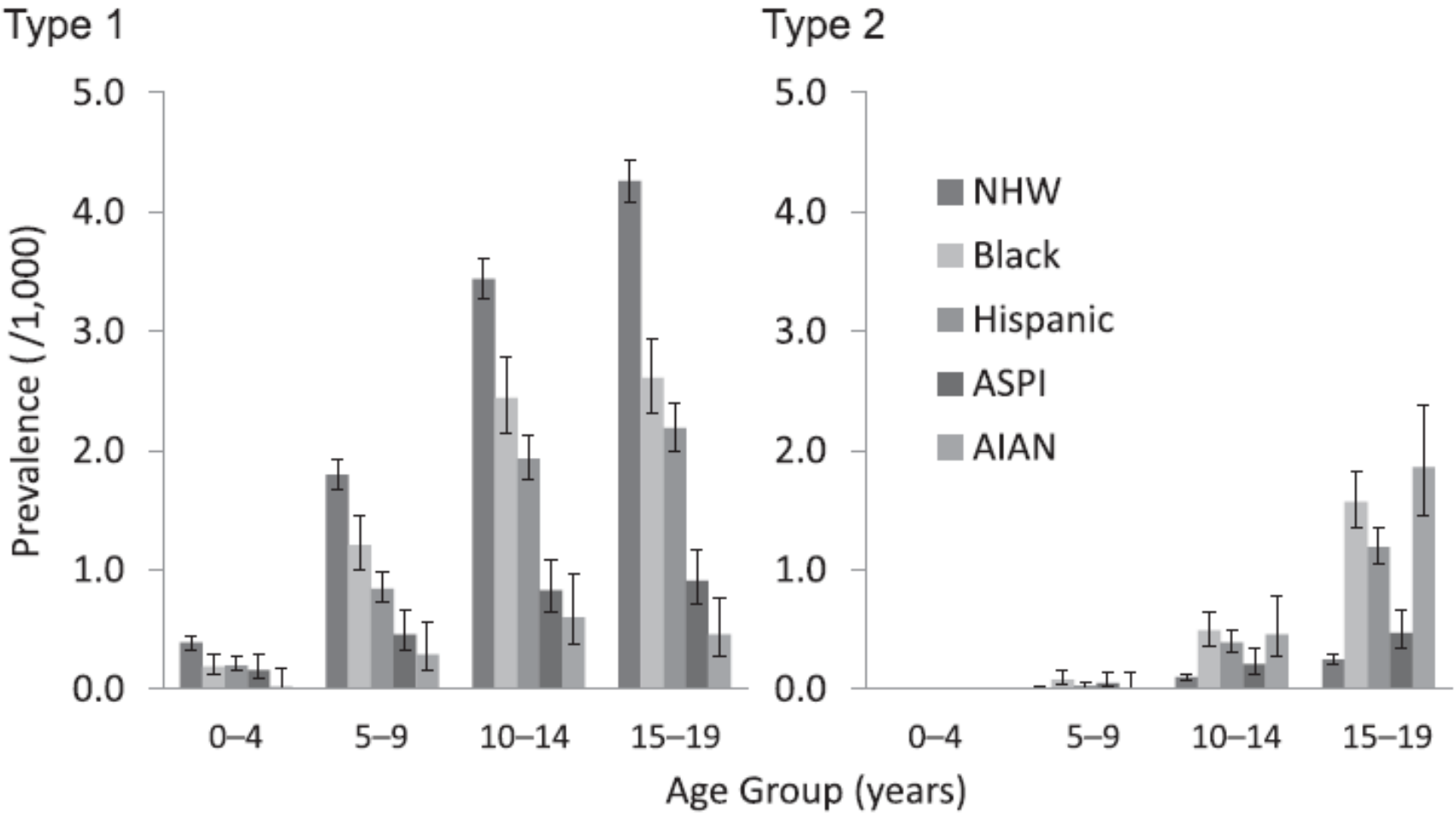
IDF. Diabetes Atlas 5th Ed. 2011

Prevalence of Diabetes in U.S. Youth in 2009: The SEARCH for Diabetes in Youth Study



Pettitt, D. J., et al. (2014). "Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study.“ Diabetes Care **37(2): 402-408.**

Prevalence of Diabetes in U.S. Youth in 2009: The SEARCH for Diabetes in Youth Study



Diabetes Care **37(2): 402-408.**

Obesity and type 2 diabetes mellitus in a birth cohort of First Nation children born to mothers with pediatric-onset type 2 diabetes

- Historical evidence indicates that the Oji-Cree people did not have diabetes before colonization and at the beginning of the 20th century.
- As of April 2008, 7/28 (25%) of the offspring aged 7–19 years have diabetes including 6/14 (43%) aged 10–19 years. All of the 7 offspring with diabetes have 1 or 2 copies of the G319S polymorphism.
- Conclusions: The prevalence of type 2 diabetes in this cohort of offspring of First Nation women with pediatric-onset type 2 diabetes is the highest ever reported.

Mendelson, M., et al. (2011). "Obesity and type 2 diabetes mellitus in a birth cohort of First Nation children born to mothers with pediatric-onset type 2 diabetes." Pediatr Diabetes **12(3 Pt 2): 219-228.**

Type 2 Diabetes in Youth (and other complications of obesity)

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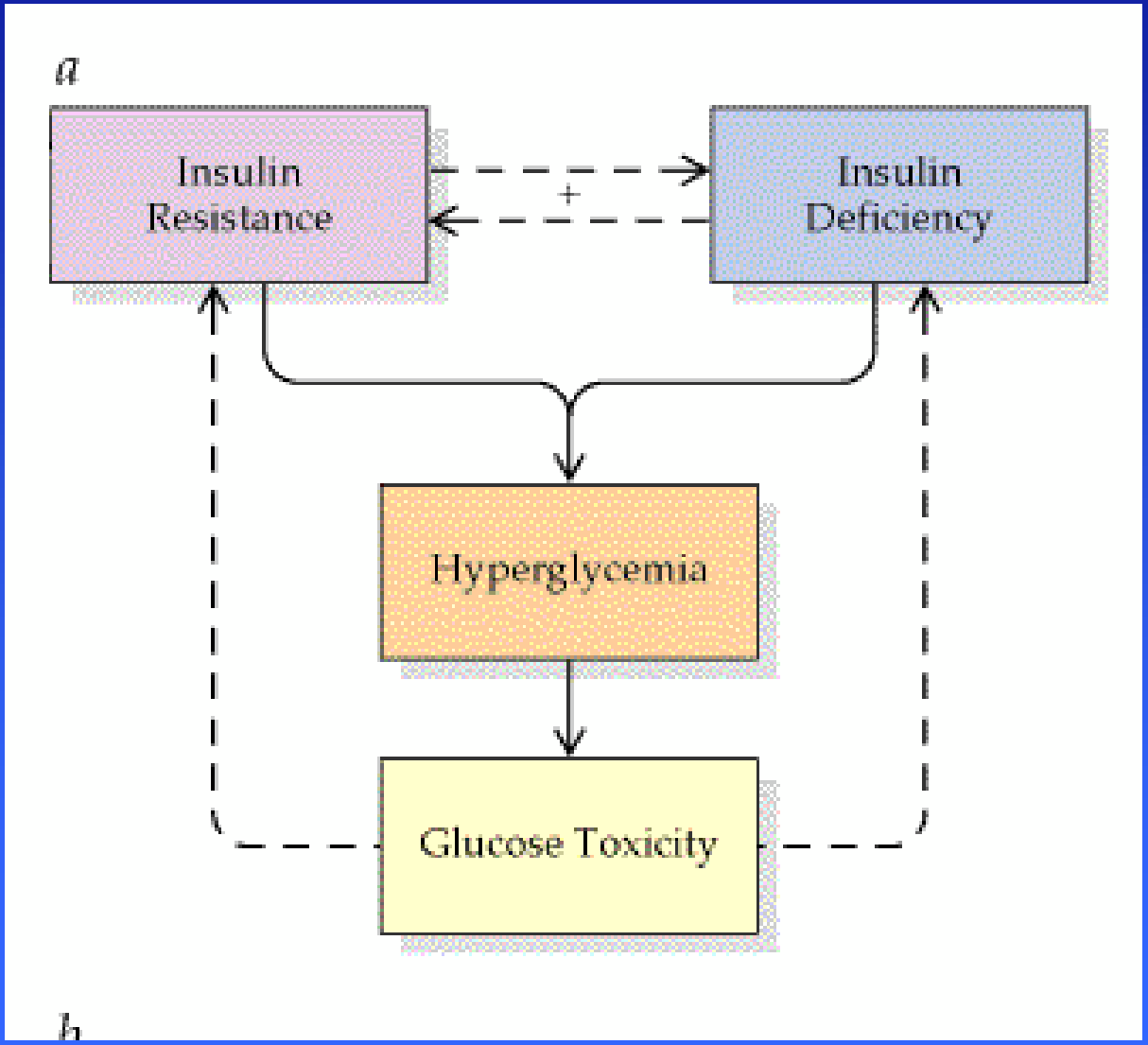
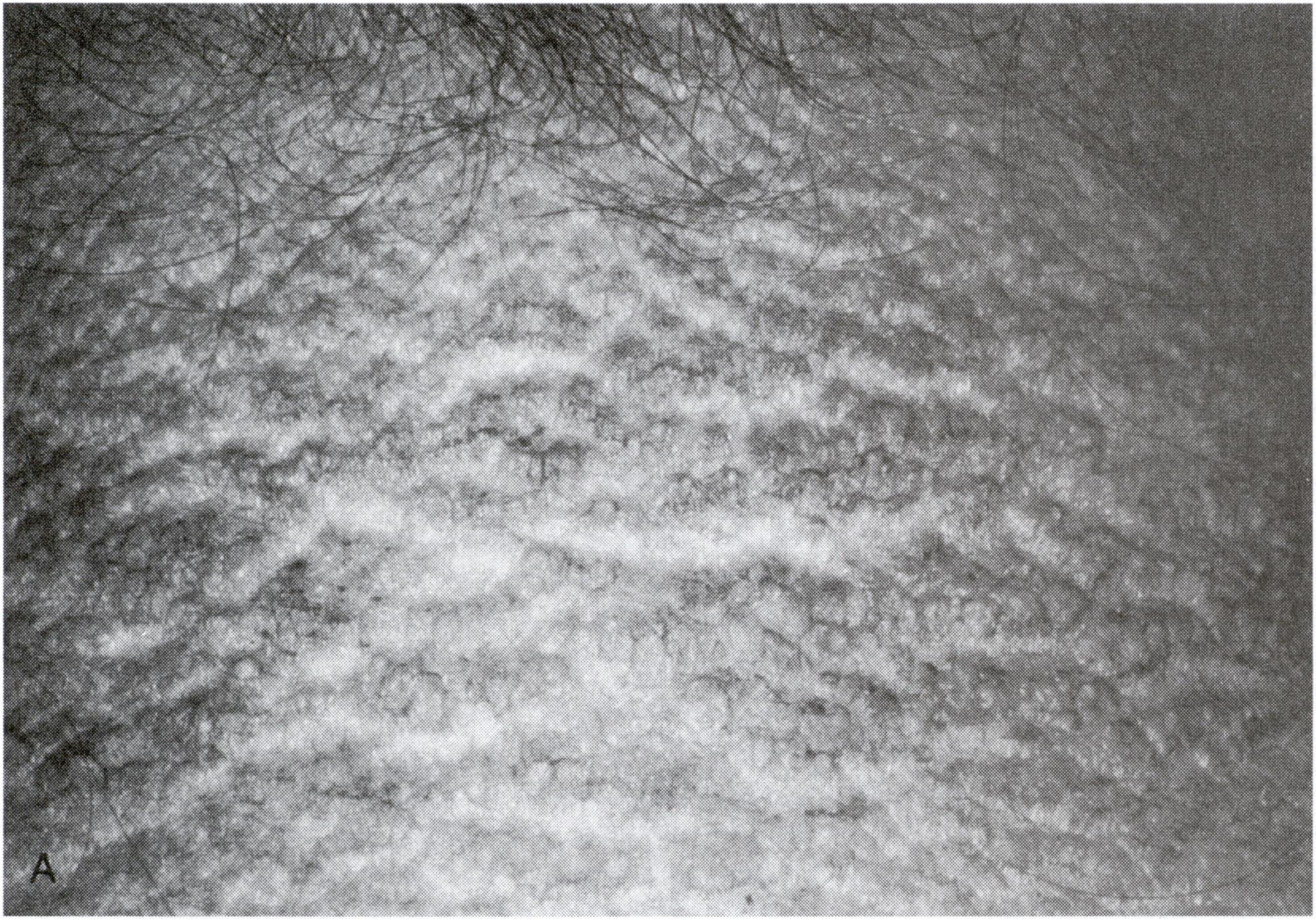
  - T2DM
  - Nephropathy
  - Hypertension
  - Dyslipidemia

Type 2 Diabetes Requires Insulin Resistance and Relative Insulin Deficiency



When Do We Suspect Diabetes?

- Classic polyuria, polydipsia
- Unexplained and unplanned weight loss
- Obesity (BMI > 95th%) in the Teen Years
- Overweight (BMI 85-95%) with risk factors
  - Family History
  - Acanthosis Nigricans
  - Other Signs or Symptoms of Insulin Resistance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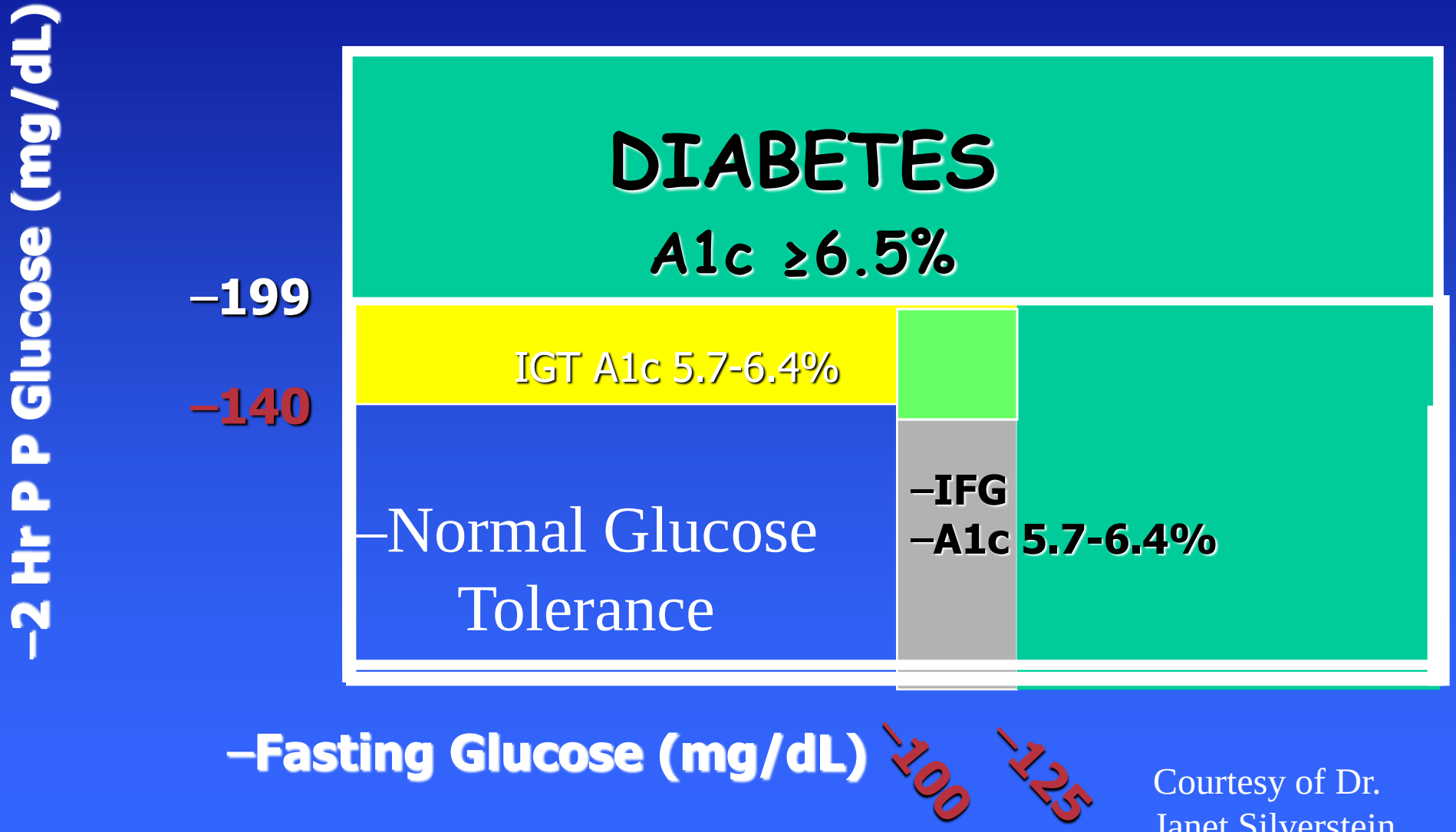
The Diagnosis of Diabetes Mellitus

Glucose tolerance test after 1.75 gm/kg carbohydrate load (75 grams maximum)

Condition	Fasting BS	1 Hour BS	2 Hour BS	3 Hour BS
Normal BS	<100	<200	<140	<130
Insulin (mu/ml)	9	51	37	20
C-peptide ng/ml	1.3	3.3	3.0	2.0
Impaired Glucose Tolerance (IGT)	101-125		140-199	130-199
Diabetes Mellitus (DM)	>126	>200	>200	>200

Diagnostic Criteria for Diabetes and Pre-Diabetes



Courtesy of Dr. Janet Silverstein

IGF, IGT in Adolescents 12-19 years old NHANES 2005-2006

IFG	IGT	Pre-Diabetes
13.1%	3.4%	16.1%

Li C, et al. Diabetes Care 32(2):342-347; Feb 2009

Predictors of Pre-Diabetes

- Overweight sibling of child with T2DM
  - 40% of OW (>95% BMI) sibs vs 14% OW controls without a T2DM sib had abnormal IGT*
- 2 of the following cardiometabolic risk factors:
  - Central obesity
  - TG> 150 mg/dL
  - HDL-C< 40 mg/dL
  - HTN
- Infant of a mother with diabetes during pregnancy

*Magge SN et al. J Pediatr: 562-566; Apr 2009

Testing for Type 2 Diabetes in Children

- **Criteria*: Overweight (BMI> 85th %ile for age and sex, wt for ht >85th %ile, or wt > 120% of ideal for ht)**

PLUS: any two of the following risk factors:

- **Family history of DM 2 in 1st or 2nd degree relative**
- **Race/Ethnicity**
- **Signs of insulin resistance**

- **Age of Initiation: age 10 or at onset of puberty**
- **Frequency: every two years**
- **Test: Fasting plasma glucose preferred**

***Clinical judgment should be used to test for diabetes in high risk patients who do not meet these criteria.**

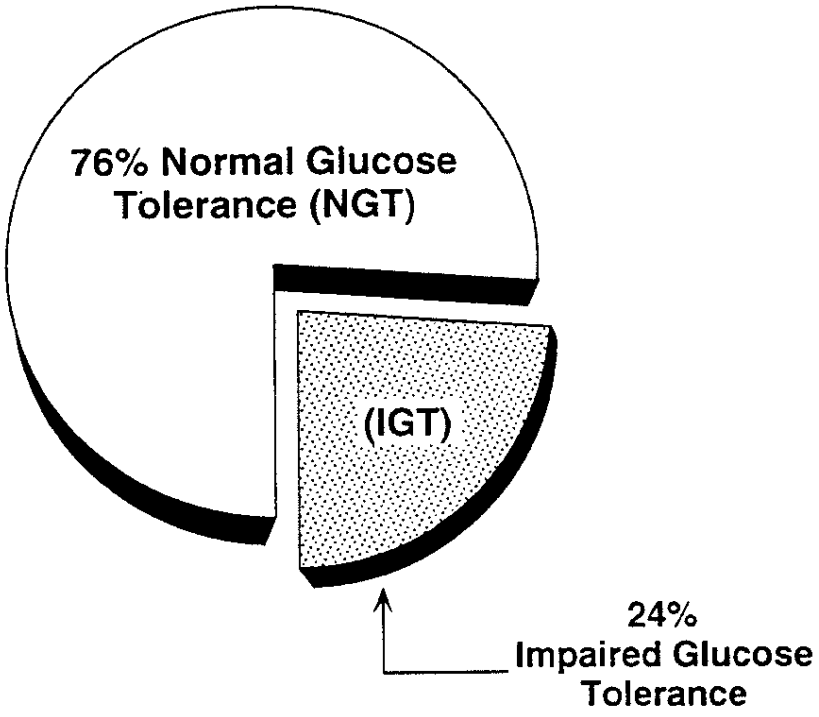
ADA/AAP Recommendations, Diabetes Care 23:2000

When Should we do a Glucose Tolerance Test in Childhood?

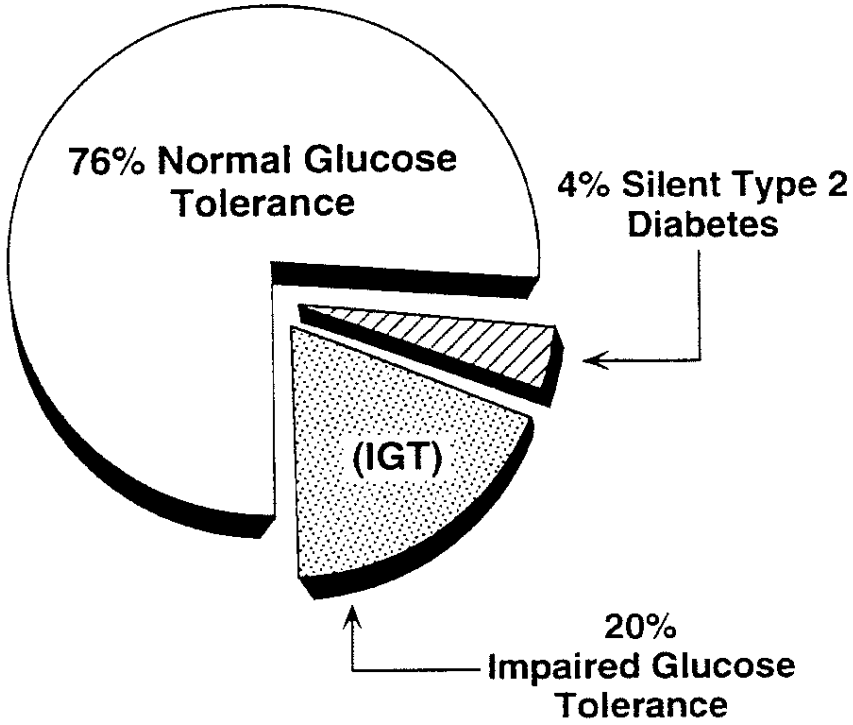
- Probably Never in Strongly Suspected 2 Diabetes
  - Fasting Hyperglycemia (>126 mg/dl) or casual BG (>200mg/dl) with Polyuria and Polydipsia and Weight Loss:
  - Even Obese Children Can Get Type 1 Diabetes Mellitus!
- Differentiate Type 1 from Type 2 in Difficult Cases?
  - Extremely difficult in the early “honeymoon” period
  - Antibody levels might help but not infallible
  - Two hour post prandial vs. oral glucose tolerance test after CH2O loading
  - C peptide determination, especially if insulin already administered

PREVALENCE OF IMPAIRED GLUCOSE TOLERANCE AMONG CHILDREN AND ADOLESCENTS WITH MARKED OBESITY

Obese Preadolescents



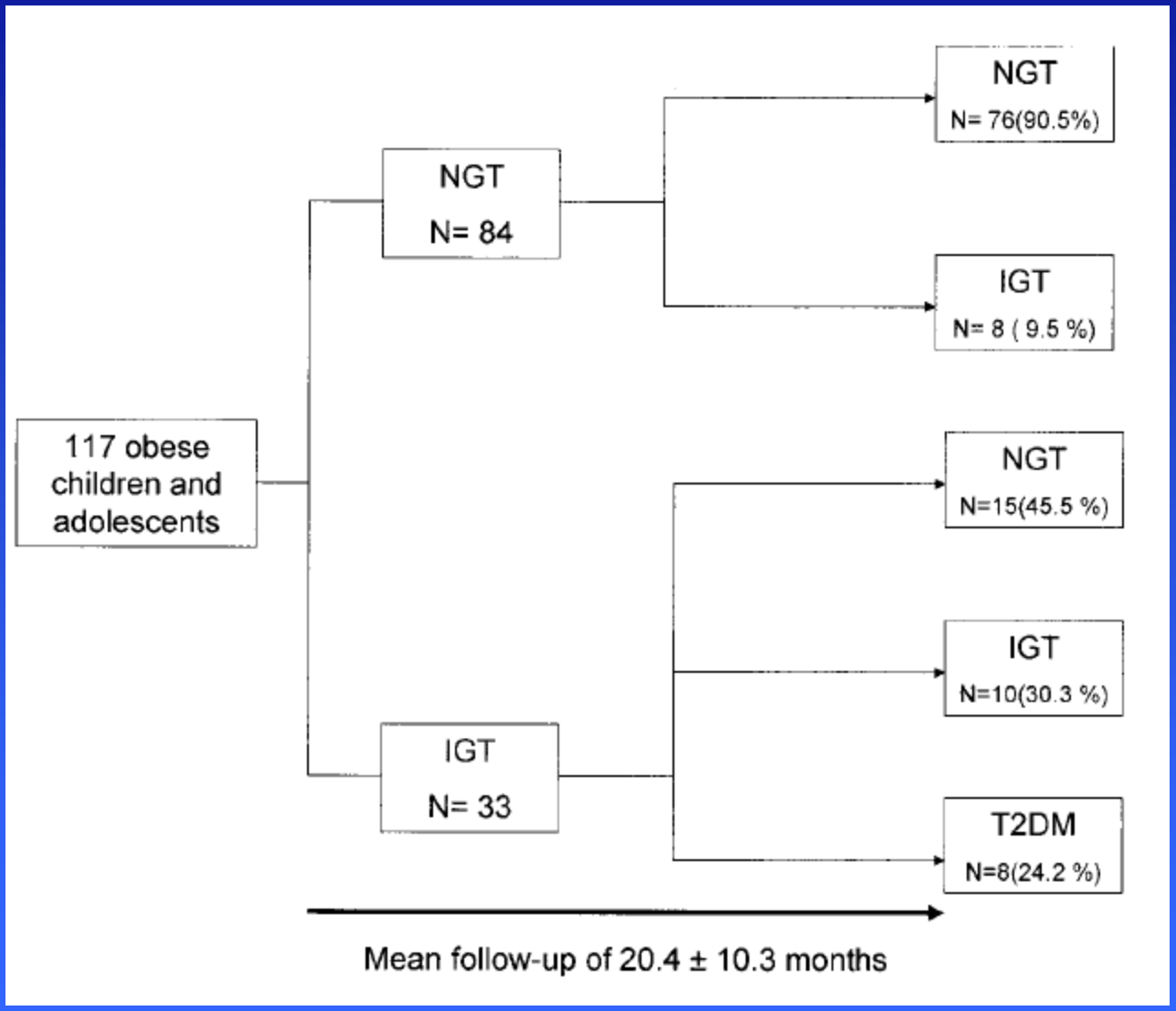
Obese Adolescents



RANJANA SINHA, M.D., GENE FISCH, PH.D., BARBARA TEAGUE, R.N., WILLIAM V. TAMBORLANE, M.D., BRUNA BANYAS, R.N., KARIN ALLEN, R.N., MARY SAVOYE, R.D., VERA RIEGER, M.D., SARA TAKSALI, M.P.H., GINA BARBETTA, R.D., ROBERT S. SHERWIN, M.D., AND SONIA CAPRIO, M.D.

(N Engl J Med 2002;346:802-10.)

Progression from Pre-Diabetes to Diabetes in Adolescents



Weiss R. et al. Predictors of Changes in Glucose Tolerance Status in Obese Youth. *Diabetes Care* 2005; 28:902-909

Progression from Pre-Diabetes to Diabetes in Adolescents

- Progressors and non-progressors had
  - same pubertal status and same age
  - same insulin sensitivity
  - significant slightly higher BG values in progressors
  - significantly lower β cell function in progressors
- At 30 months:
  - Si and β cell function deteriorated in progressors but stayed unchanged in non-progressors

- Cali AMG, et. al. Diabetes Care 32(3):456-461; Mar 2009

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  - Hypertension
  - Dyslipidemia

Type 1	Type 2
Not usually overweight Proportionate to obesity in general population	85% are overweight
Short course	Indolent Course
35-40% present with ketoacidosis	33% with ketonuria 5-25% may have ketoacidosis
5% with a 1st or 2nd degree relative with type 1	74-100% with 1st or 2nd degree relative with T2DM
Increased incidence of other autoimmune d/o: thyroid; adrenal; vitiligo; celiac. + antibodies	Increase in PCOS Acanthosis nigricans (in up to 90%) Increase in hypertension
Decreased C-peptide & Insulin No increase with glu challenge	Nl or increased C-P & Insulin Increase with glucose challenge
Caucasians predominate	NA; AA; Latino; Asian; Pacific Islander

Differences in Management Between T1DM and T2DM

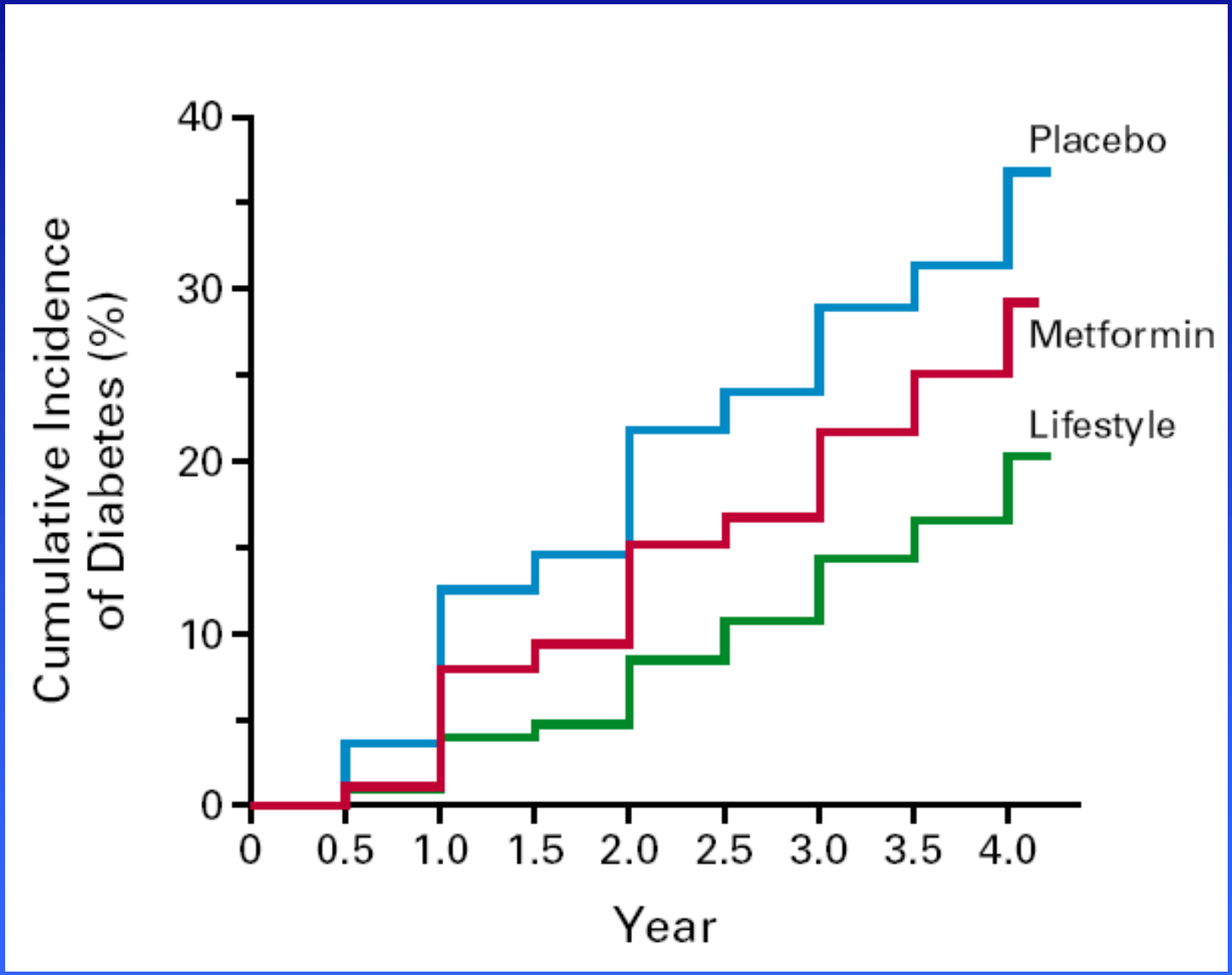
Type 1 DM

- Insulin is mainstay of treatment
- Lifelong insulin needed
- Monitor for complications after 10 yo and 3-5 yrs DM

Type 2 DM

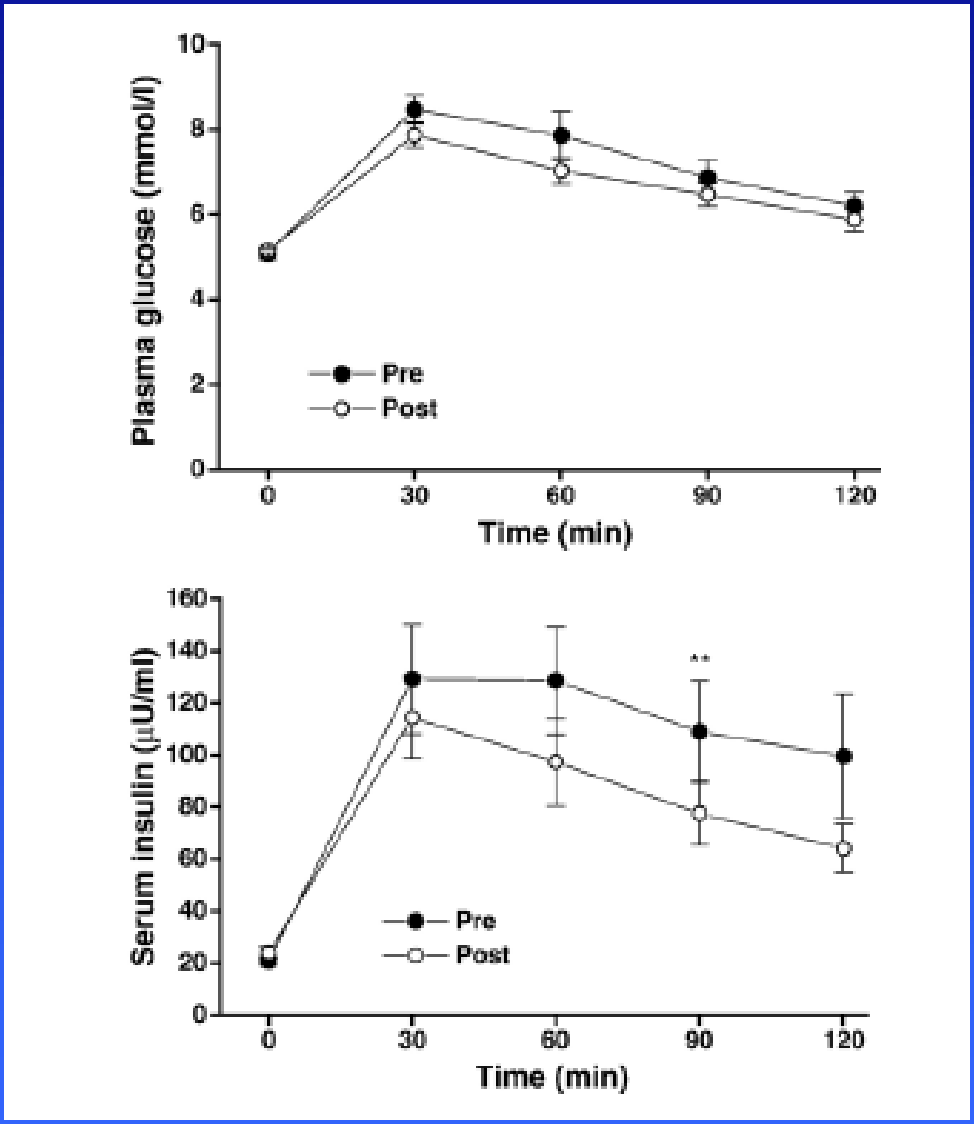
- Lifestyle modification is key treatment
- May not need insulin for first several years
- Monitor for complications at DM onset

Lifestyle Trumps Medication



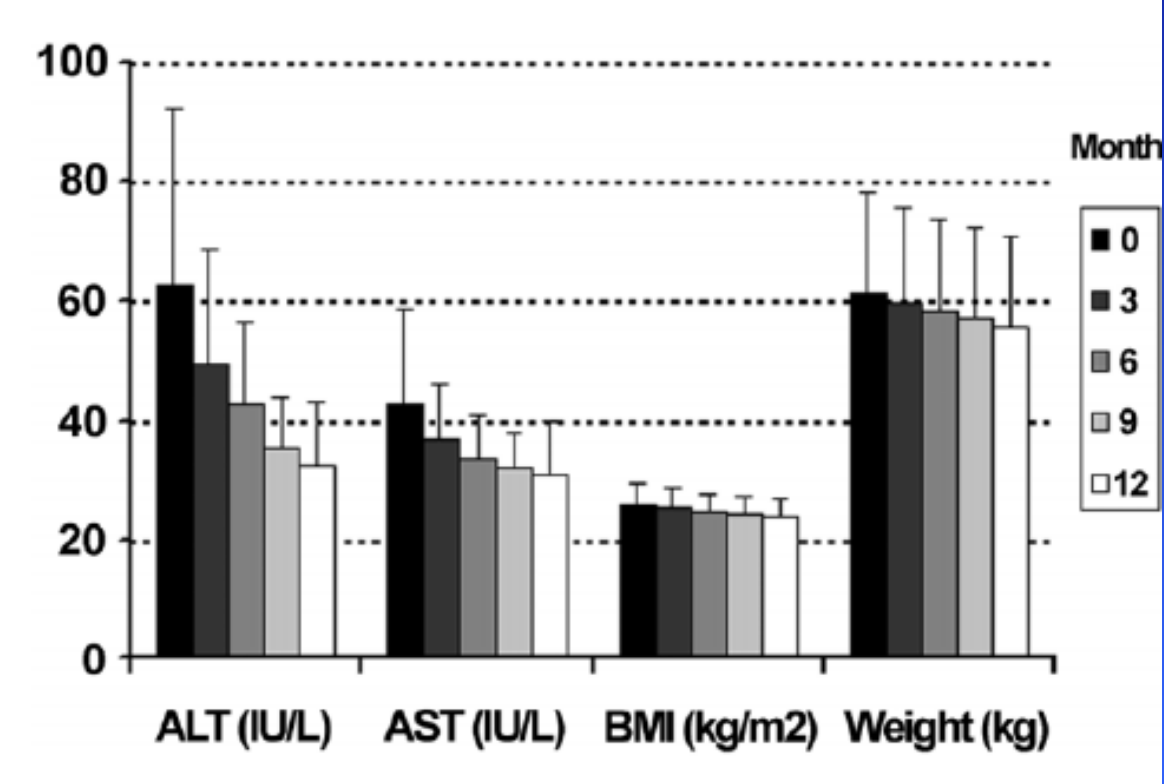
Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403.

Exercise Improves Insulin Sensitivity



Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. Nassis GP, Papantakou K, Skenderi K, Triandafillopoulou M, Kavouras SA, Yannakoulia M, Chrousos GP, Sidossis LS. Metabolism. 2005 Nov;54(11):1472-9.

LifeStyle Improves NAFLD



Nobili V, Marcellini M, Devito R et al. NAFLD in children: a prospective clinical-pathological study and effect of lifestyle advice. Hepatology 2006; 44(2):458-465.

AAP Key Action Statements

Clinicians encourage youth with T2DM to

- **Engage in moderate-to-vigorous exercise for at least 60 minutes daily**

- **Limit non- academic screen time to less than 2 hours a day.**

What Did we Learn from the DCCT?

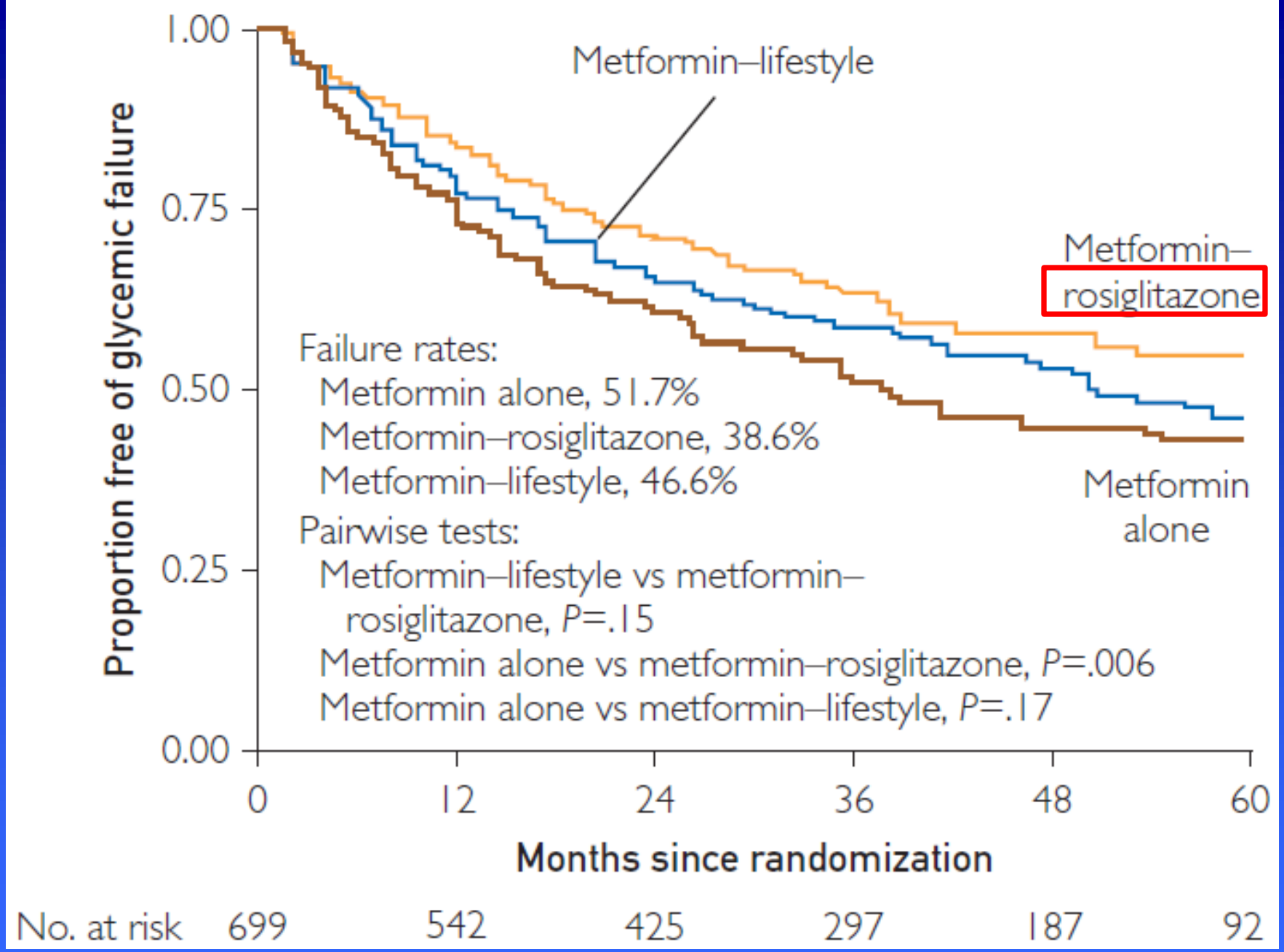
- Good control will forestall the complications of Type 1 Diabetes Mellitus
  - Retinopathy Development reduced by 76%
  - Retinopathy Progression reduced by 61%
  - Microalbuminuria development reduced by 56%
  - Neuropathy (adults) reduced by 60%
- Good control will increase the likelihood of hypoglycemic episodes
- Good control will best be achieved by the use of the team approach: Doctor, Nurse-educator, Dietician, Social Worker: this is the state of the art for therapy
- These findings probably will apply to Type 2 Diabetes Mellitus

AAP Key Action Statements

- **Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM**
  - **who are ketotic or in diabetic ketoacidosis**
  - **who have venous or plasma blood glucose levels $\geq$ 250 mg/dl**
  - **whose Hemoglobin A1c is > 9 percent; or**
  - **in whom the distinction between Type 1 and Type 2 diabetes is unclear.**

AAP Key Action Statements

In all other instances, clinicians should start metformin as first-line therapy for children and adolescents at the time of diagnosis with T2DM, and initiate a lifestyle modification program including nutrition and physical activity.



Narasimhan, S. and R. S. Weinstock (2014). "Youth-Onset Type 2 Diabetes Mellitus: Lessons Learned From the TODAY Study." Mayo Clin Proc.

AAP Key Action Statements

- Clinicians should monitor Hemoglobin A1c (A1c) levels every three months and intensify treatment if treatment goals for BG and A1c levels are not being met.
- A biological lie detector!

AAP Key Action Statements

- **Advise patients to monitor finger-stick BG levels in those who:**
  - **are taking insulin or other medications with a risk of hypoglycemia; or**
  - **are initiating or changing their diabetes treatment regimen; or**
  - **have not met treatment goals; or**
  - **have intercurrent illnesses.**

Initial Treatment of Blood Glucose

Symptoms	Blood Glucose	Ketones	Treatment
No	<250	Negative	Metformin
No	>250	Negative	Insulin ± Oral agents
Yes	>200s	Negative	Insulin
Yes	>200s	Positive	Insulin

Major Classes of Oral Medications

1. Drugs that sensitize the tissues to insulin and/or control hepatic glucose production → Thiazolidinediones*** Biguanides+++

2. Drugs that stimulate beta-cell insulin production → Sulfonylureas Meglitinides (short acting)

3. Drugs that slow the absorption of starches → Alpha-glucosidase inhibitors

4. Drugs that increase GLP-1 → Exenatide (injection!) DPP-4 Inhibitors

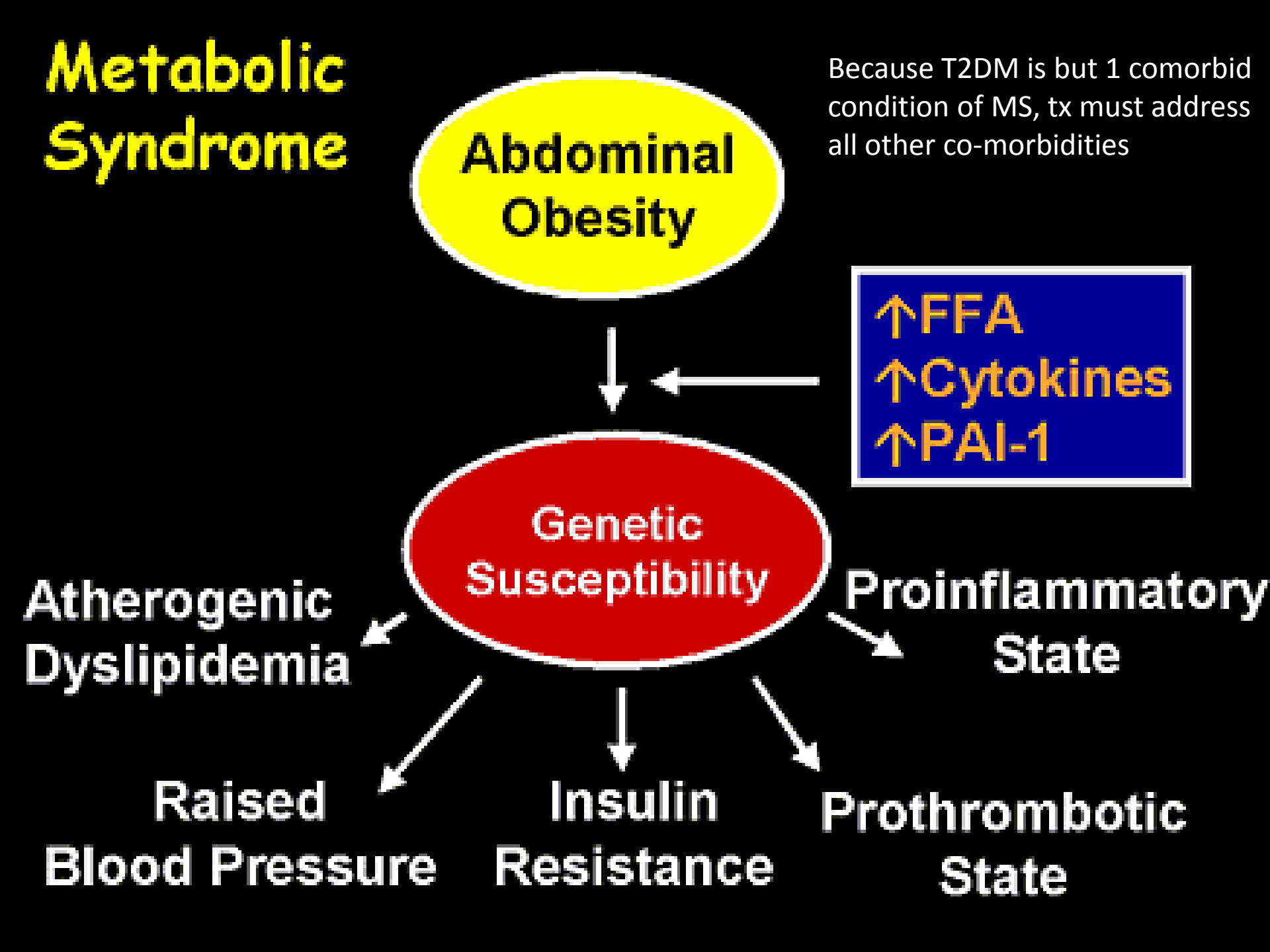
Glycemic Targets*

Parameter	Normal	Reasonable Goals
Fasting (or Preprandial) Glucose	<100	70-130
Postprandial Glucose	<140	<180
Bedtime BG	<120	90-150
HbA_{1c} (DCCT Method)	<6%	<7%

- Glucose values are plasma (mg/mL).

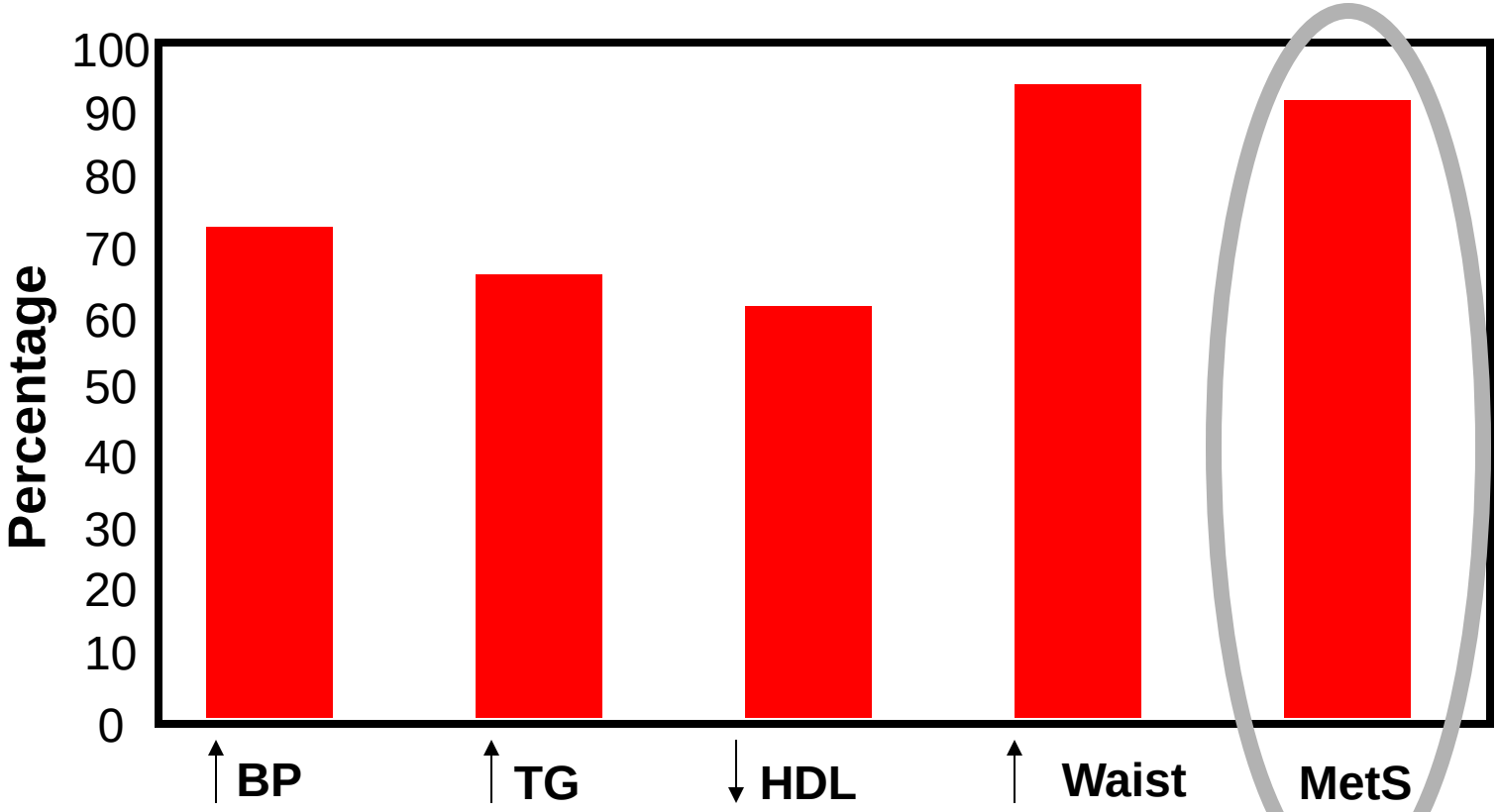
*Combined WHO recommendations and ADA guidelines.

Metabolic Syndrome



Because T2DM is but 1 comorbid condition of MS, tx must address all other co-morbidities

Prevalence of Cardiovascular Risk Factors and Metabolic Syndrome in Youth with Type 2 DM



Mayer-Davis 2008

Complications Occur Early in T2DM in ADOLESCENTS

Frequency Within 1.3 Years of DM Onset

- Microalbuminuria 28%
  (7% at 3 mos)
- Hypertension 36%

Mean A1c 7.3%.....thus, not due to poor glucose control

Eppens MC, et al. Diabetes Care 2006;29(6):1300-1306

Treatment Goals

- Weight reduction
  - decreases insulin resistance
- Normoglycemia and normal HbA1c
  - decreases microvascular disease
- *Control co-morbidities of insulin resistance, the most important contributors to macrovascular disease*
  - Hypertension
  - Dyslipidemia
  - Acanthosis
  - Hyperandrogenism: PCOS and hirsutism

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Microalbuminuria

- Normal <30 mg/gm creat on spot urine
- Represents inflammatory state of vessels
- Increased in white coat HTN and non-dippers
- Obtain 2 additional urine samples at least 1 month apart over the next 3-6 months
  - Ideally with first morning void
- If all 3 abnormal, treat with ACE-I

Micro to Macroalbuminuria

- Elevated albuminuria is infrequent and largely transient in nondiabetic youth, but is relatively frequent and largely persistent in those with diabetes. Microalbuminuria in youth with type 2 diabetes strongly predicts progression to macroalbuminuria, supporting annual screening for albuminuria.

Kim, N. H., et al. (2010). "Predictive value of albuminuria in American Indian youth with or without type 2 diabetes." Pediatrics **125(4): e844-851.**

Potential Ways To Decrease Risk of Nephropathy

Dart AB, Sellers EA, Dean HJ. Int J Pediatr. 2012; 2012: 237360. Published online Jan 2012

Clinical parameter	Intervention	Treatment target
Glycemic control	Lifestyle/Insulin/ Metformin	HbA1c ≤ 7%
Prehypertension (BP > 90th –95th)	Lifestyle	BP < 90th percentile
Hypertension (BP > 95th percentile)	Lifestyle ± Ace inhibitor or ARB	BP < 90th percentile
Dyslipidemia LDL ≥2.6mmol/L	Lifestyle	LDL < 2.6mmol/L
Dyslipidemia LDL >4.1mmol/L	Lifestyle + Statin	LDL < 2.6mmol/L
Overweight/ Obesity	Lifestyle	BMI < 85th percentile
Smoking	Cessation tools	Discontinue smoking

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Hypertension in Childhood Obesity

- Measure it right
  - Correct cuff
    - May be enormous
    - Repeat it
- Relate it to height
- Refer to Pediatrics 114:555-576 2004
- Ambulatory BP Urbina et. al. Hypertension 2008;52:433-451 NEW
- Remarkably low cutoffs that may surprise you

Hypertension in Childhood Obesity

- Life style modification first
  - Initial treatment: dietary (limit salt) and lifestyle interventions for weight reduction & exercise
  - If BP doesn't reach target of ≤ 95% for age, gender, height within 3-6 months, treatment with anti-hypertensive agent should be initiated

Hypertension in Childhood Obesity

- Therapy with “adult drugs”
  - ACE inhibitors particularly in diabetes
    - Anti-hypertensive
    - Anti-thrombotic: inhibits platelet aggregation & endothelin
    - Vasodilation: ↓ production of angiotensin II ; ↑ bradykinin levels
    - Limits smooth muscle proliferation & plaque rupture
    - Slows progression of nephropathy & retinopathy
    - THEY ARE TERATOGENIC; USE CONTRACEPTION

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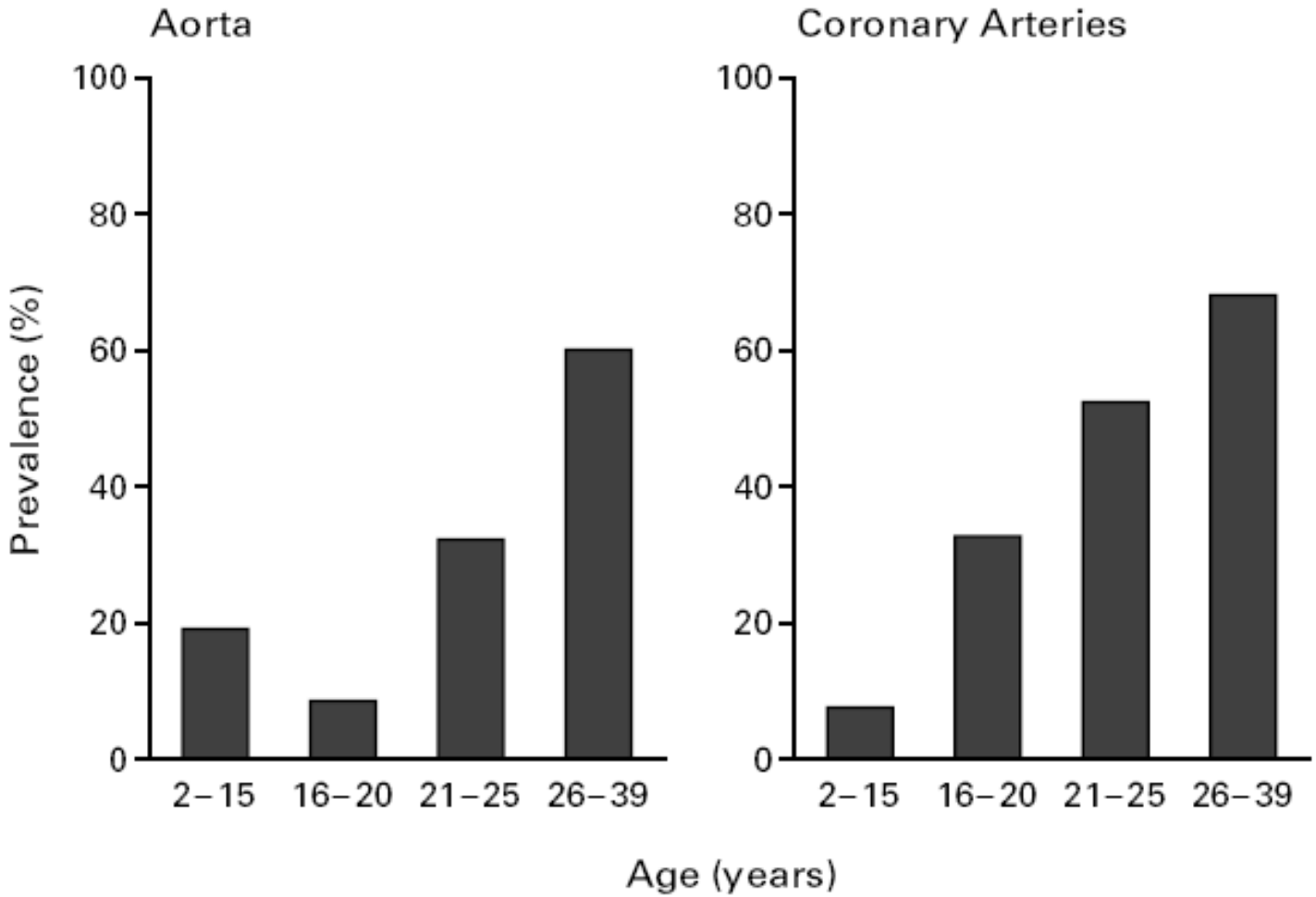
Atherosclerosis Starts in Infancy



–Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998; 338(23):1650-1656.

Hyperlipidemia in a Fasting Sample

Measurement	High	Borderline high	Desirable
Total cholesterol	>=200 mg/dl	170-199	<170
LDL Cholesterol	>=130	110-129	<110
HDL Cholesterol	<35 (Low)	35-45 (Borderline low)	>45
Triglycerides < 10 years	>=100	75-99	<75
Triglycerides 10-19 years	>=130	90-129	<90

From Expert Committee NIH 1991

Recommendations for Lipid Treatment: Basic Guidelines

- Treatment should be based on lipid values obtained after diabetes treatment initiated
- Initial treatment: diet & exercise if LDL-C >100

- Pharmacologic rx should be considered if medical nutrition therapy has failed after 3-6 months, even if chronic hyperglycemia is present
  - Medications should be instituted if LDL is > 160 mg/dl
  - Medication should be considered if LDL is 130-159 based on the child's CVD risk profile

Recommendations for Diet

AHA Step 2 diet

- saturated fat < 7% of calories
- cholesterol < 200 mg/day
- For children and youth, must have adequate calories for growth and development

Medical Therapy of Hyperlipidemia in Childhood

- 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors or statins
  - No large or long term studies
  - No proof of improvement in long term outcome
  - **They are teratogenic! Girls must use contraception or abstinence**
  - None-the-less, in small studies,
    - Lovastatin tolerated and effective
    - Pravastatin similar

Summary for Clinical Management of Safety Issues

- Measure baseline AST, ALT before statin use
- Can continue statins if ALT/AST are <3X upper limits of normal if monitor closely
- D/C statin if muscle symptoms appear and measure CPK
- If CPK is WNL or <3X normal, can continue statin and monitor symptoms. Consider dose reduction
- Statin must be discontinued if CPK is >10X normal

- Pasternak RC, et al. J Amer Coll Cardiol. 2002;40:7-572

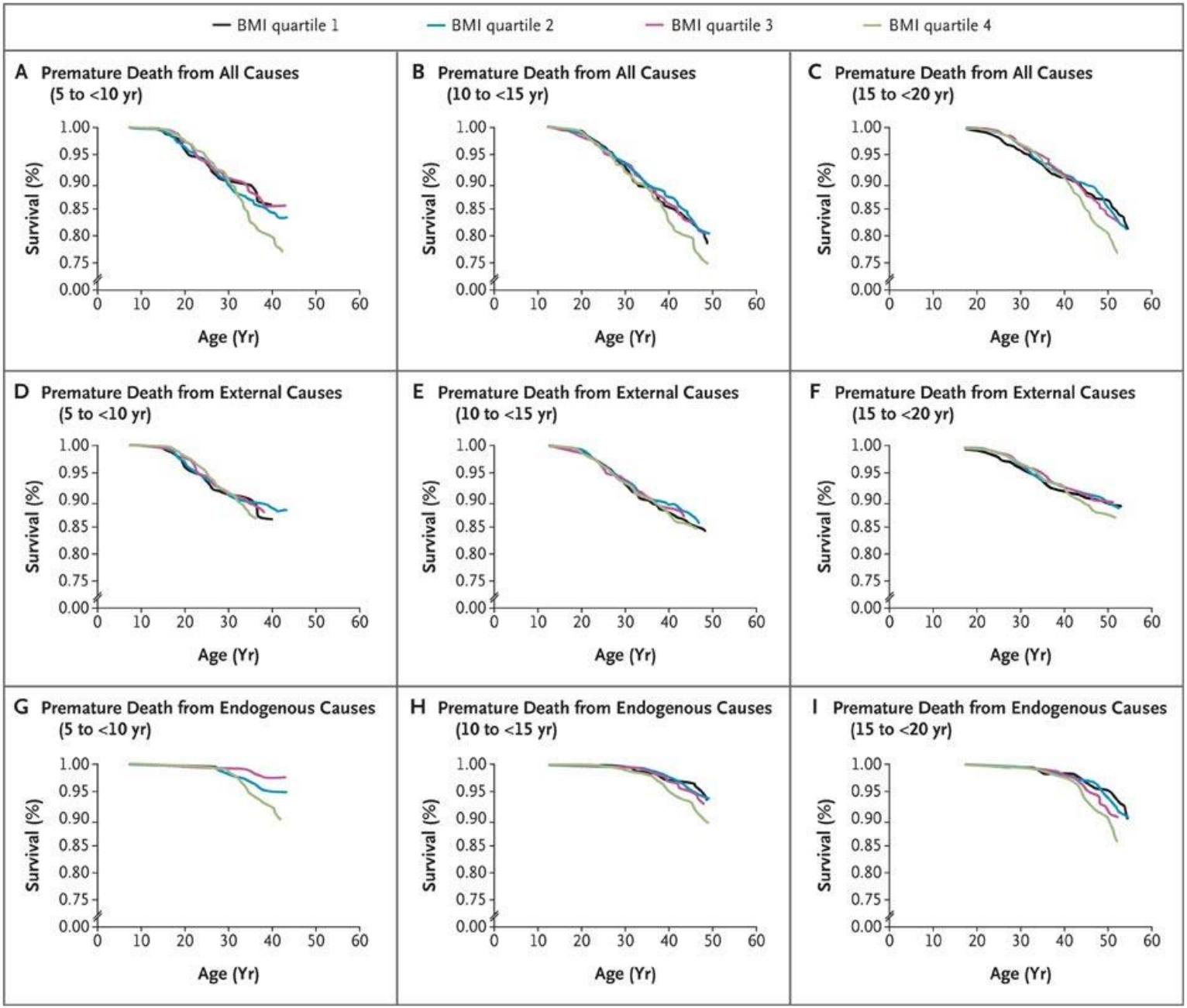
Table 1
Screening for diabetes complications and comorbidities in children with type 2 diabetes

Complication/Co-Morbid Condition	Indications and Intervals for Screening	Screening Test
Dyslipidemia	Screening should commence at diagnosis of diabetes and every 1–3 years thereafter, as clinically indicated	Fasting TC, HDL-C, triglycerides, and calculated LDL-C
Hypertension	At diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least twice annually)	BP measurement using appropriate-sized cuff
NAFLD	Yearly screening commencing at diagnosis of diabetes	ALT
Nephropathy	Yearly screening commencing at diagnosis of diabetes	• First morning (preferred) or random ACR. • Abnormal ACR requires confirmation at least 1 month later with a first morning ACR, and if abnormal, follow-up with timed, overnight or 24-hour split urine collections for albumin excretion rate. • Repeated sampling should be done every 3–4 months over a 6- to 12-month period to demonstrate persistence.
Neuropathy	Yearly screening commencing at diagnosis of diabetes	Questioned and examined for: • Symptoms of numbness, pain, cramps, and paresthesia • Skin sensation • Vibration sense • Light touch, and • Ankle reflexes
PCOS	Yearly screening commencing at puberty in women with oligo-amenorrhea, acne and/or hirsutism	Androgen levels including DHEAS and free testosterone
Retinopathy	Yearly screening commencing at diagnosis of diabetes	• 7-standard field, stereoscopic-color fundus photography with interpretation by a trained reader (gold standard); or • Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or • Digital fundus photography

Sellers, E. A., et al. (2009). "Clinical management of type 2 diabetes in indigenous youth." Pediatr Clin North Am **56(6): 1441-1459**

Where is the Lesion in Poor Control of Diabetes Mellitus?

- The biology is now relatively easy to manage
- Tight Control, however is more difficult
- Poor control of Diabetes Mellitus is a condition that resides between the ears more than in the pancreas
  - Compliance?
  - Quality of life?
  - Normal human inertia?



Franks PW et al. N Engl J Med 2010;362:485-493

The NEW ENGLAND JOURNAL of MEDICINE

Conclusions

- Type 2 Diabetes occurs in an individual with a genetic background in which the environment brings out the tendency
- Screening is appropriate for select children for T2 DM and other insulin resistant conditions
- Treatment choice is based upon presentation
- Comorbidities must be sought out and treated