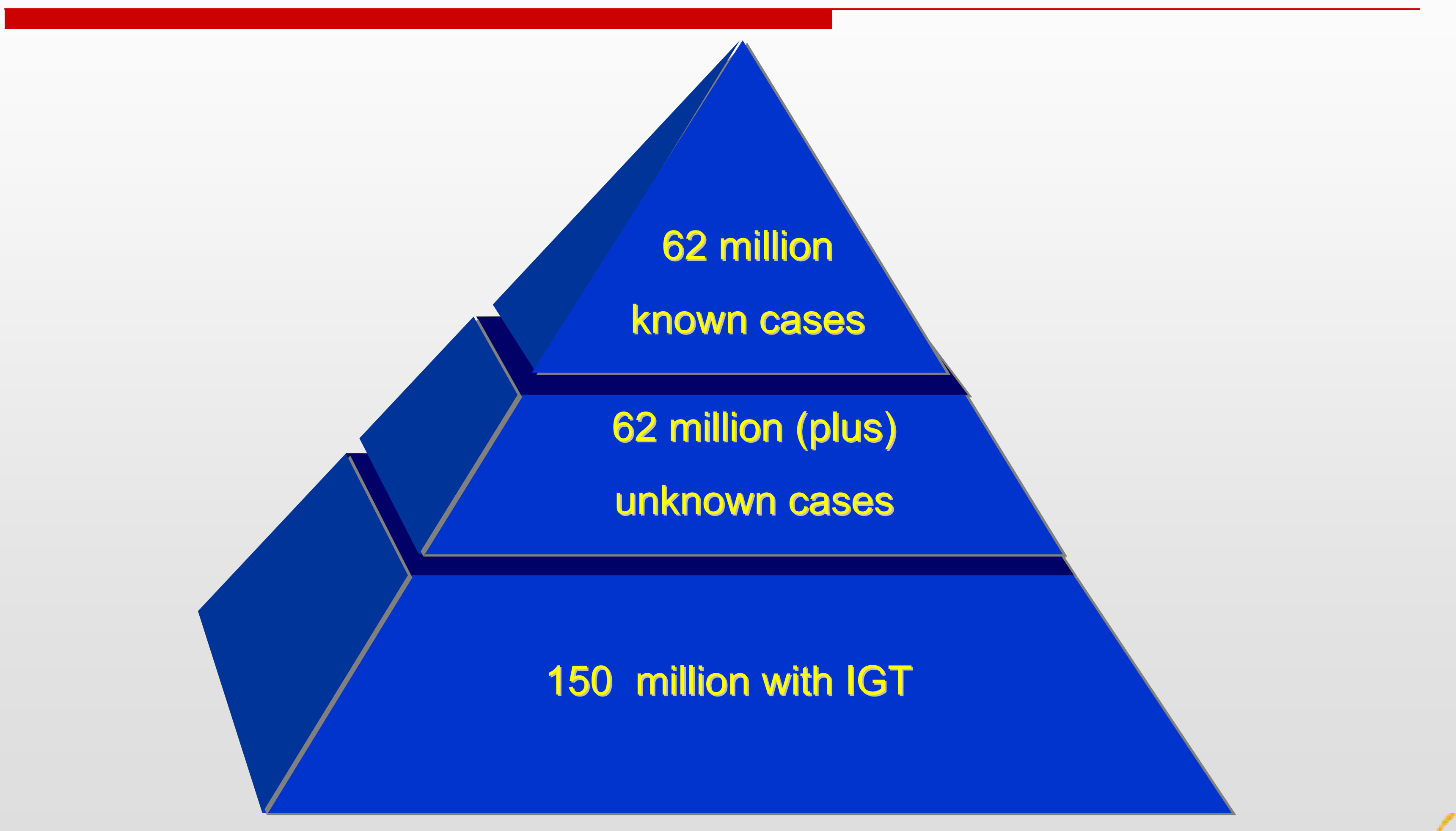
Childhood Obesity and Type 2 Diabetes Mellitus

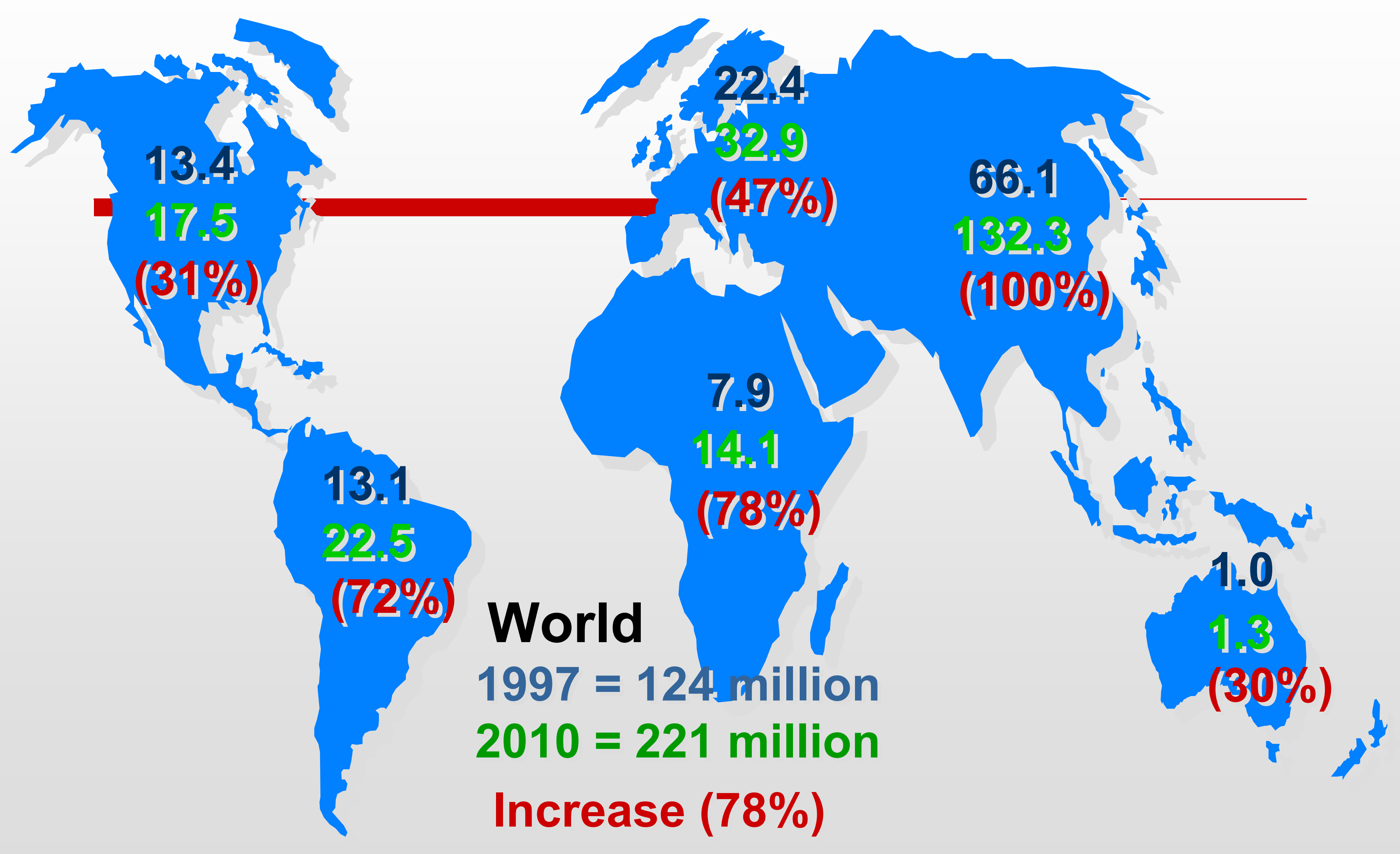
Research & Education
Institute of Child Health

Savvas C Savva MD

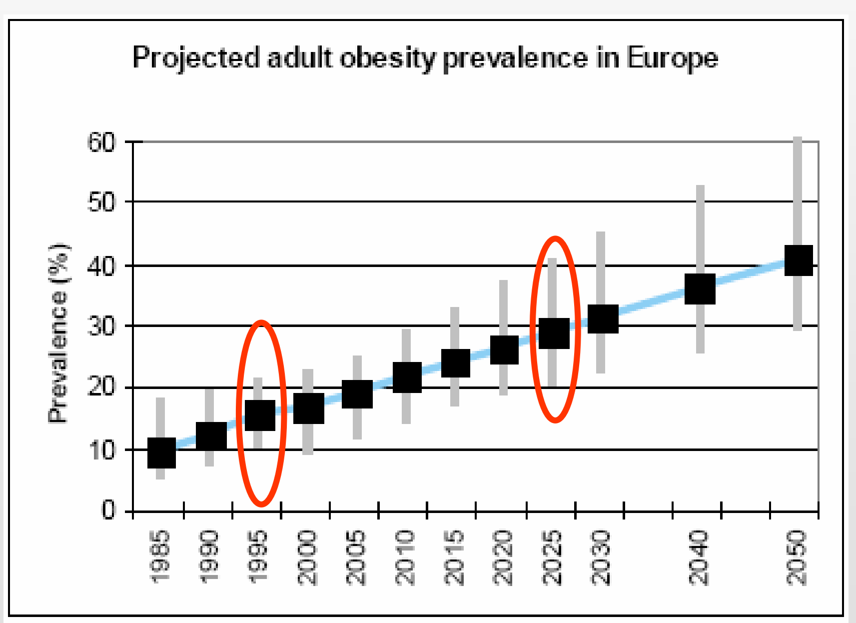
Type 2 Diabetes: The Hidden Epidemic

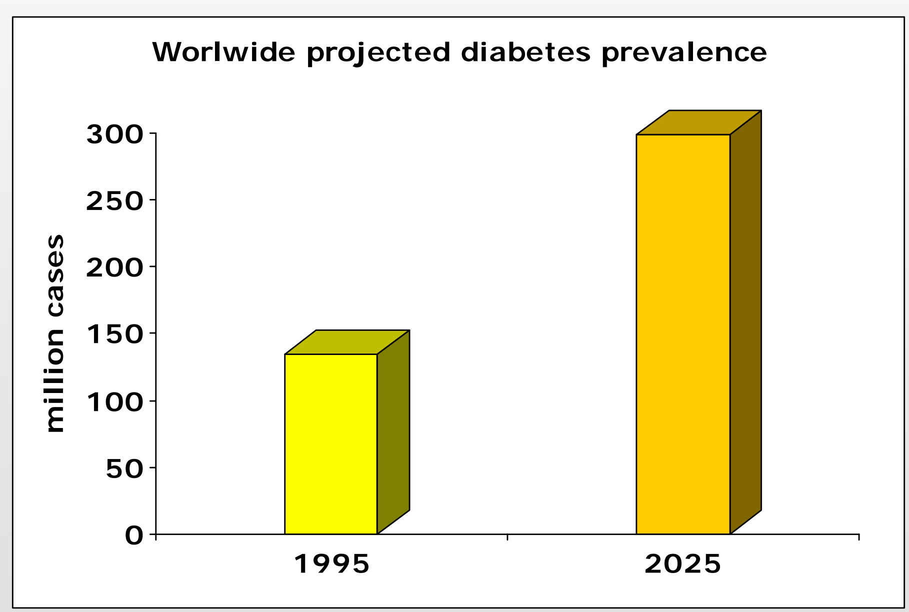


Global Projections of the Number of Diabetics (in millions) 1997-2010



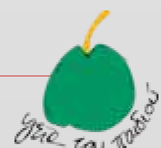
Escalating trends in obesity and diabetes



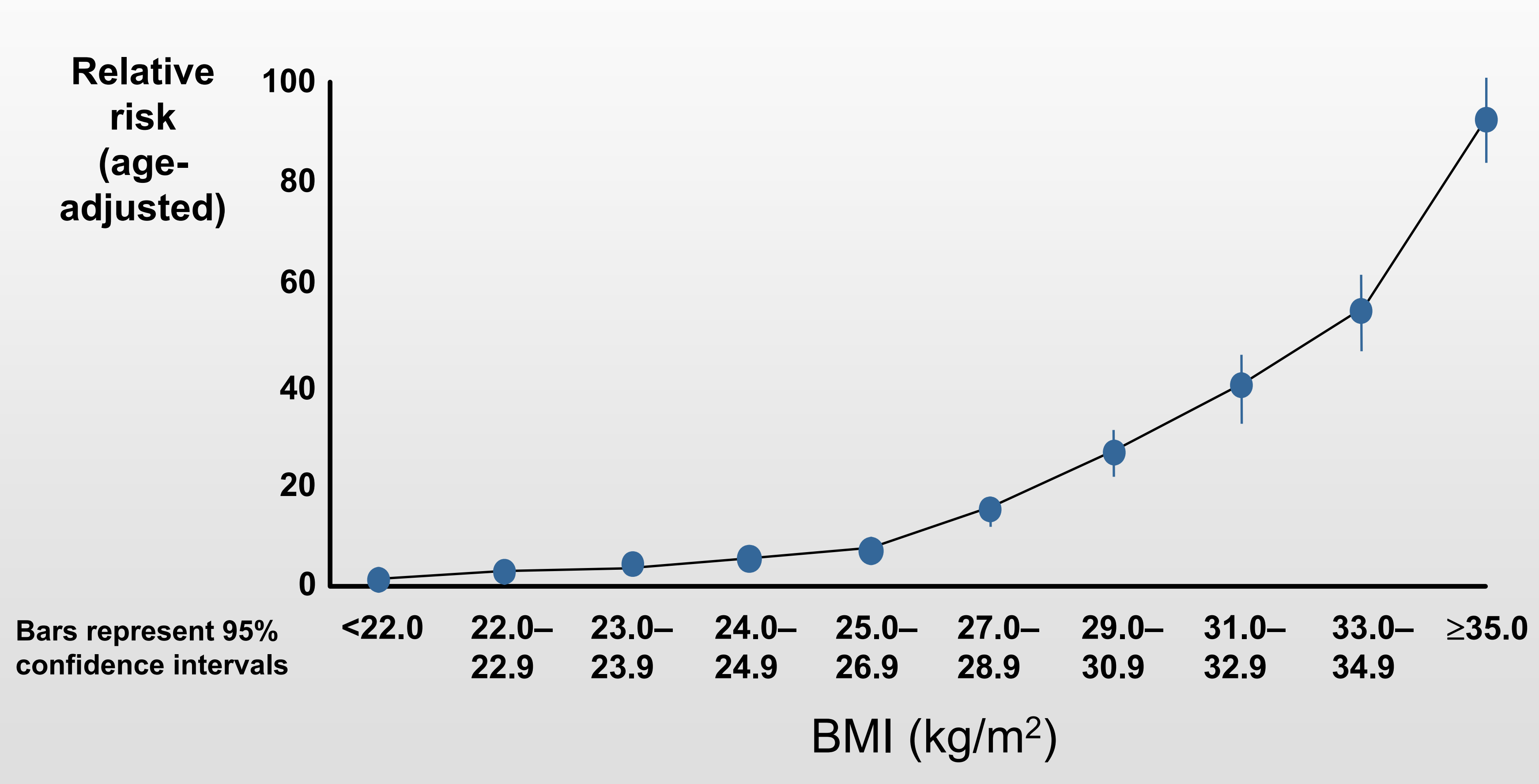


International Obesity TaskForce (IOTF) 2006

World Health Organization



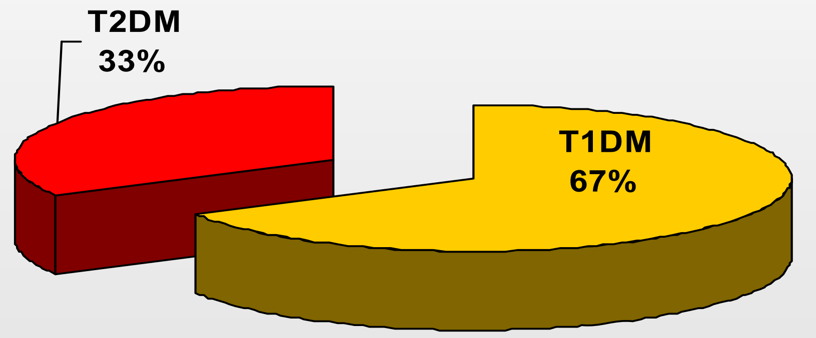
Relative risk of type 2 diabetes in US women according to BMI



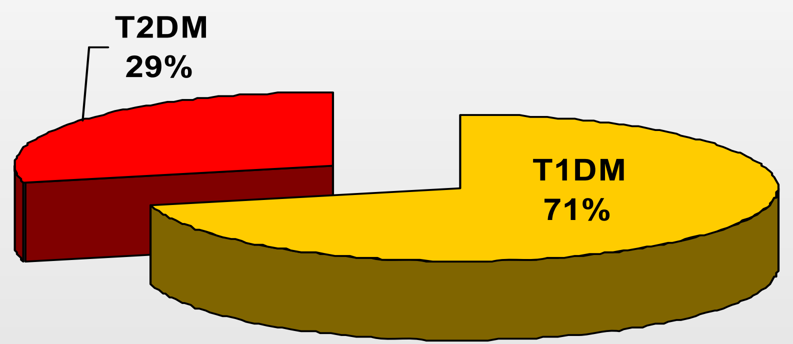
Colditz et al. Ann Intern Med 1995; 122: 481–7

Increasing trends of T2DM in children and adolescents

Diabetes Incidence - USA
10-19y

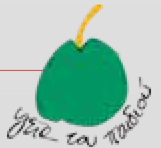


NHANES 1999-2002 - USA
12-19y

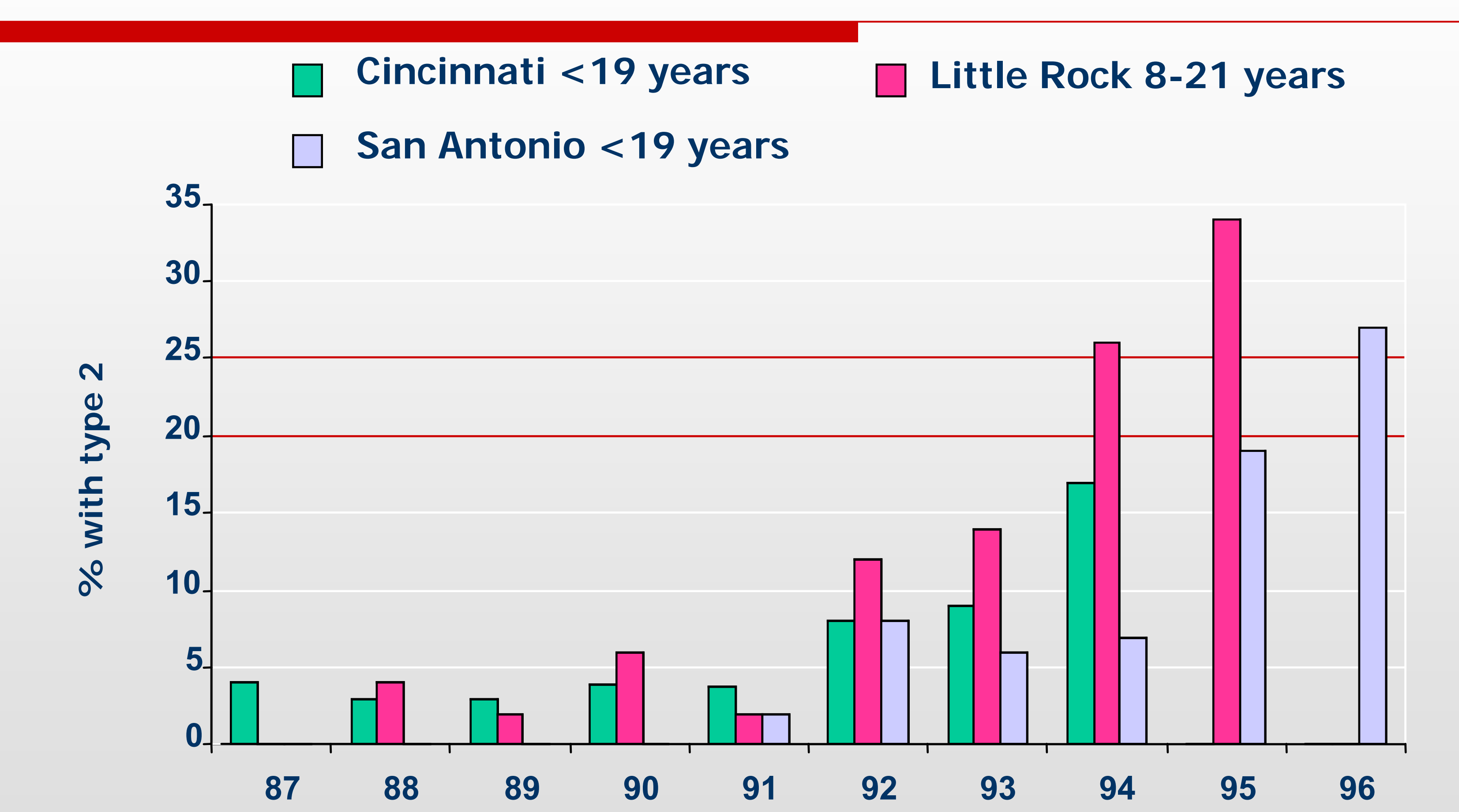


J Pediatr 1996; 128: 608-15

Arch Ped Adolesc Med 2006; 160: 523-8

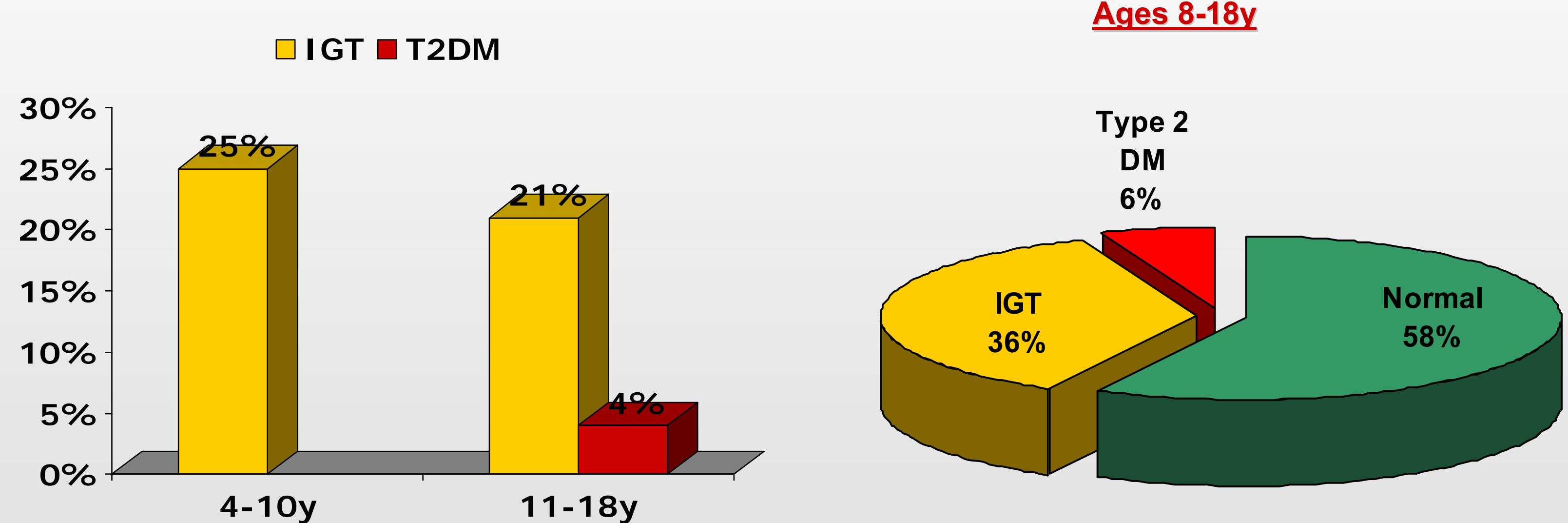


Changing Face of Diabetes in Youth in US



Fagot-Campagna et al. J Pediatr 2000;136:664-672

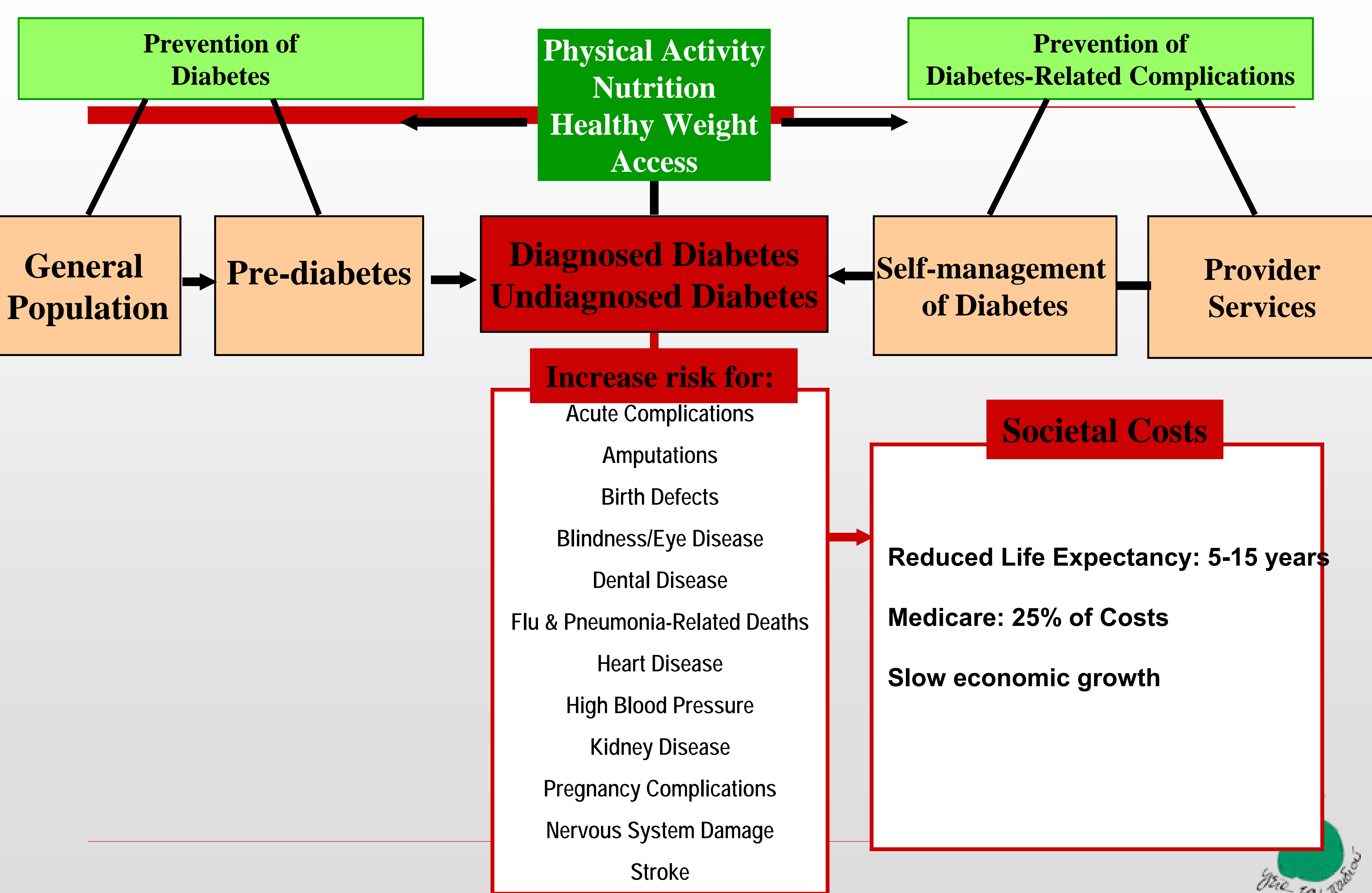
IGT and T2DM in markedly obese children & adolescents



Sinha R et al. NEJM 2002; 346:802-10

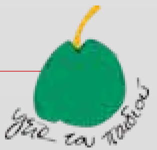
Wiegand S et al. Eur J Endocrinol 2004; 151:199-206

Diabetes Model



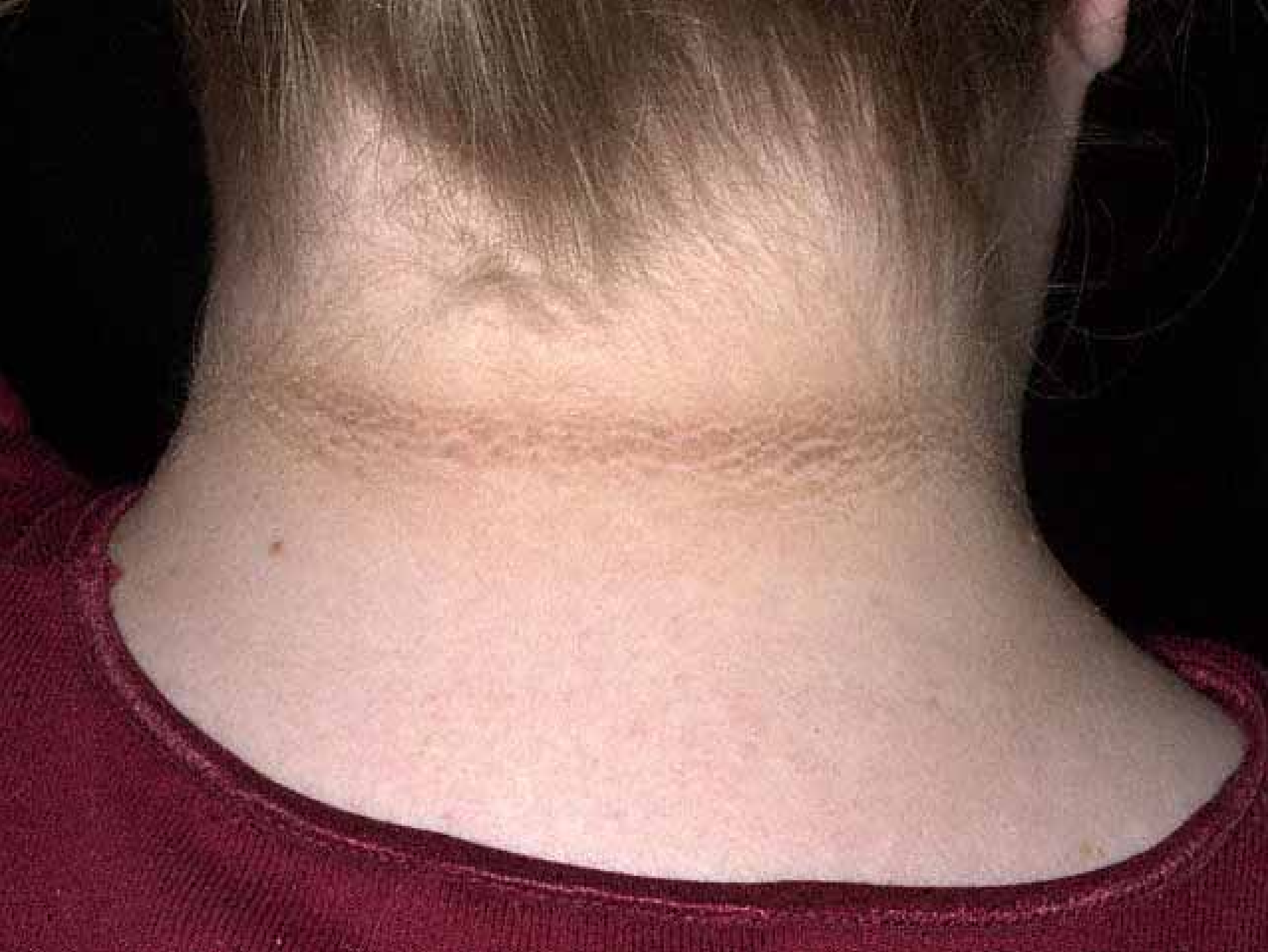
Plasma Glucose Criteria for the Diagnosis of Impaired Glucose Tolerance and Diabetes

Plasma Glucose	Normal	Impaired	Diabetes
Fasting	<100 mg/dl	100-125 mg/dl **(IFG)**	≥ 126 mg/dl
Oral Glucose Tolerance test (OGTT), 2hPG	<140 mg/dl	140-199 mg/dl **(IGT)**	≥ 200 mg/dl
Casual			≥ 200 mg/dl + symptoms

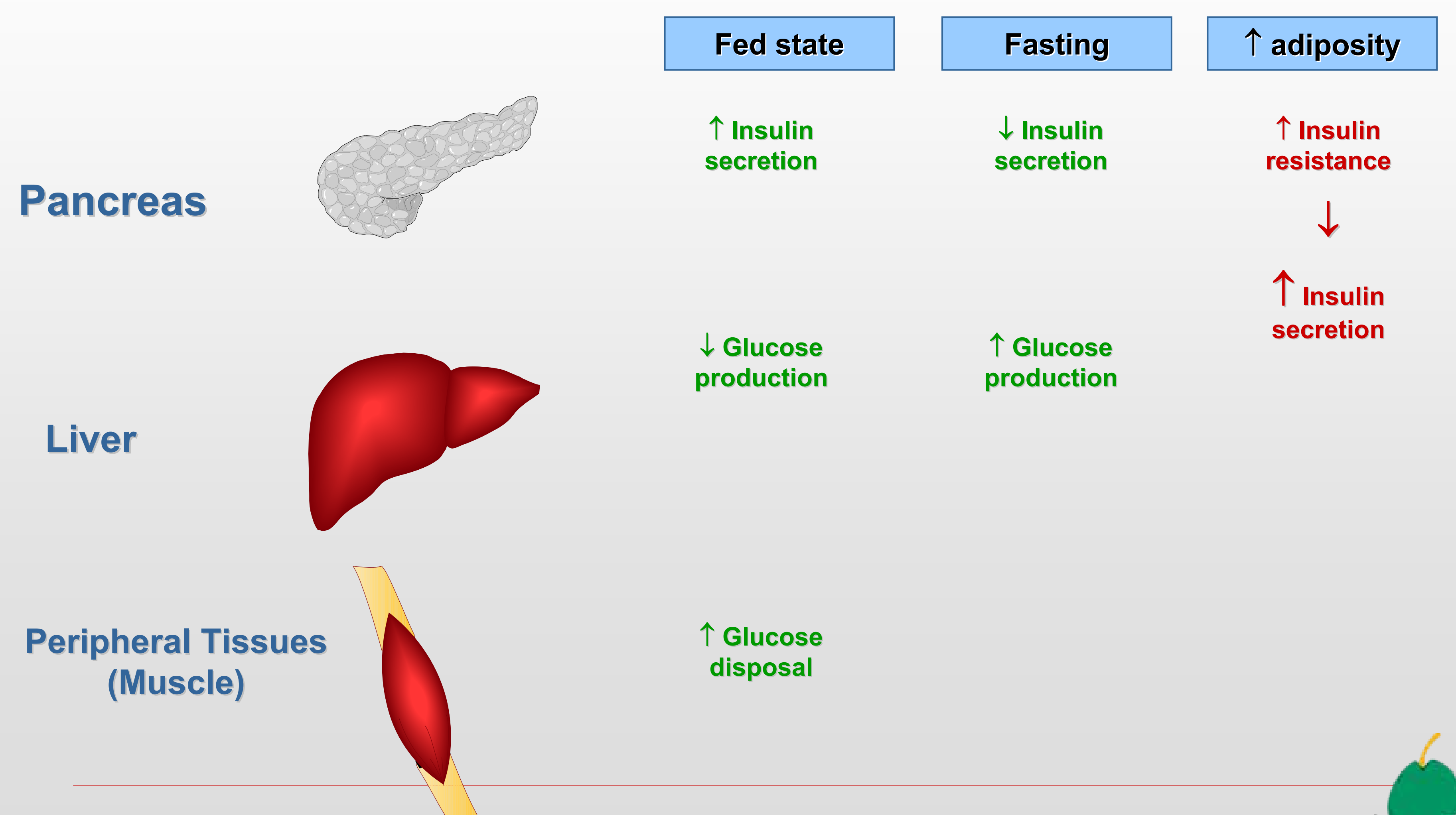


Features to differentiate type 1 and 2 diabetes in young people

	Type 1 diabetes	Type 2 diabetes
Onset	Acute —symptomatic	Slow—often asymptomatic
Clinical picture	● Weight loss ● Polyuria ● Polydipsia	● Obese ● Strong family history type 2 diabetes ● Ethnicity—high-prevalence populations ● Acanthosis nigricans ● PCOS
Ketosis	Almost always present	Usually absent
Insulin	C-peptide negative	C-peptide positive
Antibodies	● ICA positive ● Anti-GAD positive ● ICA 512 positive	● ICA negative ● Anti-GAD negative ● ICA 512 negative
Therapy	Insulin invariably	Oral hypoglycemic agents
Associated autoimmune diseases	Yes	No



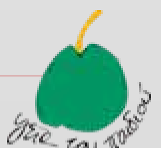
Pathophysiology of Type 2 Diabetes



Saltiel AR, Olefsky JM. Diabetes. 1996;45:1661-1669

Insulin Resistance: Central to development of T2DM

- Insulin Resistance: Condition in which greater than normal amounts of insulin are required to produce a normal biological response
  - **VISCERAL ADIPOSITY promotes INSULIN RESISTANCE to a higher degree than subcutaneous adiposity**



Insulin Resistance (IR)

Glucose

Glucose

Glucose

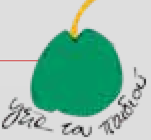
IR with Normal Glucose levels

IR with Impaired Glucose Tolerance

Type 2 Diabetes

Glucose

Insulin



Type 2 Diabetes

Other conditions

Insulin resistance

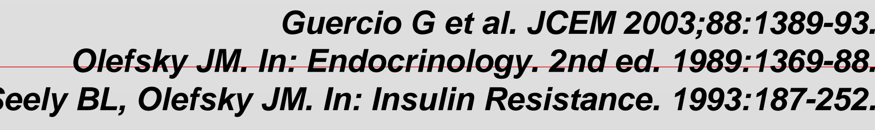
Environmental factors

SGA

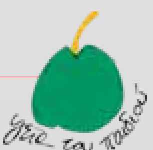
Genetic factors

Puberty

Gestational diabetes

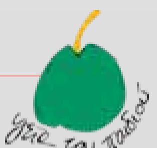


Guercio G et al. JCEM 2003;88:1389-93.
Olefsky JM. In: Endocrinology. 2nd ed. 1989:1369-88.
Seely BL, Olefsky JM. In: Insulin Resistance. 1993:187-252.

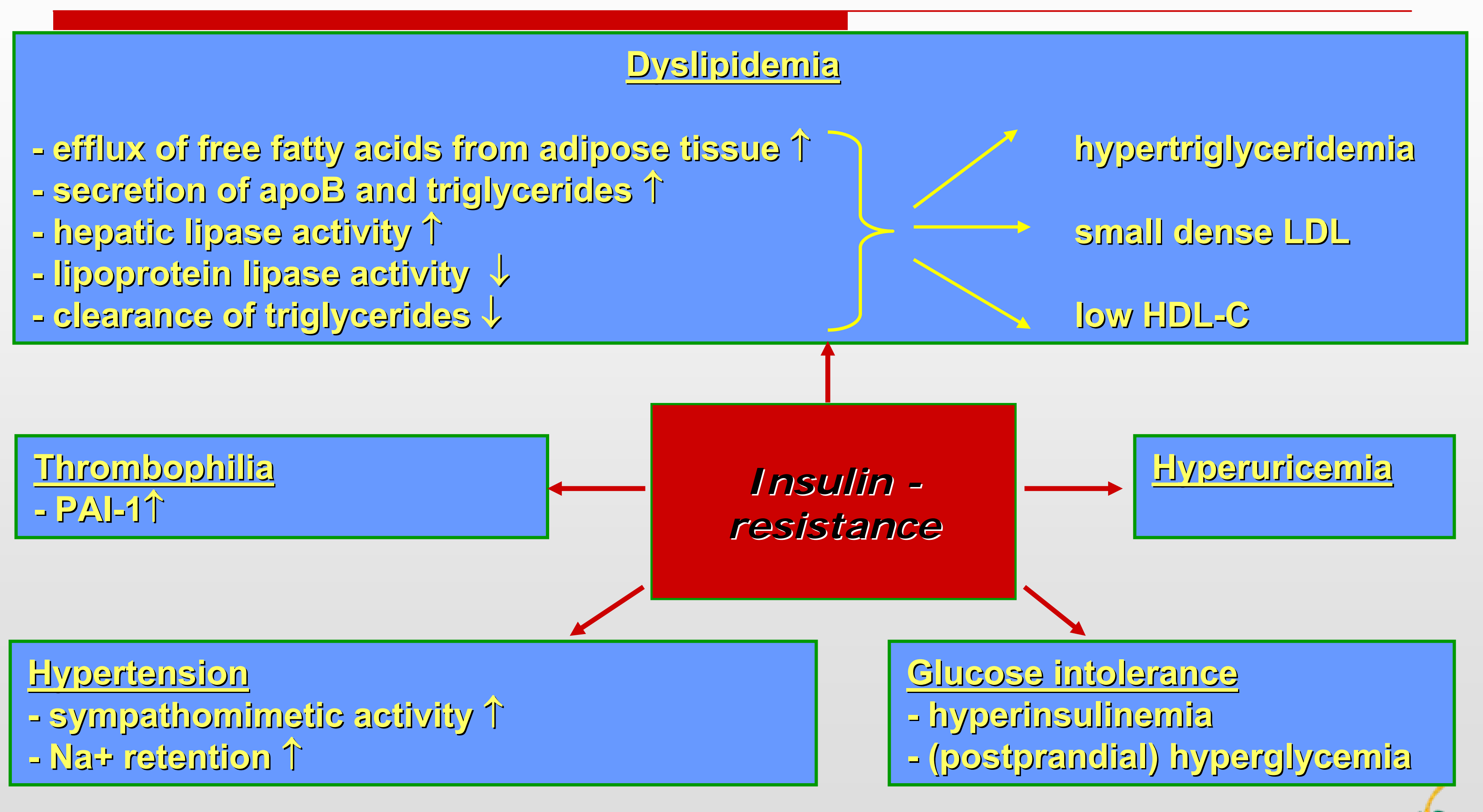


Modifiable risk factors for type 2 diabetes

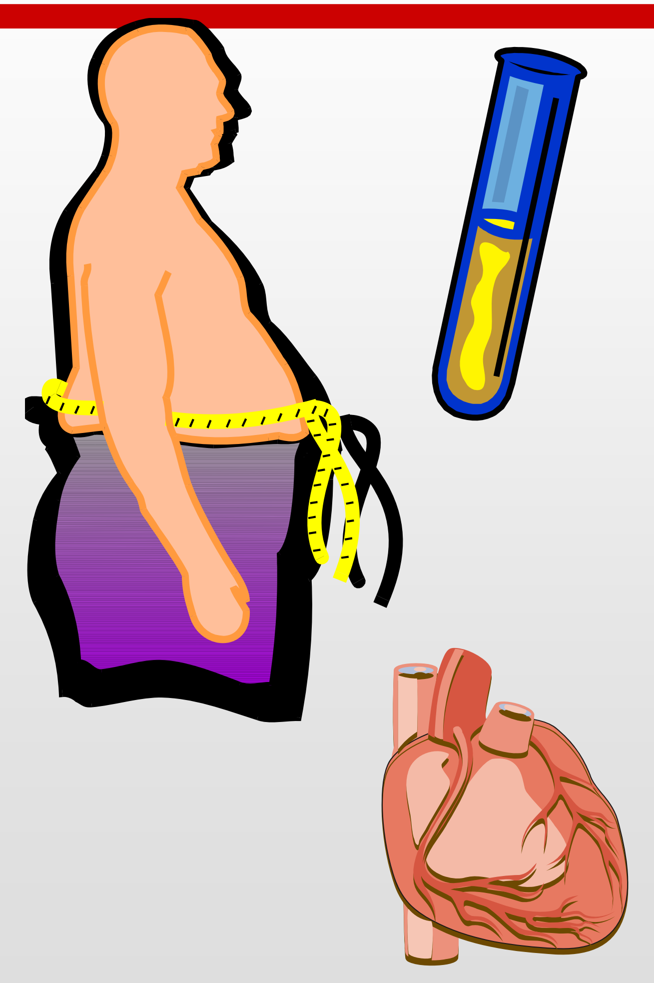
- obesity
- central obesity
- sedentary lifestyle
- high-fat diet
- high-saturated-fat diet
- low-fibre diet



Metabolic Consequences of Insulin Resistance



Metabolic Syndrome

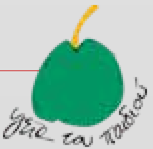


- Central obesity
- Hyperinsulinemia

  Hyperglycemia

  Impaired Glucose Tolerance
- ↑ triglycerides

  ↓ HDL-cholesterol
- Hypertension



Metabolic Syndrome Increases Risk for CHD and Type 2 Diabetes

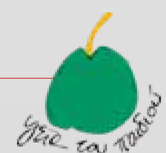
High LDL-C

Metabolic Syndrome

Type 2 Diabetes

Coronary Heart Disease

JAMA 2001;285:2486-2497



Incident Diabetes after Stratification by Age or BMI, IGT, and the Metabolic Syndrome

p<0.0001
60
50
P=0.018
40
%
30
p<0.0001
20
10
Yes
0
No
MET
Yes
IGT
No

Lorenzo et al, Diabetes Care, 2003, 26: 3153-3159

Stages in the Development of T2DM

↑ adiposity

Visceral adiposity

Genetic predisposition

↓ Insulin sensitivity

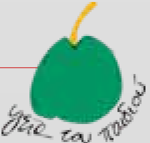
β cell compensation

↓ weight

↑ Insulin sensitivity

β cell failure

diabetes



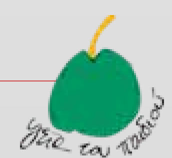
ADA criteria for considering screening for diabetes in children

Overweight (BMI≥ 85th %le)
+ any two of the following
Family Hx of T2DM (1st or 2nd degree relative)
Race/ethnicity
Signs of Insulin Resistance ● Acanthosis nigricans ● Hypertension ● Dyslipidemia ● PCOs

•Age: 10y or at onset of puberty

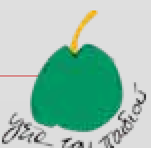
•Fasting plasma glucose preferred (OGTT alternative)

ADA. Diab Care 2000;23:381-9.

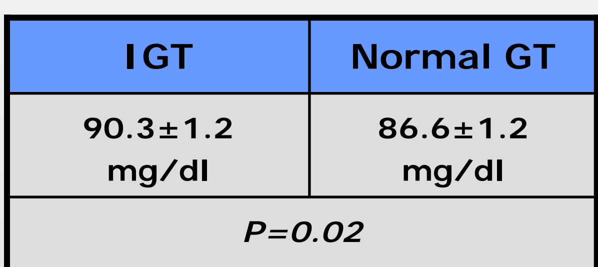


Challenges of ADA criteria

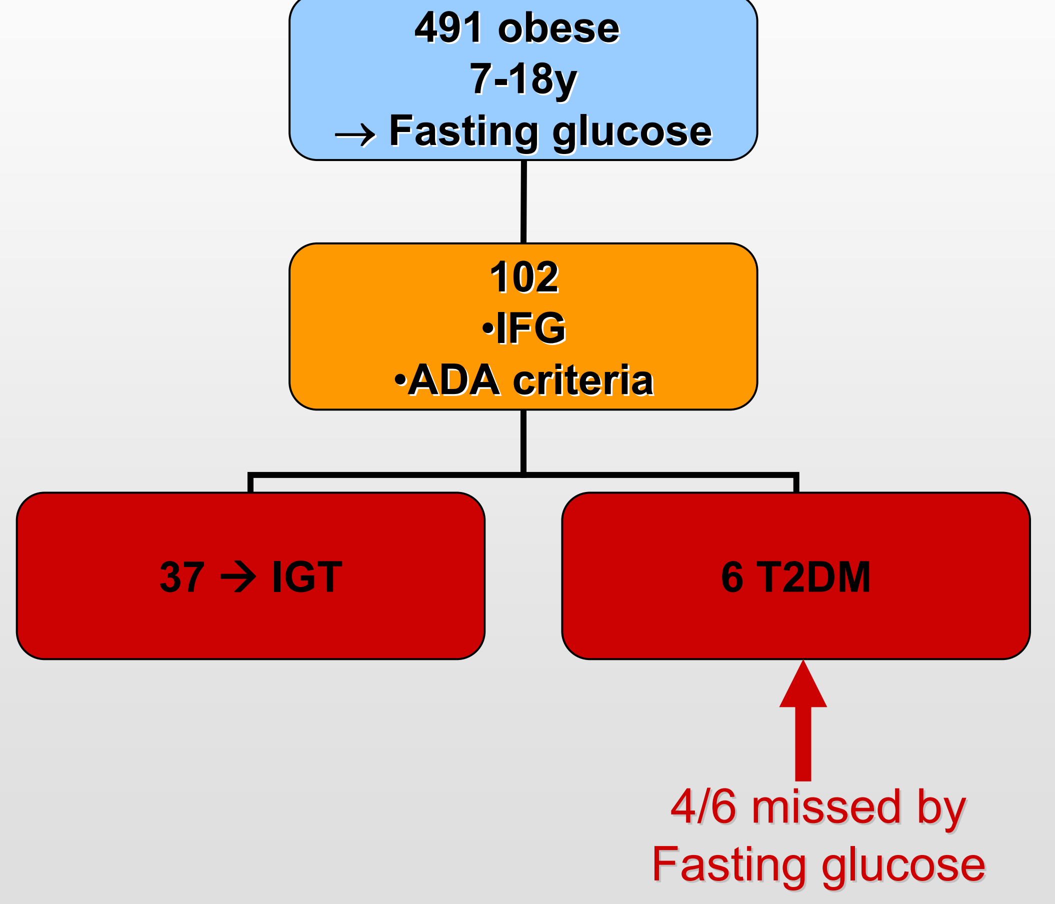
- In adults, 30% of undiagnosed diabetes have normal fasting glucose



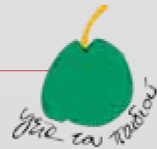
Fasting Glucose vs. OGTT



IGT	Normal GT
90.3±1.2 mg/dl	86.6±1.2 mg/dl
P=0.02	



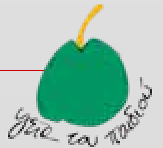
Wiegand S et al. Eur J Endocrinol 2004; 151:199-206



Diabetes complications

- Chronic complications at younger ages
- Micro- and macrovascular complications
- Canada study
  - Follow up T2DM children at 18-33y
    - 9% died
    - 6% dialysis
    - 2% amputation
    - 2% blind

Dean H et al. Diabetes 2002;51(suppl 1):A24



- Japan study (development of nephropathy)
  - 30y follow up diabetic Pts, diagnosed in young age
    - T1DM 20.2%
    - T2DM 44.0%

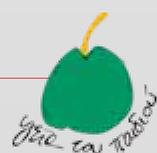
Yokohama H et al. Kidney Int 2000;58:302-11

- Pima Indians (T2DM Dx <20y)
  - Microalbimunuria
    - At diagnosis 22%
    - At 20-29y → 60%

Arslanian S. Hormone Res 2002; 57 Suppl 1: 19-28

  - Retinopathy→ less severe than in adults

Krakoff J et al. Diabetes Care 2003;26:76-81



Life expectancy reduction in diabetic patients

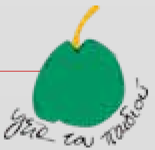
Life expectancy reduction (years)

30
25
20
15
10
5
0

12 17 25 35 45 55 65 >70

Age at diagnosis (years)

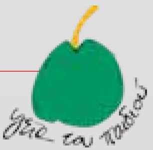
Marks and Krall Goodkin et al Panzram et al



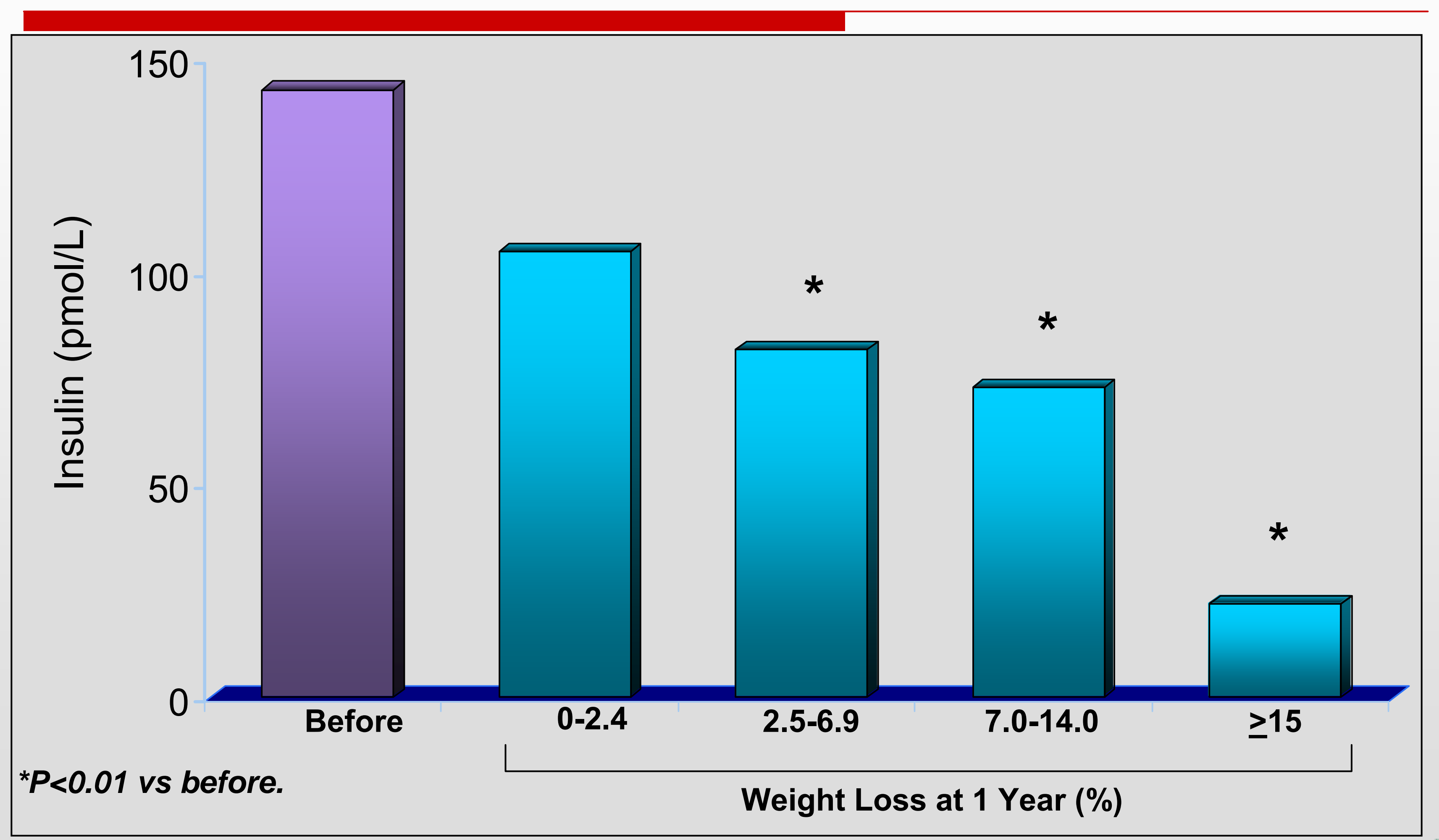
Impact of Weight Loss on Risk Factors

	~5% Weight Loss	5%-10% Weight Loss
HbA1c	↓ [1]	↓ [1]
Blood Pressure	↓ [2]	↓ [2]
Total Cholesterol	↓ [3]	↓ [3]
HDL Cholesterol	↑ [3]	↑ [3]
Triglycerides		↓ [4]

1. Wing RR et al. Arch Intern Med. 1987;147:1749-1753.
2. Mertens IL, Van Gaal LF. Obes Res. 2000;8:270-278.
3. Blackburn G. Obes Res. 1995;3 (Suppl 2):211S-216S.
4. Ditschunheit HH et al. Eur J Clin Nutr. 2002;56:264-270.



Insulin Sensitivity Improves with Weight Loss in Patients with Type 2 Diabetes



Wing et al. Arch Intern Med 1987;147:1749.

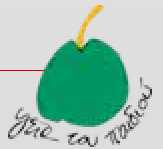
Childhood Obesity Treatment Guidance

- Treat motivated patients and families
- Weight maintenance or weight gain at a slower rate is the most appropriate approach for most patients
- Modify diet. Encourage healthy eating habits. NO RESTRICTING DIETS
- Encourage sustainable lifestyle activities and reduced television viewing
- Provide more time for consultations with families

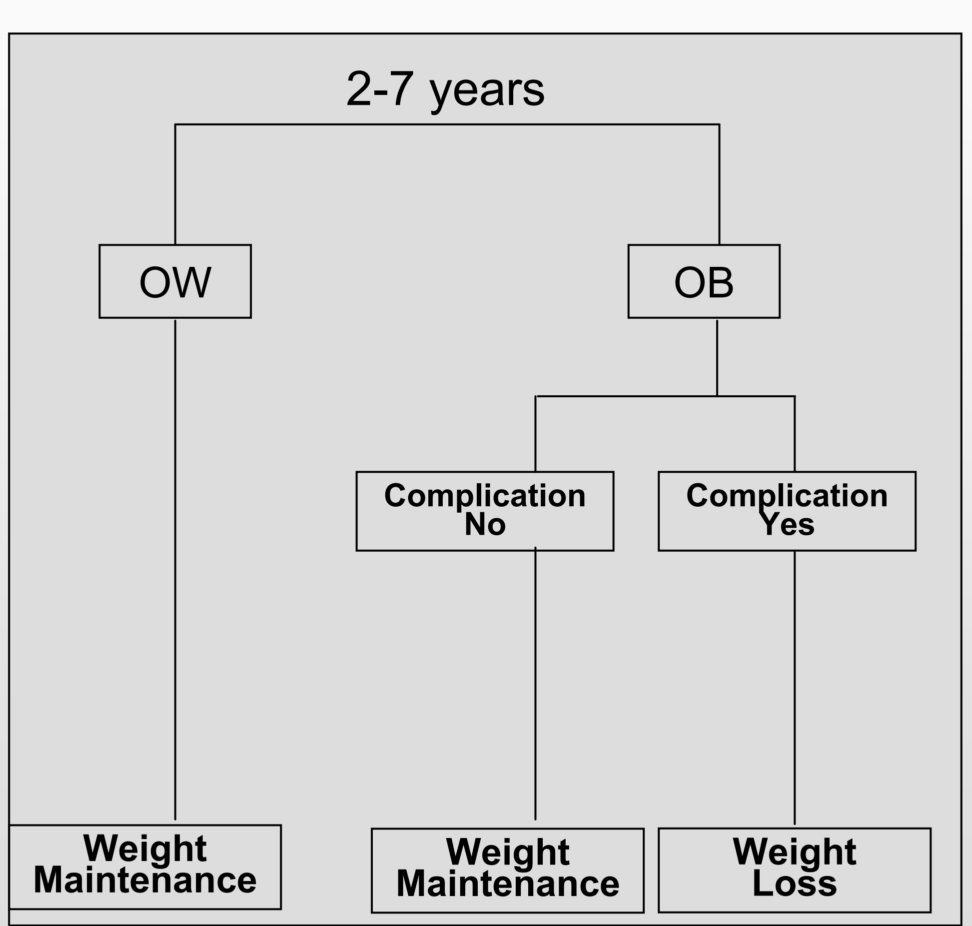
Reilly JJ. Post Med J 2006; 82: 429-37

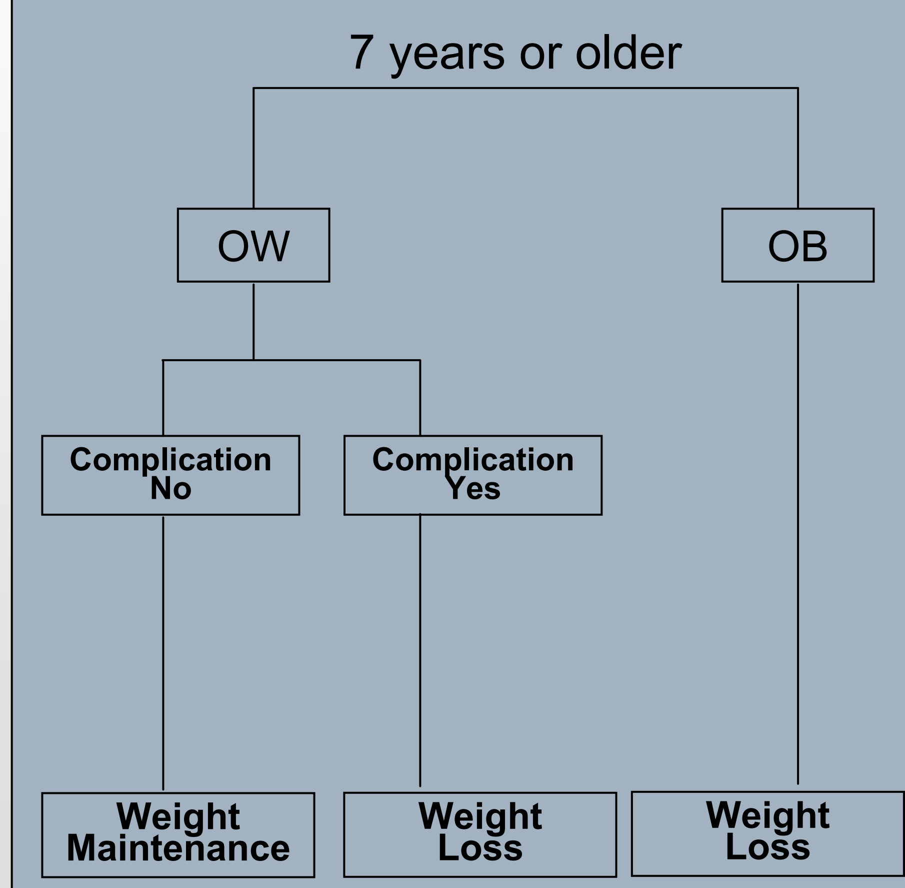
Edmunds L et al. BMJ 2001;322:916-9

Barlow & Dietz. Pediatrics 1998; 102:29



Recommendations for weight goals

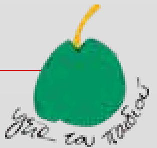




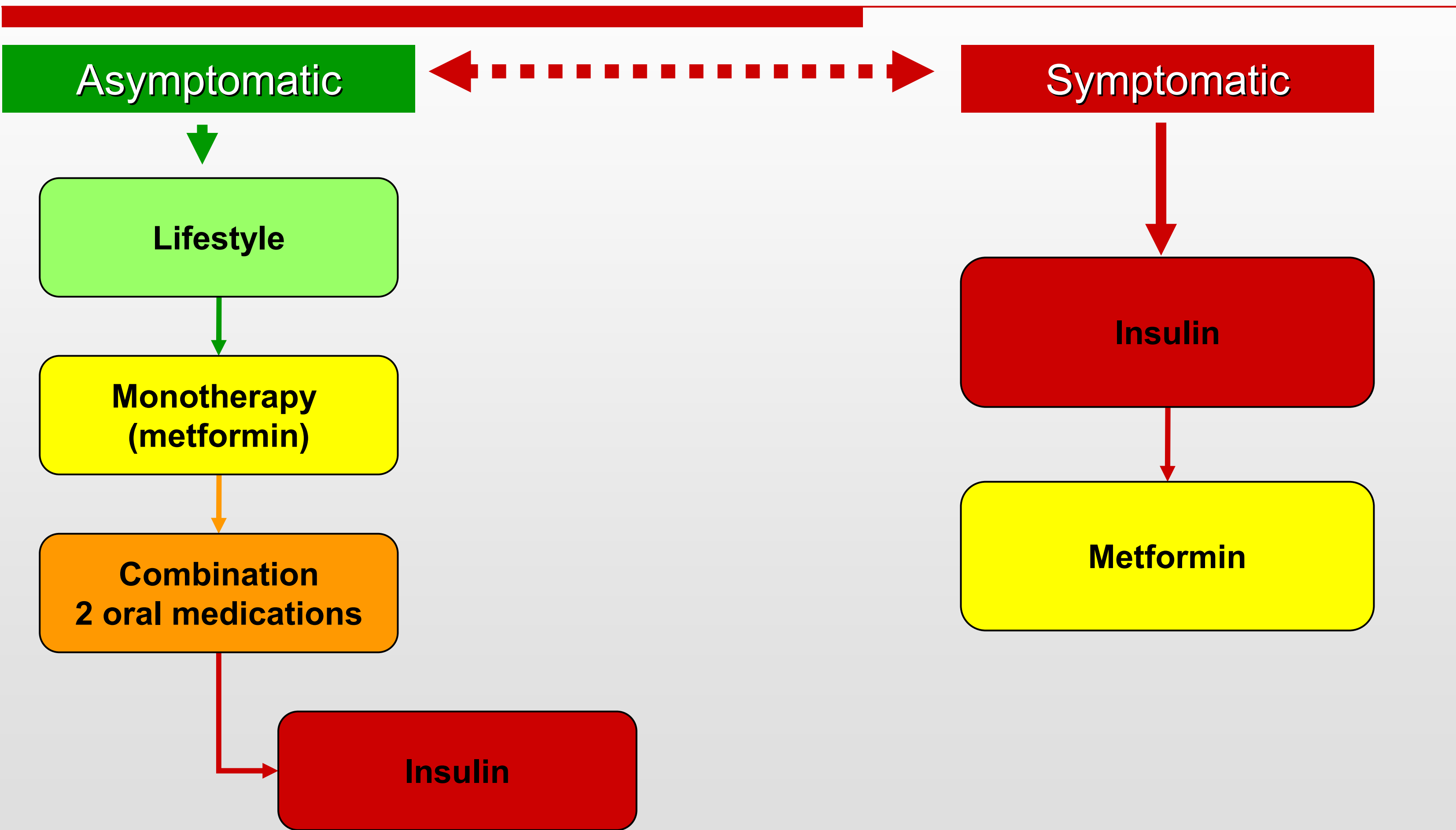
Barlow & Dietz Pediatrics 1998; 102:29

Goals of Treatment for T2DM

- Physical well-being
- Long term glycemic control (HbA1c<7%)
- Prevention of microvascular complications
- Prevention of macrovascular complications
- Psychological well-being



Glycemic control (HbA1c<7%)

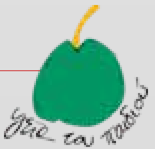


IDF Consensus Workshop. Diabetes Care 2004; 27:1798-811

Self Monitoring of Blood Glucose

Ideal targets: more than 50% of SMBG concentrations within target range:

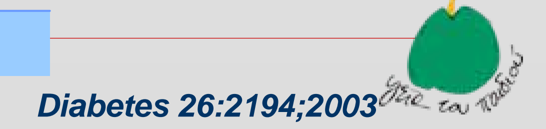
- Fasting: 80 to 120 mg/dL (4.4–6.7 mmol/L)
- Postprandial (2 hours after start of meal): 100 to 160 mg/dL (5.6–8.9 mmol/L)
- Bedtime: 100 to 160 mg/dL (5.6–8.9 mmol/L)



Management of dyslipidemia in children/adolescents with diabetes

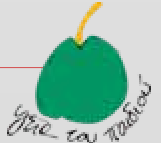
Goals
LDL <100 mg/dl
HDL >35 mg/dl
Triglycerides <150 mg/dl
Treatment strategies
Diet
Maximize glycemic control
Weight reduction, if indicated
Medications
• Age >10 years
• LDL ≥160 mg/dl
• LDL 130–159 mg/dl: consider based on CVD risk profile
• Statins ± resins
• Fibric acid derivatives if triglycerides >1,000 mg/dl
Manage other CVD risk factors

Diabetes 26:2194;2003



Management of Hypertension in children/adolescents with diabetes

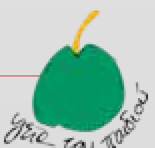
- BP measurement in every health care visit
- Treatment
  - Lifestyle changes
  - ACE inhibitors
  - Angiotensin II receptor antagonists (2nd line)



Three prevention strategies for type 2 diabetes

- **Population-based strategy** / information; health promotion and more effective lifestyle counselling; prevention of overweight and obesity; promotion of physical activity
- **High risk strategy** /prevention or postponing diabetes in those at risk
- **Early diagnosis and treatment strategy** / prevention of complications in those diagnosed having diabetes

- Strategies
  - Lifestyle interventions
  - Drugs



Intensive lifestyle intervention in IGT DPS Study

- 522 subjects with IGT in two oral glucose tolerance tests (OGTT)
- Age 40-65 years
- BMI > 25 kg/m^2
- Intervention group

→ individualized counseling aimed at

- ↓weight
- ↓ total intake of fat
- ↓ intake of saturated fat
- ↑ fiber intake
- ↑ physical activity

Tuomilehto J et al. NEJM 2001; 344:1343-50

Development of diabetes during the lifestyle intervention in the intervention and control groups

Intervention group
Control group

Cumulative Probability of Remaining Free of Diabetes

1.0
0.9
0.8
0.7
0.6
0.5

0 1 2 3 4 5 6

Year

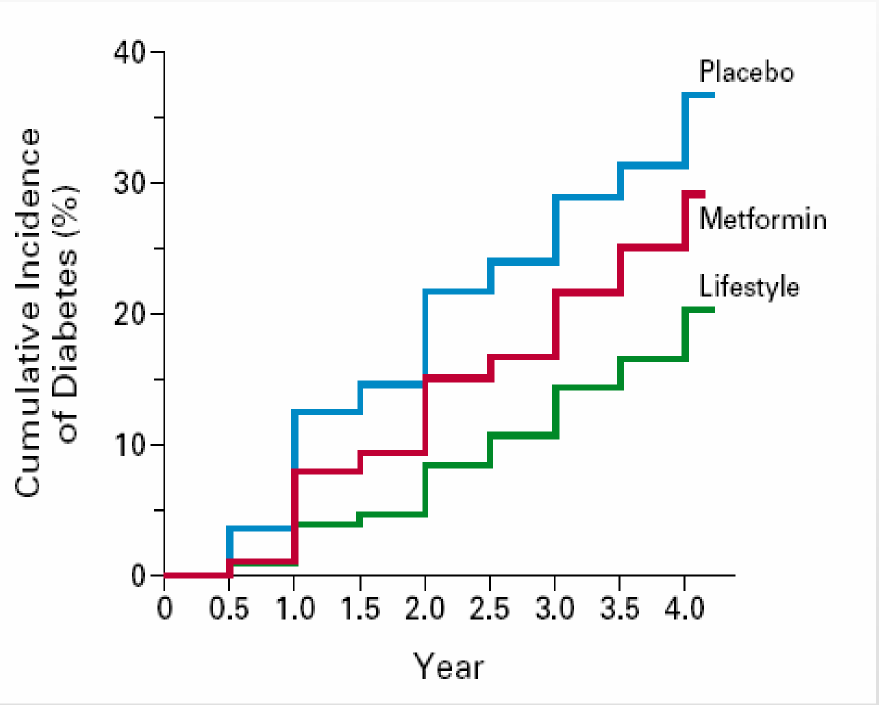
Risk reduction: 58%

Tuomilehto J et al. NEJM 2001; 344:1343-50

Lifestyle intervention vs. Metformin – Adults DPP study

- 3234 subjects with IFG or IGT
- Mean age 51y
- Mean BMI 34kg/m^2
- 1.8-4.6y of intervention

39% lower incidence in lifestyle intervention compared to metformin group ($p<0.001$)



NEJM 2002; 346:393-403

Diabetes Incidence Rates by BMI

Lifestyle Metformin Placebo

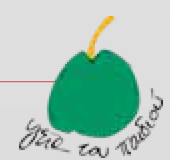
Cases/100 person-yr

16
12
8
4
0

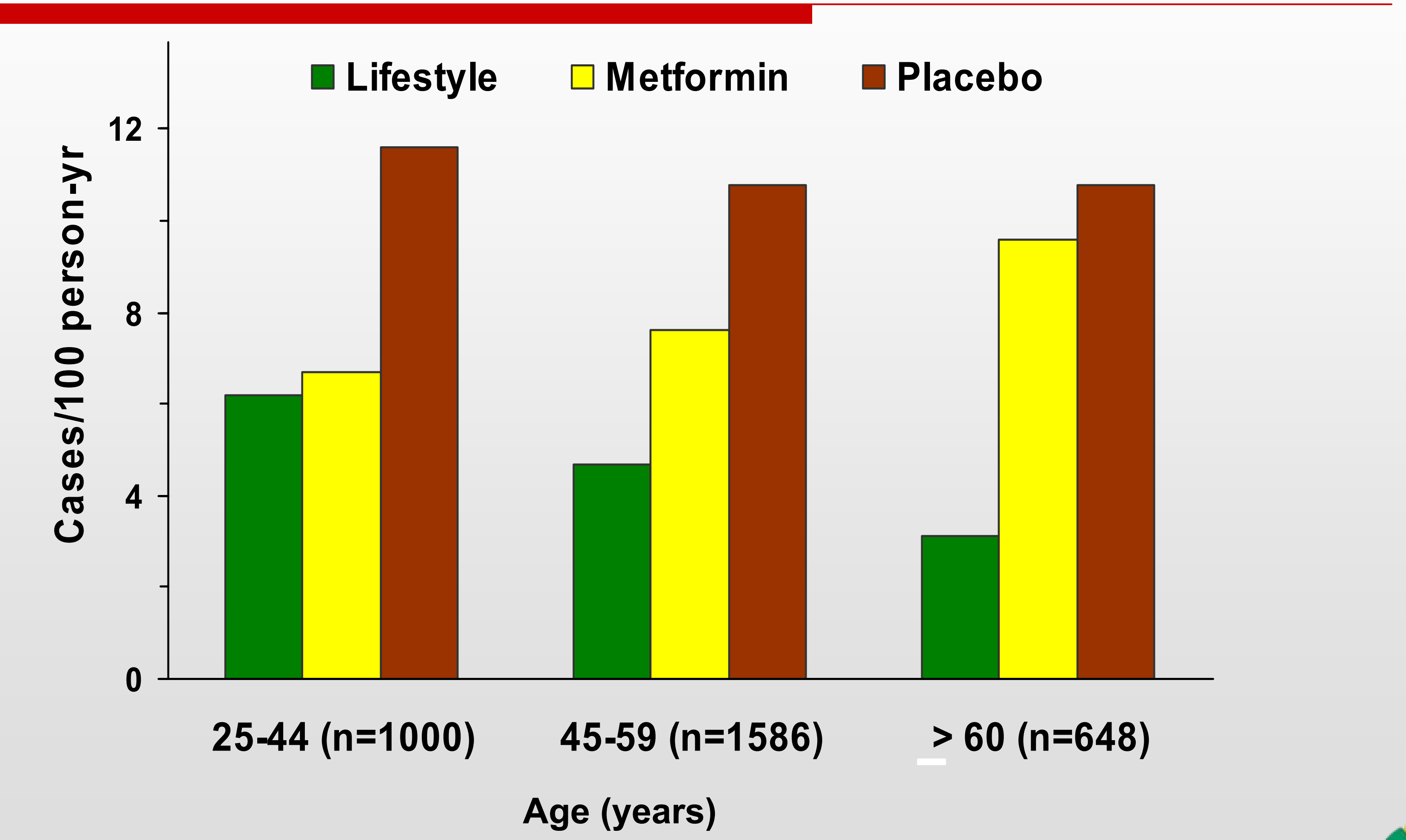
24 - < 30
30 - < 35
> 35

Body Mass Index (kg/m^2)

NEJM 2002; 346:393-403



Diabetes Incidence Rates by Age



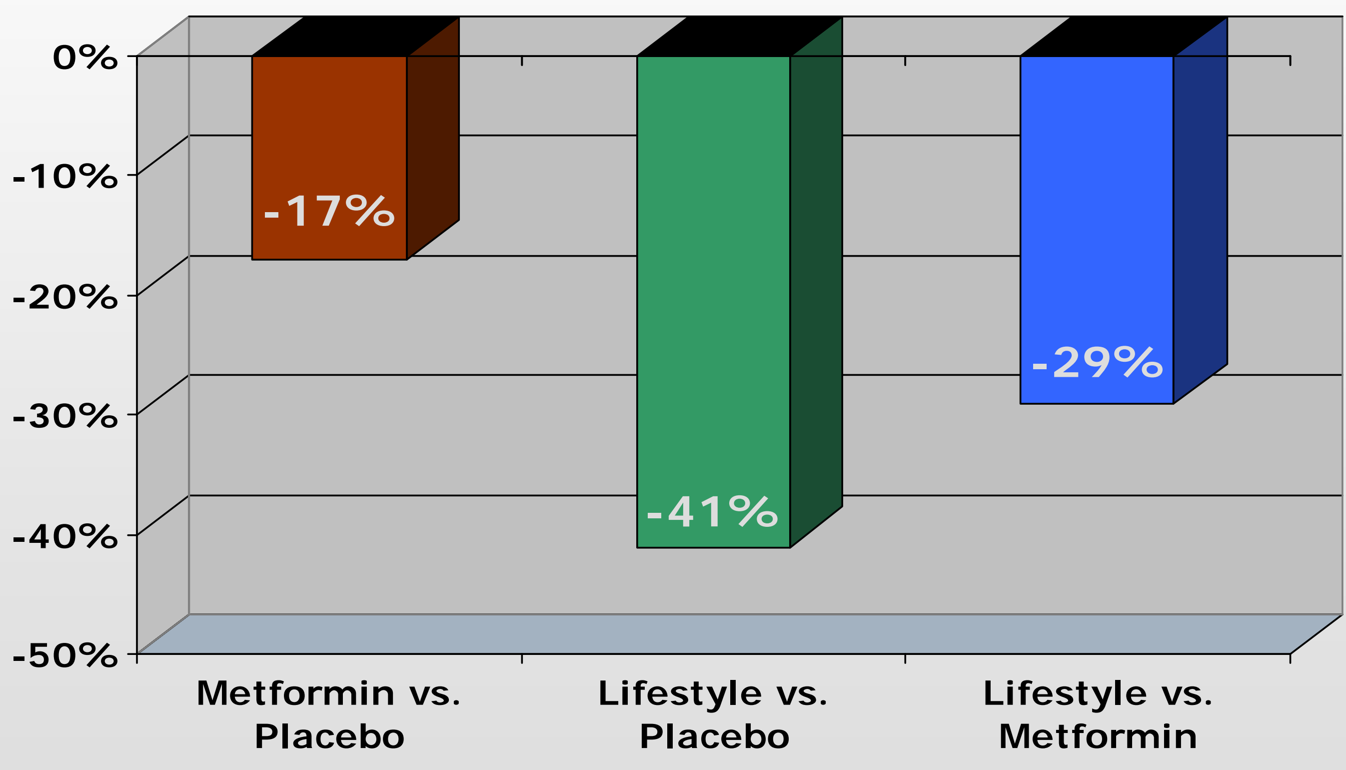
NEJM 346:393-403, 2002

Prevalence of the Metabolic Syndrome at Baseline and Follow-up in Diabetes Prevention Program

	Baseline	Follow-up	P-Value
Placebo	55%	61%	$p = 0.003$
Metformin	54%	55%	$p > 0.02$
Lifestyle	51%	43%	$p < 0.001$

Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

Reduction in Incidence of the Metabolic Syndrome in IGT patients

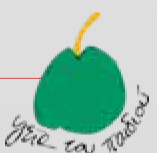


Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

No such studies in children/adolescents!!

- Weight loss and/or prevention of weight gain appears to be the best way to prevent T2DM among children with risk factors

Barlow & Dietz Pediatrics 1998; 102:29



School interventions for prevention of obesity

- Cochrane Database → 2005 review
- 22 studies
- Diet and Physical activity approaches did not significantly improve BMI

Summerbell et al. ***Cochrane Database Syst. Rev****, Jan 2005; (3): CD001871.*

- **Systematic literature review**
- 24 studies
  - 8 report +ve results
  - 16 no benefits

Flodmark CE et al. Int. J.Obes (2006) 30, 579–589.

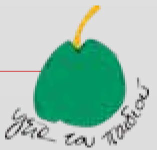
Almost all studies have invariably shown improved dietary habits and physical activity among children

Prevention of T2DM in high risk (IFG, IGT) pediatric patients

- consideration should be given to the use of metformin in adolescents at highest risk for the development of T2DM, ***after*** unsuccessful (6-12 mo) lifestyle intervention

- the long-term safety and efficacy of pharmacological agents in children at risk for T2DM and the metabolic syndrome are unknown

- Safety and efficacy of other pharmacological agents not established in children with IFG or IGT



Lifestyle & Medical Interventions' Limitations

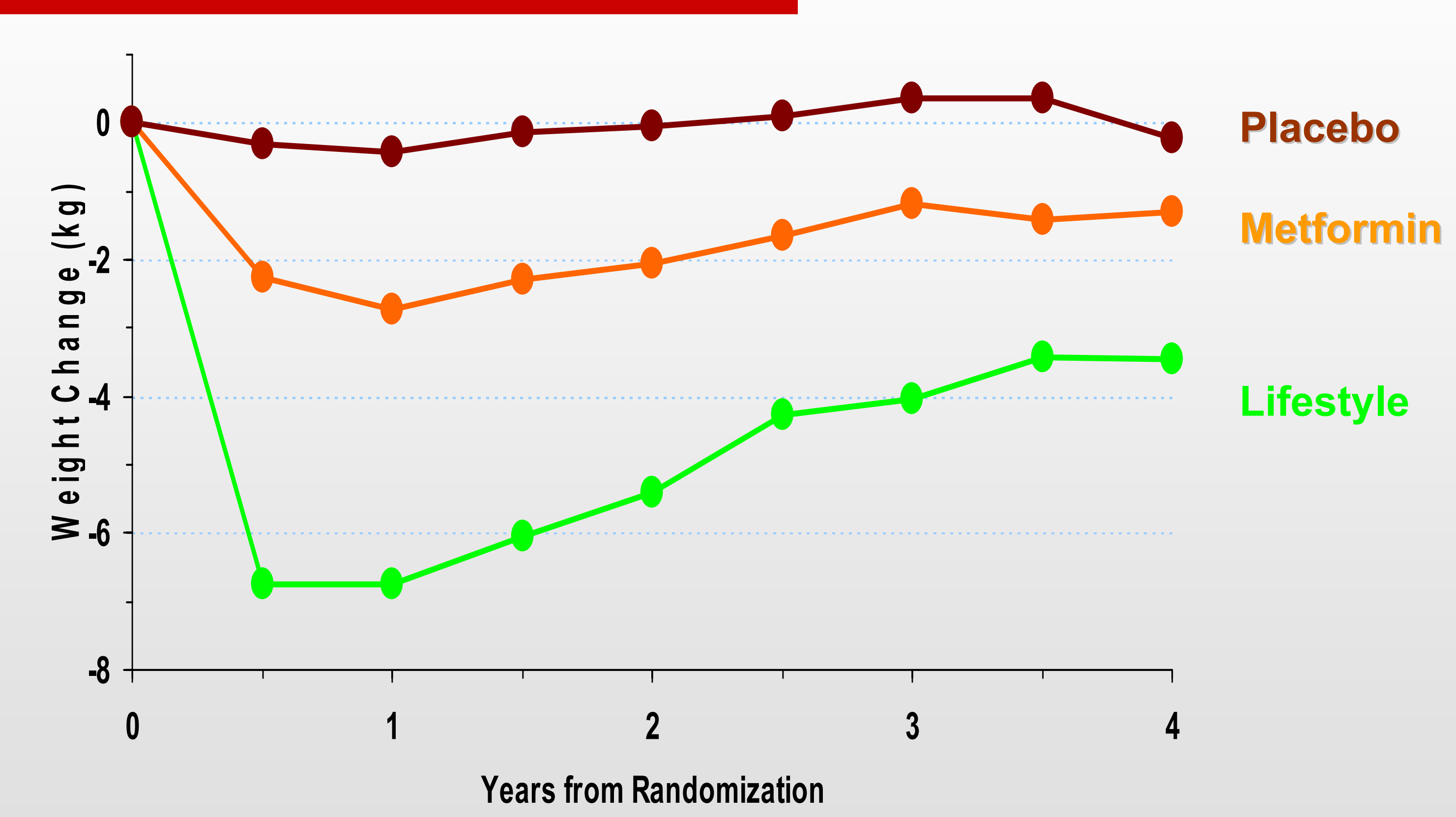
Lifestyle Interventions

- Labor intensive
- Difficult to replicate in health care systems
- Evaluated IFG or IGT patients → difficult to generalize

Drug trials

- Medicalising a lifestyle issue!!
- Side effects
- Beneficial only during Tx
- No agreement on duration of Tx

Mean Weight Change



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

Successful prevention of lifestyle diseases such as diabetes needs . . .

- individual and community-based interventions
- changes in government policies and legislation
  - mandating a greater emphasis on more exercise and dietary education in schools,
  - banning the advertising of unhealthy products
  - subsidizing healthy food at the expense of less healthy food