

Type 2 Diabetes Mellitus in Children: The Story Starts with Obesity

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WHO statement

“...an apparent epidemics of diabetes had occurred....which is strongly related to lifestyle and economic changes...”

Introduction

- 100 million worldwide affected by DM (>90% with T2DM)
- Diabetes ranks #1 in direct costs for health care of any disease category
- Majority of the costs due to complications steaming from the disease
- Incidence is steadily escalating
- Wide range of ethnic groups
- All socio-economic levels
- Projections for 2010: 230 million diabetics

Obesity-Epidemiology

- Significant health problem
- Global epidemic
- >50% of the adults (35-65 y) are overweight or obese
- 54% ⇒ in prevalence among children 6-11 y
- 39% ⇒ in prevalence among children 12-17 y
- F>M in all age groups
- Obese kids more likely to become obese adults
- 2nd leading preventable cause of death in US

Obesity-Types

1. Apple shape-android-abdominal obesity

■ Risk factor for IR

-Waist-to-hip ratio

>0.9 in males $\Rightarrow$ risk of IR

>0.8 in females $\Rightarrow$ risk of IR

■ CVD

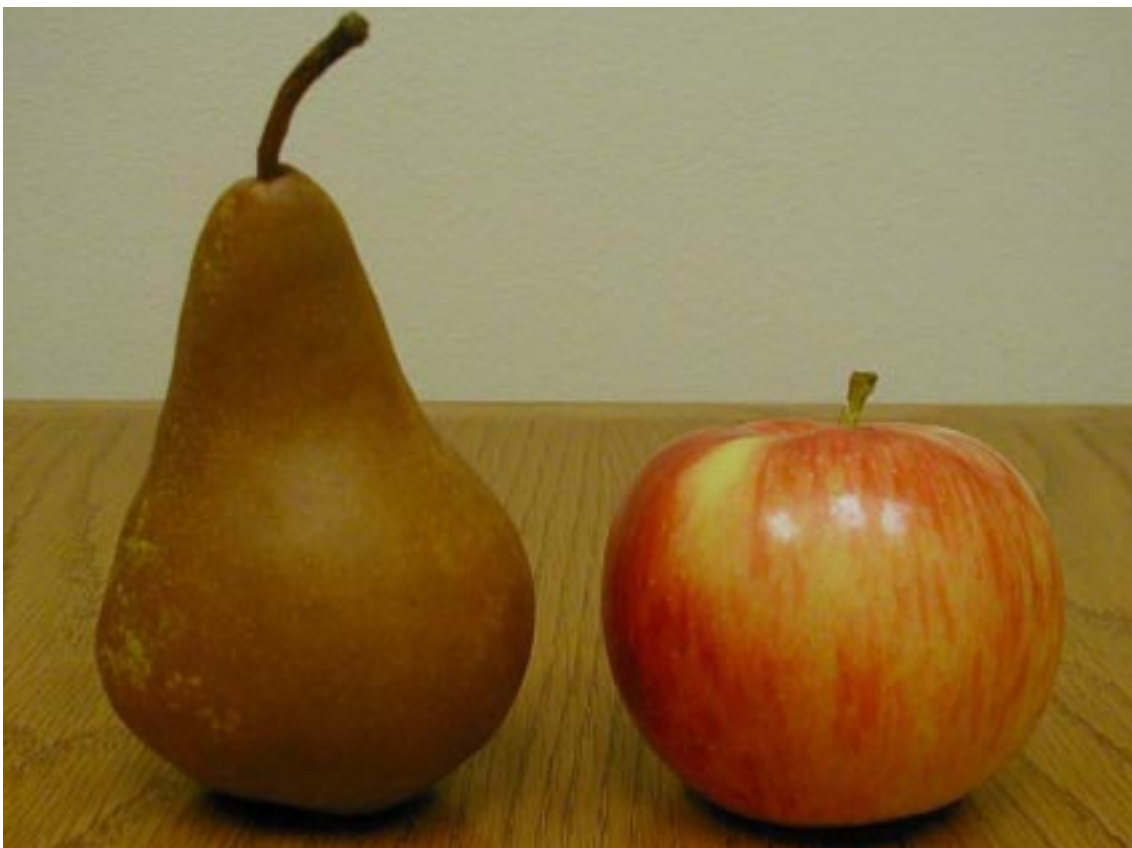
■ T2DM

■ Stroke

■ Hyperlipidemia

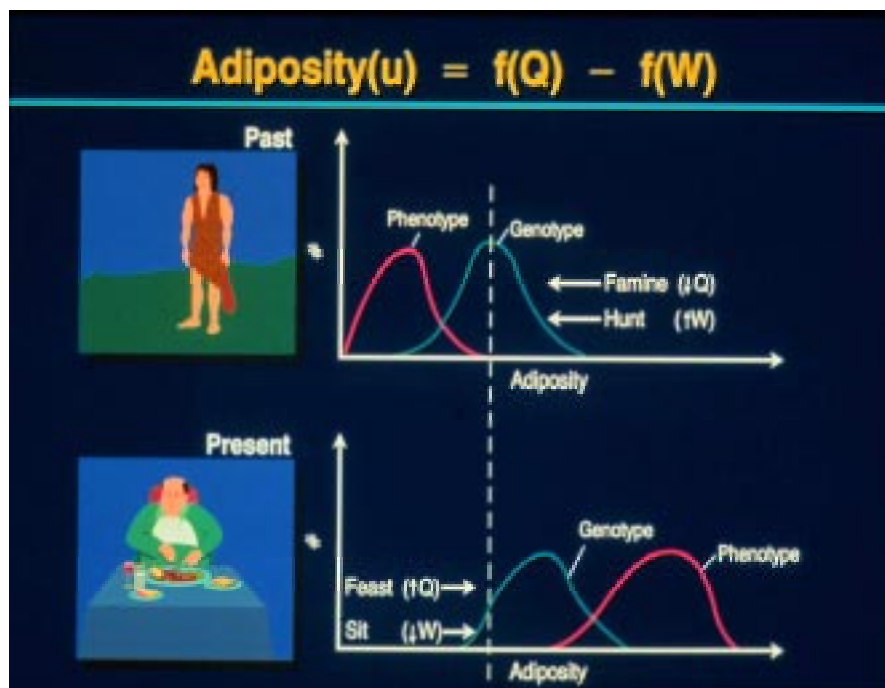
■ Metabolic Syndrome

2. Pear shape-gynoid-lower body obesity



Obesity-Causes

- Syndromes-RARE!!!
(PWS, Alstrom, Laurence-Moon-Bardet-Biedl)
- Endocrine-RARE!!! ($\Leftrightarrow$ thyroid, $\Leftrightarrow$ GH, $\Rightarrow$ F)
- Familial predisposition
- Environmental factors -"Disease of civilization"
- Food abundance ($\Rightarrow$ fat, $\Rightarrow$ concentrated CH, empty calories)
- Sedentary life style



Obesity-Metabolic Aspects

- Hyperinsulinemia
- Insulin resistance
- Increased FFA
- Increased cytokines (TNF α)
- Impaired total body glucose disposal
- Impaired hepatic glucose production
- β -cell dysfunction
- Hyperglycemia
- **T2DM**

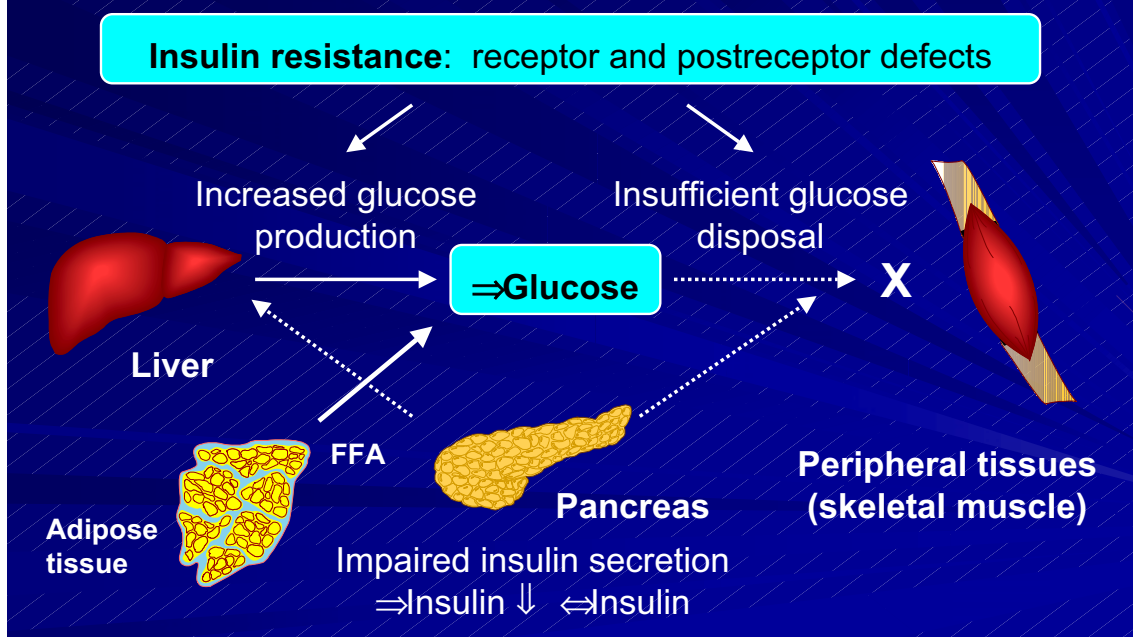
Obesity-Complications

- Orthopedic: genu varum/valgus deformities, SCFE, tibia vara
- Pseudotumor cerebri: HA, vomiting, diplopia
- Obstructive sleep apnea - cor pulmonale
- Gallstone formation
- Non-alcoholic steatohepatitis ("Fatty liver")
- Psychosocial consequences
- PCOS
- **T2DM**

Obesity-Treatment

- **Dietary therapy**
 - well balanced diet
 - achieve caloric deficit ($\div$ # of calories not the kind)
- **Exercise/Activity**
 - linear relationship between hours TV watching and obesity
 - aerobic exercise 3-4 x week
- **Life style changes/behavior modification**
 - parental involvement
- **Drug therapy:**
 - still experimental, not approved for children
- **Surgical techniques**
 - limited data, only for morbidly obese children

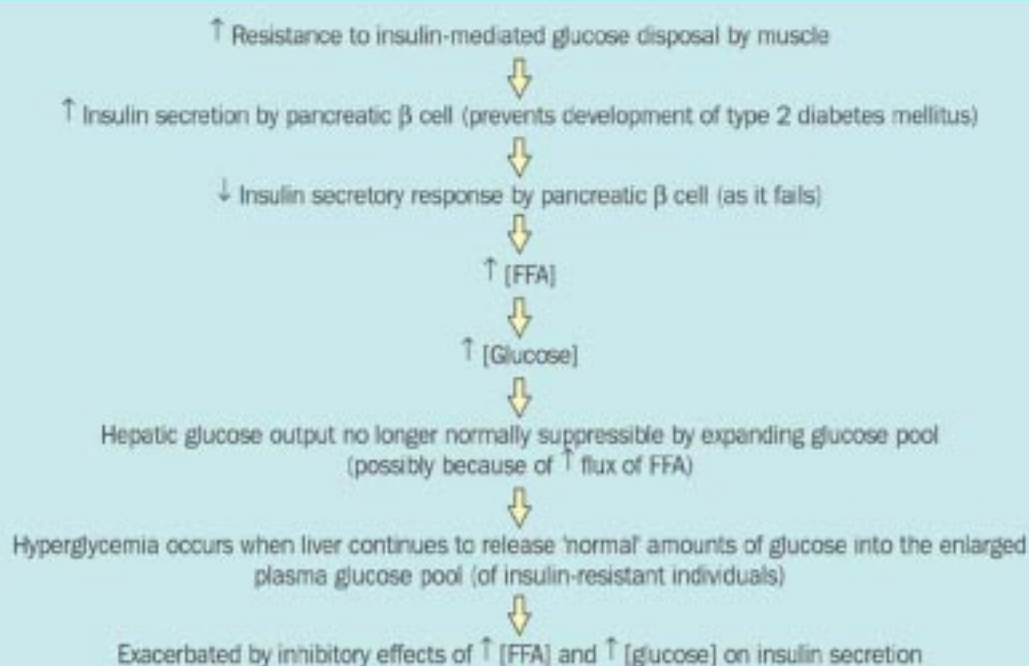
Causes of Hyperglycemia in Type 2 Diabetes



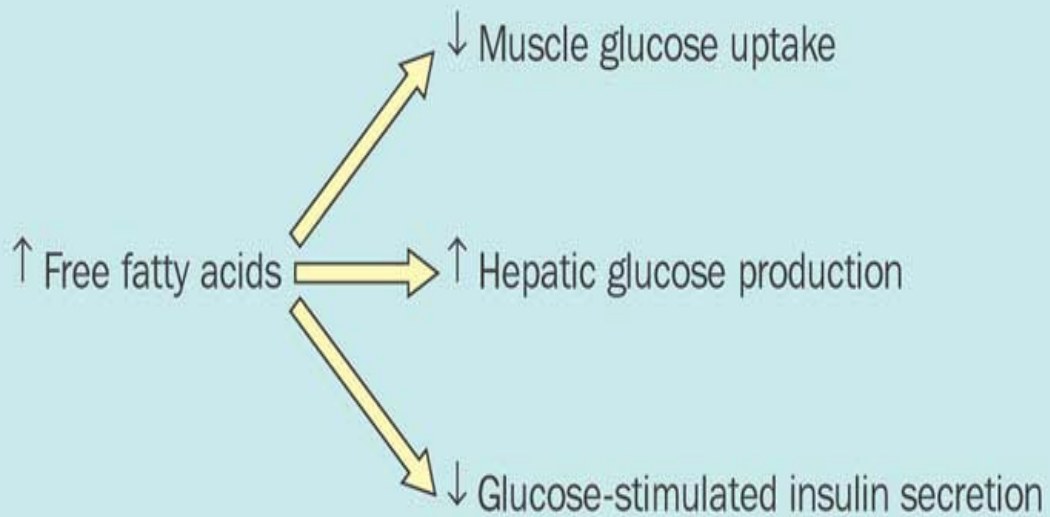
η -cell Dysfunction Central feature in the Natural History of T2DM

- Present in subjects with DM, IGT and first degree relatives of subjects with DM
- Predicts the development of DM in prospective studies
- Subjects with NGT have a balance between insulin sensitivity and secretion

Development of type 2 diabetes mellitus



Role of free fatty acids in type 2 diabetes mellitus



Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
Elsevier Science Ltd

Clinical Cases

Case #1

- 6-7/12-year-old AA girl, referred for the evaluation of morbid obesity (BMI 34 kg/m²) and possibility of T2 DM
- Presented with complaints of burning and itching on urination.
- Glucose reported: 300 mg/dL (15mmol/L)
- No Rx except diet ÷ and to ⇒PA.
- PMHX significant for severe weight gain since age 2
- FHx + for T2 DM and obesity in the mother

Laboratory evaluation OGTT

Glucose

0'	56	mg/dl
30'	129	mg/dl
60'	193	mg/dl
90'	220	mg/dl
120'	250	mg/dl
	[12.5	mmol/L]

Insulin

0'	189.4	σIU/ml
	[1359	pmol/L]
30'	860.0	σIU/ml
60'	1072.6	σIU/ml
90'	1488.6	σIU/ml
120'	1675.8	σIU/ml
	[12023	pmol/L]

Elevated: HgbA1C, C-peptide, LDL

Normal: σalb, thyroid, BCP



Case #2

- 15 y/o AA female
- Burning and itching on urination
- Some weight loss
- Overweight - BMI 37.2 kg/m²
- Severe AN
- BS 450 mg/dL (22.5 mmol/L)
- HgbA1C 15.0% (4-6 %)
- Normal: thyroid, σ alb; Ab-;
- Normal HCO₃⁻, ketones in urine
- Abnormal lipid profile

T2 DM in Youth

- Has not been considered a pediatric disease
- Alarming trend of increasing numbers of children developing T2DM
- Data on youth T2 DM still quite limited

Clinical Characteristics

- Obese adolescents
- Minority populations
- Strong family history (1st or 2nd degree relatives)
- Elements of Metabolic syndrome
- Acanthosis Nigricans
- Presents at time of the puberty
- Female predominance

Clinical presentation

- Wide spectrum
- Obesity-universal feature
- Acanthosis Nigricans
- Asymptomatic child-incident diagnosis (routine medical check up-glycosuria)
- Vaginal candidiasis-females
- Severe form-classical symptoms
- Ketoacidosis-rare
- Distinction form T1 DM often not possible at the Dx until insulin requirements decline

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WORKSHOP III



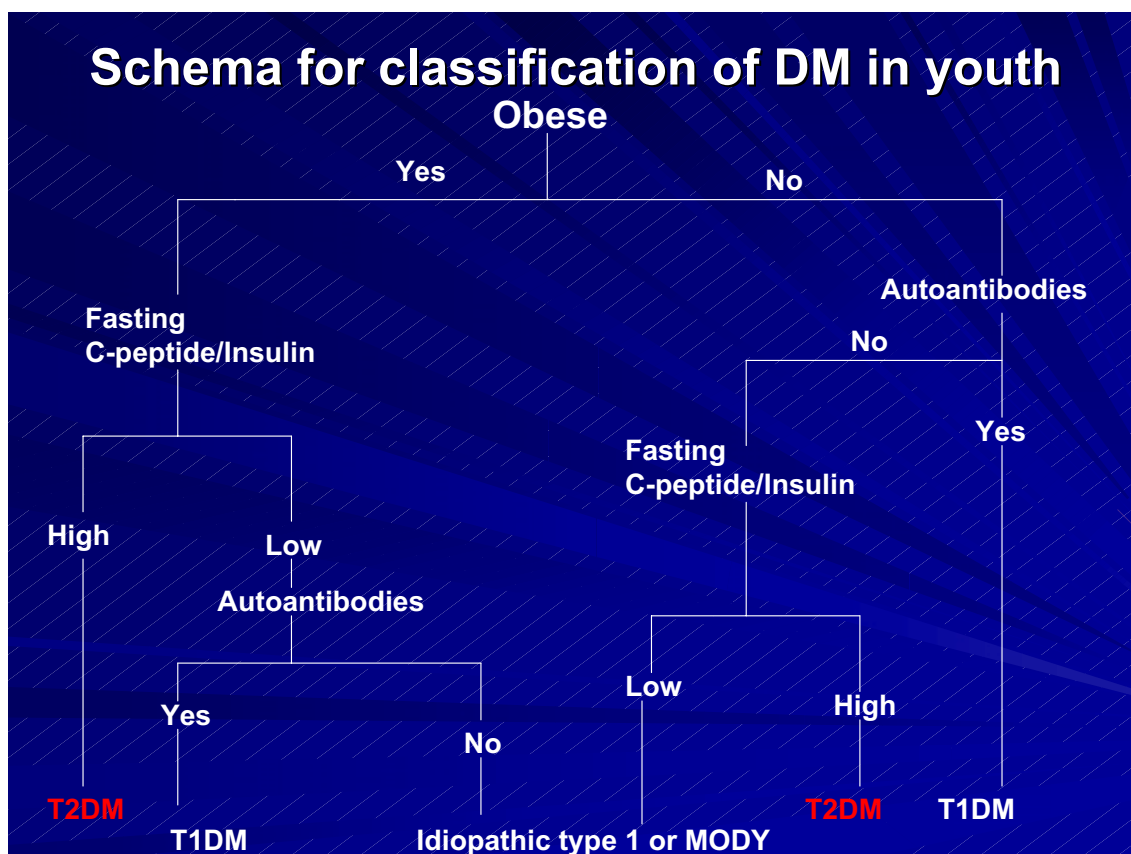


Biochemical abnormalities

- Less severe than in T1DM
- Plasma glucose less elevated
- Ketones less often present
- Acidosis infrequent
- C-peptide $\Rightarrow\Rightarrow$
- Insulin $\Rightarrow\Rightarrow$

Characteristics of T1DM and T2DM in Youth

Characteristic	T1DM	T2DM
Gender	F=M	F>M
Age at Dx	Child/Adol	Adol
Ethnic group	White	AA, HA, NA
Autoimmunity	Common	Uncommon
Obesity	Uncommon	Common
AN	Uncommon	Common
F HX	Infrequent	Frequent
Insulin dependence	Lifelong	Episodic



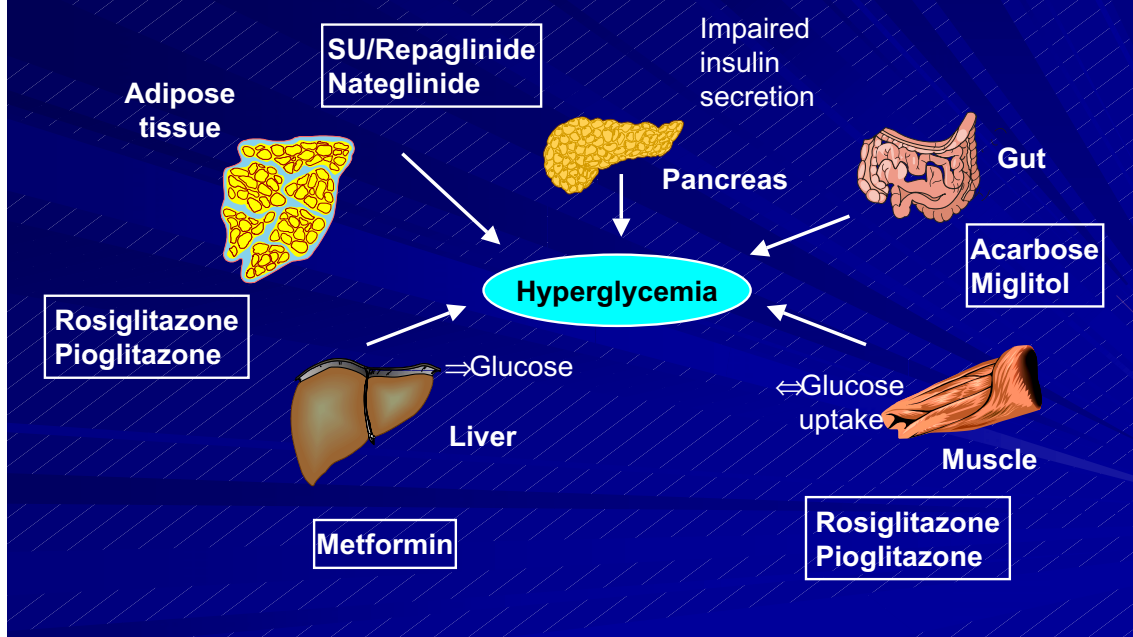
Epidemiology in Youth

- Not well studied
- Ranges from 8-45% of new diabetes case depending on location and patient population
- In adults 1/3 undiagnosed-probably same in youth
- Large studies in Pima Indians (have highest prevalence of DM in the world); incidence doubled in past 10 years-follows increase in obesity
- Japan: incidence increased 1.5x over 15 years
- Cincinnati: incidence increased 10x over 10 years

Management of T2DM: Long-term Challenges

- Weight loss
- Glycemic control
- Prevent microvascular complications
- Prevent macrovascular complications
 - Improve dyslipidemia
 - Control BP
 - Improve vascular abnormalities
 - Endothelial function
 - Fibrinolytic mechanisms
- Promote long-term glucose homeostasis

Oral Therapy for Type 2 Diabetes: Sites of Action



Biguanides: Metformin

Advantages

- High initial response rate
- Rare hypoglycemia
- **Limited weight gain**
- **← macrovascular complications with monotherapy as observed in UKPDS**

Disadvantages

- GI side effects up to 50%
- Not tolerated in up to 4%
- Risk of lactic acidosis
- Contraindicated in patients with impaired renal function and CHF
- Twice daily dosing

Metformin in Children

- Well tolerated
- Approved by FDA
- Adverse effects similar to adults
- Used for Rx of IR/IGT

Thiazolidinediones

Advantages

- Glycemic control without hypoglycemia
- Positive lipid effects
- Can be used in renal insufficiency
- Preservation of η -cell function
- Protective vascular effects
- Protective renal effects
- Reduce intrahepatic and visceral fat
- Increase subcutaneous fat

Disadvantages

- Delayed onset of action
- Weight gain
- Fluid retention
- Liver monitoring required
- Unknown long term side effects
- Clinical cardiovascular outcomes not formally proven

Metabolic Effects of Oral Agents in Monotherapy

	TZD	Metformin	SU	ζ -GI
Weight	$\Rightarrow$	$\Leftrightarrow$	$\Rightarrow$	$\Leftarrow$
LDL	$\Rightarrow$	+/- or $\Leftrightarrow$	$\Leftarrow$	$\Leftarrow$
HDL	$\Rightarrow\Rightarrow$	+/- or $\Rightarrow$	$\Leftarrow$	$\Leftarrow$
Triglycerides	$\Leftrightarrow$ or $\Leftarrow$	$\Leftrightarrow$	$\Leftarrow$	$\Leftarrow$
FFA	$\Leftrightarrow$ or $\Leftarrow$	$\Leftrightarrow$ or $\Leftarrow$	$\Leftrightarrow$	$\Leftarrow$
IR	$\Leftrightarrow$ or $\Leftarrow$	$\Leftrightarrow$	$\Leftarrow$	$\Leftarrow$
HTN	$\Leftrightarrow$	$\Leftarrow$	$\Leftarrow$	$\Leftarrow$

T2 DM related Morbidity

- Diabetic retinopathy
- Diabetic nephropathy
- Diabetic amputations
- Diabetic vascular disease

Complications in Youth

- Present at the Dx and F/U
- Japanese children-incipient retinopathy was detected by fluorescein angiography in 36% of cases at the Dx; 39% in 2 y F/U
- Pima Indians-22% children had σ alb at Dx; 60% at F/U and 17% with macroalb

T2DM and Co-Morbidities

- Hyperlipidemia
- Hypertension
- Microalbuminuria
- Early intervention is indicated

Summary

- Current epidemic of obesity in youth
- Increased incidence of T2DM in youth
- Important to distinguish between T1DM/T2DM/MODY
- Earlier age at diagnosis-earlier complications
- Poor DM control among the youth

Summary

- **Early recognition of risk factors**
- **Prevention of weight gain!!**
- **Weight loss!!**
- **Prevention of T2DM**

Thank you



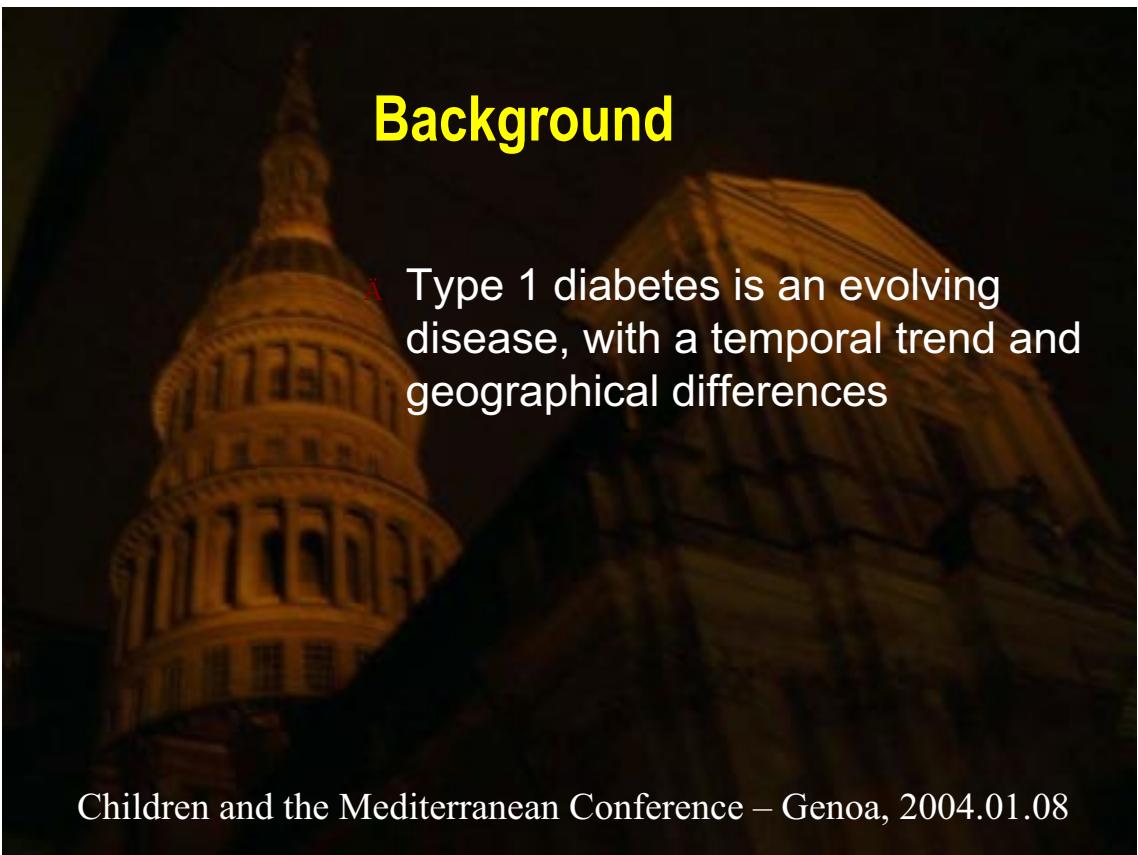
Younger onset of type 1 diabetes in immigrants' children born in Italy

Francesco Cadario
(Paediatric Clinic of Novara)
on behalf of the Diabetes Group of
Italian Society of Endocrinology
and Diabetes (S.I.E.D.P.)

Children and the Mediterranean Conference – Genoa, 2004.01.08

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WORKSHOP III



Background

Type 1 diabetes is an evolving disease, with a temporal trend and geographical differences

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Onkamo P. et al. Worldwide increase in incidence of Type 1 diabetes-the analysis of data on published incidence trends. *Diabetologia* 1999, 42: 1395-403
Gale EAM. The rise of childhood Type 1 diabetes in the 20th century. *Diabetes* 2002, 51:3353-61

A Type 1 diabetes is increasing worldwide. It is estimated that on an annual basis almost 100 000 children younger than 15 years of age develop Type 1 diabetes worldwide

A The increasing incidence is observed in all age groups, but is most pronounced in youngest age group (0-4 years)

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EURODIAB ACE Study WHO DIAMOND Project Group

A A large up to tenfold variation in the incidence of childhood Type 1 diabetes is present in Europe and Mediterranean area

A A more than 350-fold differences are documented worldwide in the incidence, with Sardinia and Finland at the top and Venezuela and China at the bottom of the list

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Incidence of T1DM worldwide, in children 0-14 years old, 100,000 /year), from 1990 to 1994. DIAMOND

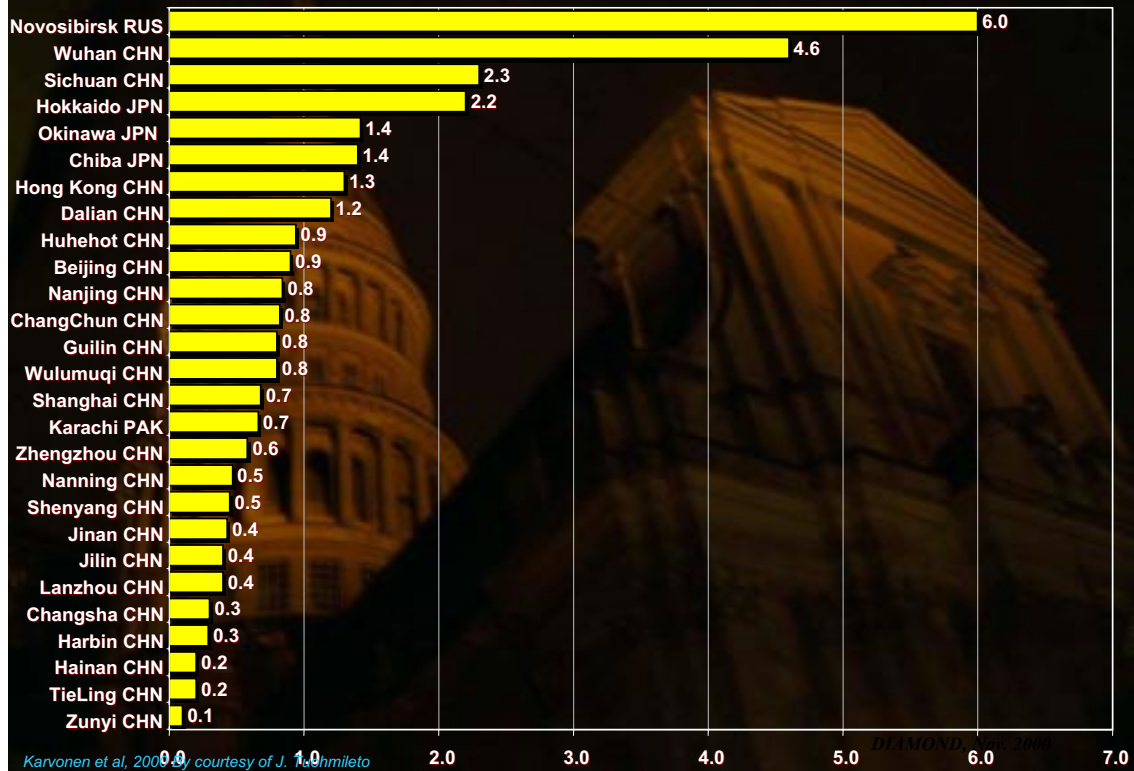
Karvonen et al, 2000 By courtesy of J. Tuohimileto



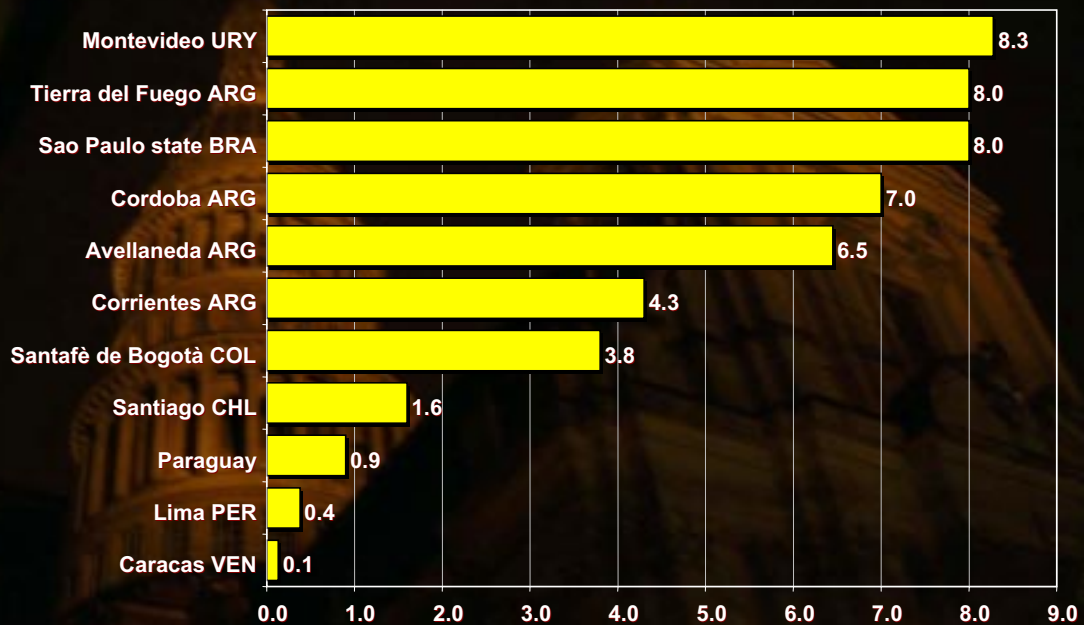
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Incidence of T1DM in ASIA



Incidence of T1DM in South America



Karvonen et al, 2000 By courtesy of J. Tuohimäki

DIAMOND, Nov. 2000

The rise of childhood Type 1 diabetes

E.A.M. Gale, *Diabetes* 2002: 51, 3353-61

- A An almost simultaneous upturn is documented in several countries around the mid-century
- A The overall pattern is linear increase, with evidence of a plateau in some high-incidence populations and a catch-up phenomenon in low incidence areas

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EURODIAB ACE Study Group, Green A, Diabetologia 2001, 44 (S3):B1-2

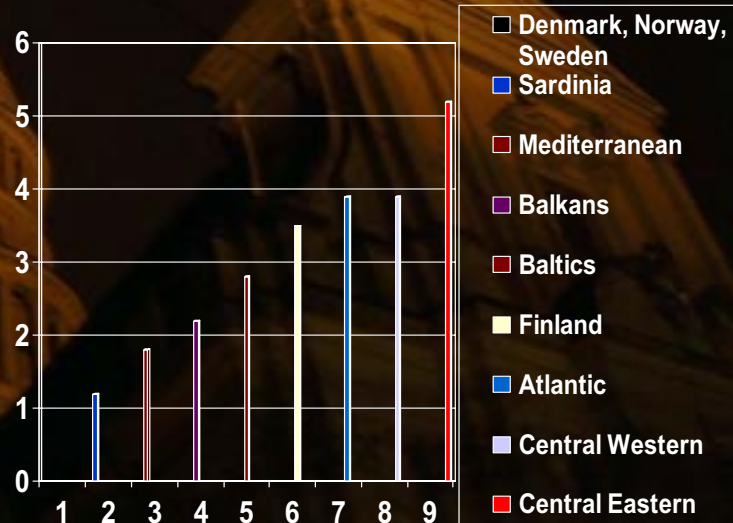
- A The increasing incidence over a relatively short period likely reflects environmental changes, and younger onset is probably an after-effect of a more aggressive pattern of promoters on genetic susceptible individuals
- A The trend in Europe is defined: the incidence is low or stable in Nordic countries, and increasing dynamically in Central Europe, or fast in Central Western countries

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WORKSHOP III

Annual rate of increase in incidence of T1DM in children (0-14 years) from 1989 to 1998 EURODIAB Study Group



We speculate

- Worldwide there is lack of data, but we presume developing countries are still at an earlier stage of the natural evolution of Type 1 diabetes

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Aims

- to research causes of increased incidence of the disease in Europe
- and identifying promoters acting now in developing countries,
- we studied children of immigrants from developing countries to a westernised area as Italy, when rapidly change environmental conditions

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Immigration

Immigration in Italy is a recent phenomenon of the last three decades, so in immigrants' children we may investigate the impact of environmental changes as just happened

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Objective

We focus on the age at onset of T1DM in immigrants' children; specifically we investigate whether the location of birth, if inside or outside Italy, influenced the age at onset of the disease

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Subjects and Methods

Inside the Italian Society for Paediatric Endocrinology and Diabetes, a Group of study was made to collect data on immigrants' children affected by Type 1 diabetes.

To enter in the Study each Unit was required to enlist entirely owns' series of diabetic children. 39 Units agree to this work

Diagnosis of Type 1 diabetes was done clinically; patients overweight, or with *Acanthosis nigricans*, or with oral hypoglycaemic drugs at diagnosis were excluded because possibly Type 2 diabetes

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39 Paediatric Diabetes Units of the Italian Society for Endocrinology and Diabetes take part to the study on immigrants' diabetic children



- **Period: 2002**
- **From 4292 T1DM, 0-18 years old, about half of current Italian diabetic children**
- **Cases: 121 T1DM immigrants' children**
- **69 born in Italy, and 52 outside European Union**

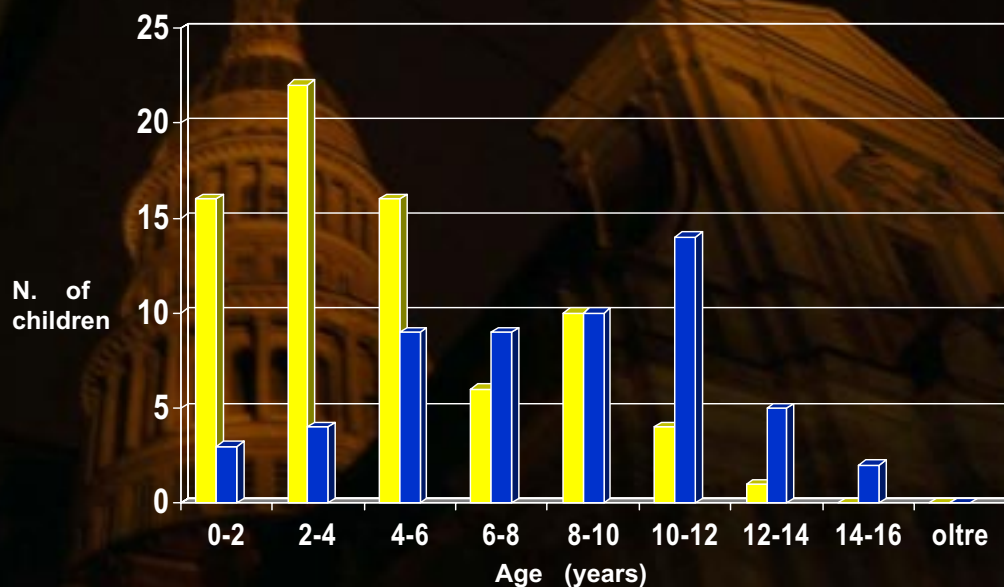
& Acqui Terme, Cuneo, Tortona, Ivrea, Cuneo, Treviglio, Tradate, Montebelluna, Asola, Castelfranco Veneto

Results

At onset of Type 1 diabetes immigrants' children **born in Italy** were significantly younger (median **4 ys**, interquartile range 2,1-6,0) then those **born outside** in developing countries (**8.4 ys**, interquartile range 5,0-10,9) $p < 0.0001$

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Age at onset of T1DM in children immigrated from developing countries either born **inside** or **outside** Italy



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Results

- 7 children immigrated in their first yr of life developed T1DM at median age of 7.0 ys
- In mixed families age at onset of the disease was less precocious than in families with both immigrant parents (5.4 ys vs 3.1 ys, $p = 0.02$)
- Median age at onset of T1DM of the Italian children was 6.7 ys

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Remark

- Children with an earlier onset of Type 1 diabetes are less likely to survive in developing countries, but younger onset of the disease in immigrants' children born in Italy was still present when the outbreak of the disease was in our country

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Regressive analysis on age and birthplace

- Despite lack of data on underlying population at risk, but probably immigrants' children born in Italy are younger than those born outside, and therefore may generate younger T1DM
- Both age ($p < 0.0001$) and birthplace ($p = 0.002$) significantly contribute at age at onset of T1DM

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Age-period-cohort analysis

<i>Subgroups according to years of birth</i>	<i>Born in Italy</i>	<i>Born outside Italy</i>	<i>p</i>
1998-2002 (n.14), 0-4 ys Age at onset ys	(n.13) 2.3	(n.1) 1.1	NS
1993-1997 (n.37), 5-9 ys Age at onset ys	(n.28) 3.9	(n.9) 4.2	NS
1988-1992 (n.48), 10-14 ys Age at onset ys	(n.23) 6.0	(n.25) 8.7	0.02
Before 1988 (n.22), 15-18 ys Age at onset ys	(n.5) 3.1	(n.17) 10.3	0.01
All children (n.121)	(n.69) 4.0	(n.52) 8.4	0.0001

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Age at onset of T1DM according to ethnic origin

	Born in Italy	Born outside	<i>p</i>
Arabic (69) age	(45) 3.4	(24) 9.0	<0.0001
Eastern European (24) age	(9) 3.0	(15) 8.5	NS
South Americans (13) age	(8) 5.1	(5) 6.3	NS
Others (15) age	(7) 5.9	(8) 9.1	NS

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Characteristics of 121 children with T1DM immigrated from developing countries either born in Italy or in their country of origin

All children (121)	Born in Italy (69)	Born outside (52)	<i>p</i>
Birth weight (g) Mean (SD)	3195 (666)	3246 (564)	NS
Breast feedings at 4 th month (%) And duration (median)	59.4 6	50.4 6	NS NS
Age at wearing (months)	5	5	NS
Glycated Haemoglobin at onset (%) Mean (SD)	10.8 (2.0)	11.8 (2.7)	0.05

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What may make different the two groups?

- ⌘ Hygiene hypothesis? In pregnancy or just after birth?
- ⌘ Different age of mothers of children born inside or outside Italy?
- ⌘ Diet differences and specifically precocious intake of gluten in the diet of babies?
- ⌘ Accelerator hypothesis?

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Hygiene hypothesis?

*E. Gale. A missing link in Hygiene Hypothesis? *Diabetologia* 2002. 45:588-94

- ⌘ The less frequent infectious or parasitic diseases may hasten T1DM in children born in a developed country*,
- ⌘ probably in pregnancy or just after birth because when children immigrated in their 1st yr of life presented the same age at onset like those immigrated later on

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Older age of mothers of children born in Italy?

The increased maternal age is a risk factor for T1DM in childhood but in Bart's-Oxford Study only a weak inverse correlation was found between maternal age at delivery and earlier onset of T1DM*

*The BOX Study Group. Influence of maternal age at delivery and birth order on risk of T1DM in childhood. BMJ 2000. 321:420-23

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Diet with intake of gluten in the first three-month period of life of babies?

Gluten containing foods cause in high risk genetic genotype children auto-antibodies against η -cells or T1DM, when gluten intake starts before 3 months age*

Gluten diet is less expensive than gluten free diet and infant feeding may be associated with variables as socio-economic status

*Ziegler. Early infant feeding and risk of developing Type 1 diabetes associated auto-antibodies. JAMA 2003. 290:1721-28

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The accelerator hypothesis?

Recently a relationship was reported between younger age at diagnosis of T1DM and increased body mass after birth, and likely immigrants' children born in Italy may gain weight than those born and living in developing countries*

*M. Kibirige. Testing the Accelerator hypothesis.
Diabetes Care 2003. 26:2865-70

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Main findings

- A Younger age at onset of T1DM is present in immigrants' children born in Italy in front of those born in developing countries,
- A even in those immigrated in the 1st year of life
- A In mixed families, with one parent immigrant and the other Italian, the age at onset was intermediate in comparison of the two groups

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Conclusions

- Environmental determinants are likely involved
- We were not able to find these
- The promoters probably act in the first year of life or in pregnancy
- In mixed families probably a partially selected genetic background limits the impact of the environmental determinants on susceptible individuals

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Future developments

- If our findings will tested and confirmed in other Mediterranean nations with recent immigration, it may open a new way to investigate environmental promoters of T1DM
- and “our future ability to prevent the disease at the level of population rest on the identification of such determinants”. *

***Edwin Gale. Can we change the course of beta-cell destruction in Type 1 diabetes? N Engl J Med, 2002. 346:1740-1**

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