

How much popular is the metabolic syndrome in children?

# Metabolic syndrome?

- 1988, Reaven

“The constellation of metabolic abnormalities including insulin resistance, glucose intolerance, type II DM, hypertension, dyslipidemia, which promote long-term cardiovascular complication”

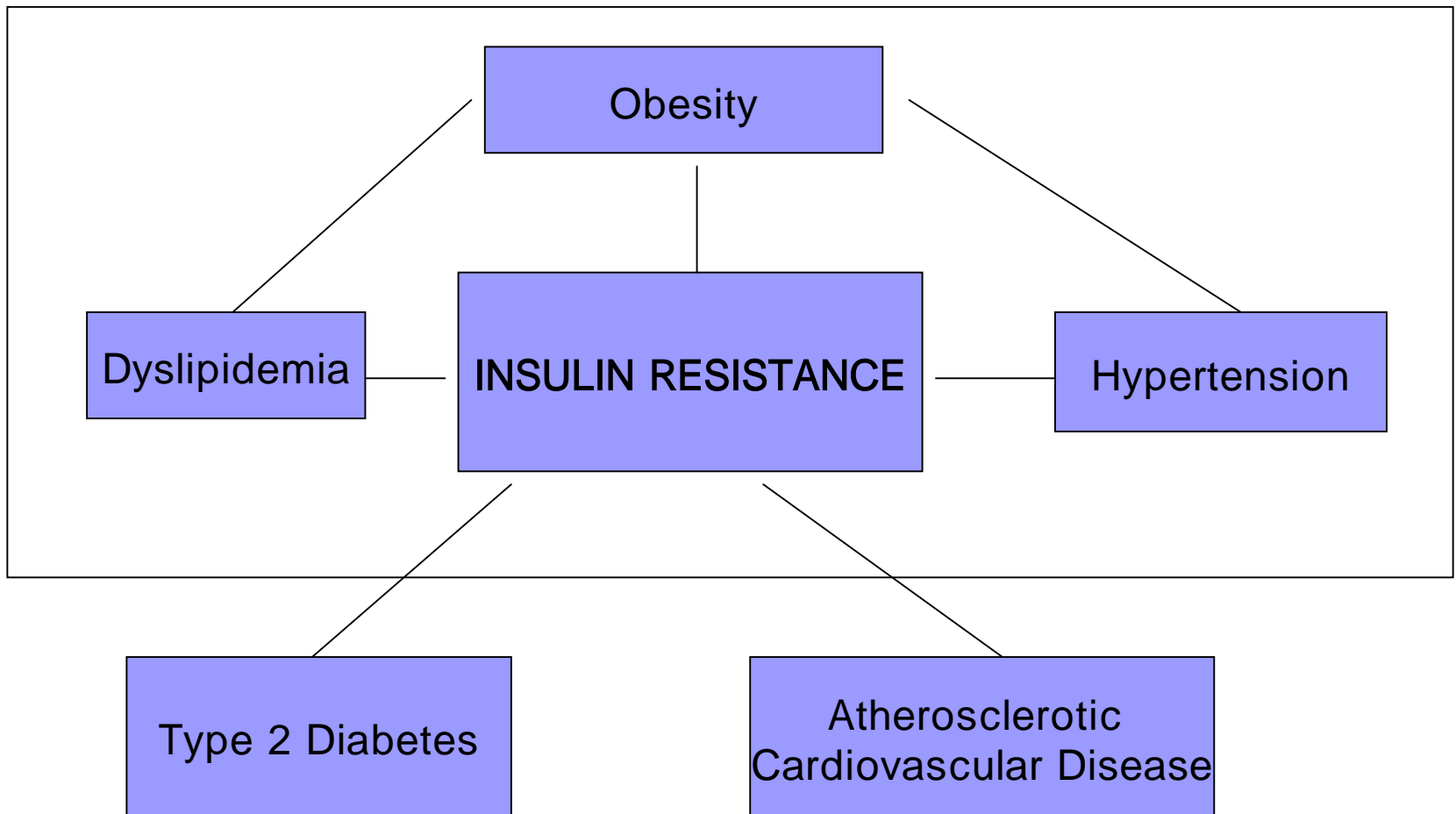
- Reaven GM. Diabetes 1988

\*Syndrome X (1933)

\*Insulin resistance syndrome

\*Cardiometabolic syndrome

# Metabolic syndrome



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- 1. Social issue- obesity, well being, diet, ...

→ preventive medicine!

- 2. ,

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# Diagnostic criteria in adult

ADA(1998)	NCEP(1998)	WHO(1998)	AACE(2002)
Glucose intolerance	Fasting plasma glucose 110-125 mg/dL	Type 2 diabetes, impaired glucose tolerance, or insulin resistance by HOMA <sub>IR</sub>	Fasting plasma glucose 110-125 mg/dL or 2-h post 75 g glucose challenge >140 mg/dL
Central obesity	Waist circumference >40 in (men) or >35 in (women)	BMI >30 or waist-hip ratio >0.90 (men) or >0.85 (women)	BMI 25 or waist circumference >40 in (men) or >35 in (women)
Dyslipidemia: high TG, low HDL, small dense LDL	TG 150 mg/dL, HDL <40 (men), HDL<50 (women)	Dyslipidemia: TG 150 mg/dL, HDL<35 (men), HDL <39 (women)	TG 150 mg/dL, HDL <40 (men), HDL <50 (women)
Hypertension	Blood pressure 130/85 mm Hg	Hypertension: on medication or untreated blood pressure 160/90 mm Hg	High blood pressure ≥130/85 mm Hg
Increased prothrombotic and antifibrinolytic factors Increased atherosclerotic vascular disease		Microalbuminuria ≥20 Ag/min	

# In children, ...

- Insulin resistance syndrome

- 1. Obesity-abdominal cavity

- 2. Insulin resistance-hyperinsulinemia

- 3. Increased triglycerides, decreased HDL cholesterol

- 4. Hypertension

- Progress in pediatr cardiol, 2001

# Metabolic syndrome :

## proposed components and associated findings

- 1. Insulin resistance
- 2. Hyperinsulinemia
- 3. Obesity: visceral(central), but also generalized obesity
- 4. Dyslipidemia: high triglycerides, low HDL, small dense LDL
- 5. Adipocyte dysfunction
- 6. Impaired glucose tolerance or type 2 diabetes mellitus
- 7. Fatty liver(nonalcoholic steatohepatosis, steatohepatitis)
- 8. Essential hypertension: increased systolic and diastolic blood pressure
- 9. Endothelial dysfunction
- 10. Renal dysfunction: micro- or macroalbuminuria
- 11. Polycystic ovary syndrome
- 12. Inflammation; increased CRP and other inflammatory markers
- 13. Hypercoagulability: increased fibrinogen and PAI-1
- 14. Atherosclerosis leading to increased cardiovascular morbidity and mortality

# Pathophysiology

- 1. Insulin resistance
- 2. Dysfunctional energy balance

Phillippa J et al. Am Heart J 2005

# How might **insulin resistance** generate other features of the metabolic syndrome?

## Mechanism

### ■ **1. Hyperglycemia**

: Moderate hyperglycemia->advanced glycosylated end products or enhanced collagen formation->accelerated atherogenesis

### ■ **2. Compensatory hyperinsulinemia**

1) muscle: stimulates glucose uptake

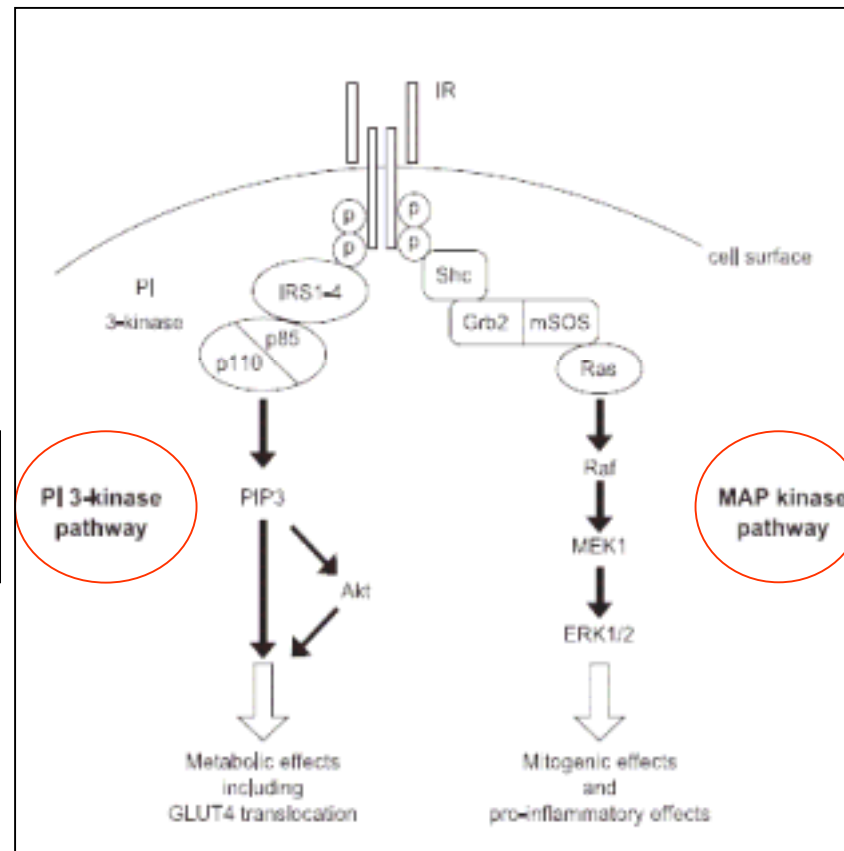
2) liver: suppresses endogenous glucose production

\*in insulin resistance state-↓the ability of insulin to augment glucose uptake and ↓ inhibit hepatic glucose production

### ■ **3. The pathways of insulin action are thrown off balance**

PI-3K pathway, MAP kinase pathway

## 2 major pathway of insulin signaling



Increase nitric oxid

PI 3-kinase pathway

MAP kinase pathway

Smooth muscle cell growth & proliferation

In metabolic syndrome, PI 3K pathway-blocked  
MAP kinase pathway-remained

## 2. Dysfunctional energy balance

Long chain fatty acyl CoA(LCAC)

->increase oxidative stress

: 가

LCAC가

ATP

adenosine nucleotide translocase

ATP가 ATP synthase

ATP

reactive oxygen

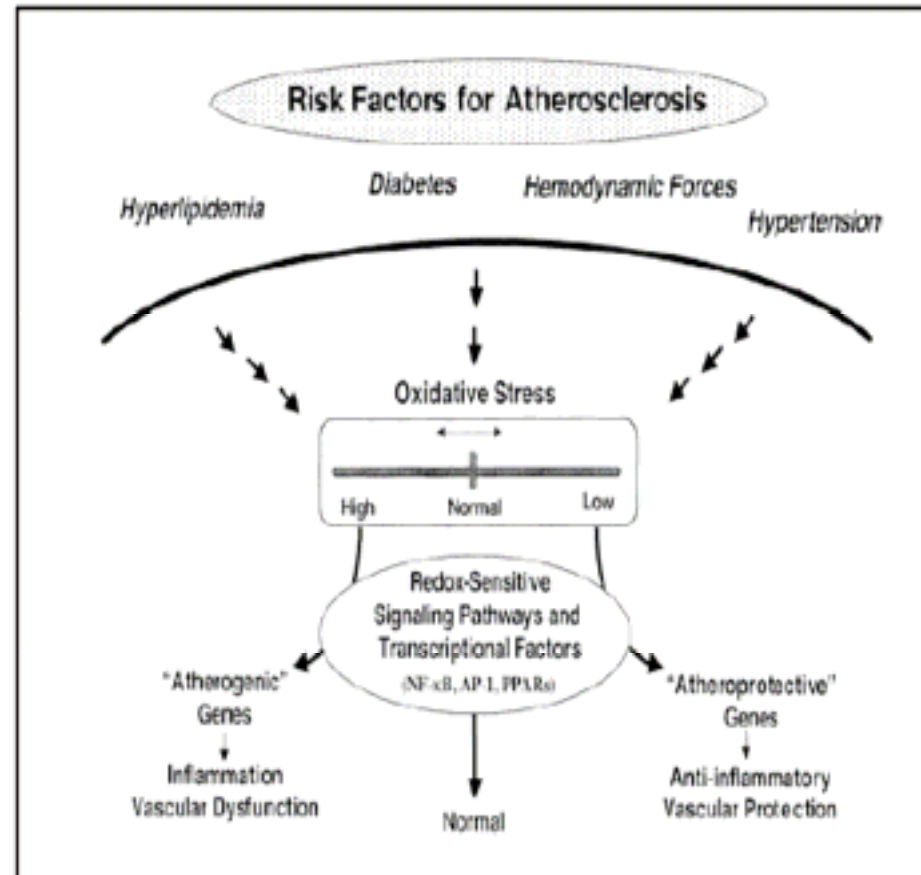
species(ROS)

$O_2^-$

가

->insulin resistance, diabetes,  
inflammation, vascular dysfunction

->atherosclerosis



Kunsch C et al. Circ Res 1999

## Insulin resistance

## Dysfunctional energy valance

Insulin resistance

Compensatory hyperinsulinemia

To maintain euglycemia, especially

Postprandially

Obesity(appetite stimulation?)

Beta - cell exhaustion and diabetes

Overstimulation of MAP kinase pathway

Dyslipidemia due to high fatty acid flux

Metabolic syndrome

Increased atherosclerosis and  
cardiovascular disease

Triglycerides and fatty acids

(molecules of energy storage and  
utilization)

Triglyceride stored physiologically in  
Small peripheral adipocytes

Energy in > energy out

With obesity, excess triglyceride goes to  
Hepatocytes(fatty liver)

Skeletal myocytes, visceral adipocytes,  
Abnormal large peripheral adipocytes

Excessive triglyceride leads to insulin  
resistance in these cell and metabolic  
syndrome with increased cardiovascular  
disease

# Prevalence of metabolic syndrome in adult

## NCEP criteria to the National Health and Nutrition Examination Survey III data set

Ford ES et al, JAMA 2002

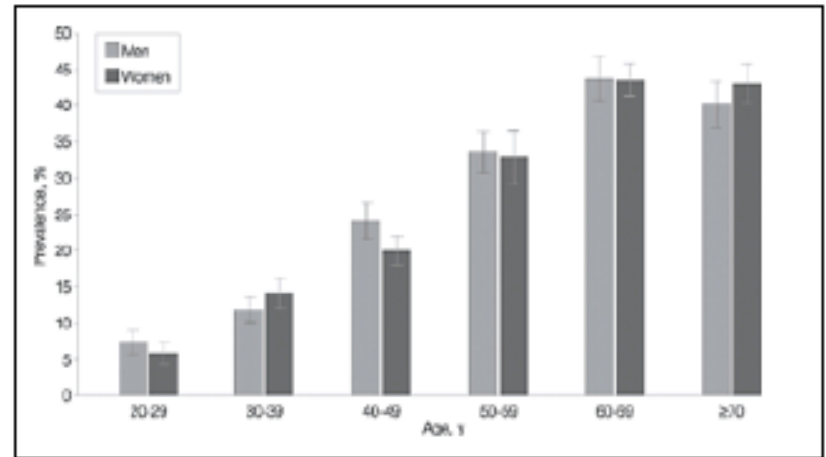
-US adult: 22%

20 to 29 y of age : 6.7%

60 to 69 y of age : 43.5%

Hispanics > blacks or whites

Black women > white women, white men > black men



## ■ Korea adult

■ male 12.8%, female 19.6%

1999

■ 30 : 20%

■ 가 가 가 가

■ 30-40 : male > female, 50 : female > male

2002

# Metabolic syndrome in children

- Similar to the trend in adults,  
increase in the rate of obesity and type 2 DM in children in the US
  - Luepker RV et al, J Pediatr 1999
- Metabolic syndrome is a **developmental disorder** strongly influenced by risk factors in the **first 2 decades of life**.  
-examined the interaction among fasting insulin, lipoproteins, blood pressure, and weight in children
- **Insulin resistance** was associated with risk factors for metabolic syndrome in **11-to 14 y olds**, regardless of body fat.
  - Sinaiko et al, J Pediatr 2001

# Obesity

- Obesity :  
body mass index(BMI) of 95<sup>th</sup> percentile for age
- At risk of obesity or overweight :  
BMI between the 85<sup>th</sup> and 95<sup>th</sup> percentile for age

- The NHANES (National Health and Nutrition Examination) surveys : the prevalence of overweight has increased from 15 to 22-23% in the latest survey  
->this means that the risk of sequelae may also be increasing among children and adolescents

\*In Korea

6.4	(1979	3.6%,	1996	23.0%),
4.7	(1979	3.3%,	1996	15.5%),
3.0	(1979	5.2%,	1996	15.4%),
2.4	(1979	6.3%,	1996	15.0%)

# Obesity and insulin resistance

- Obesity : strongly associated with insulin resistance in normoglycemic and type II DM and with cardiovascular disease.
  - Obese adults-insulin resistant when compared with normal control group and strongly correlated with cardiovascular risk.
- In children, direct association between adiposity and insulin resistance
  - Weight loss is associated with a decrease in insulin concentration and an increase in insulin sensitivity in adult and adolescents

# Hypertension

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“The second Task Force Report(1987)”

- Normal blood pressure: systolic and diastolic BP readings **below the 90<sup>th</sup>** percentile for age
- Hypertension : systolic and diastolic BP readings **greater than the 95<sup>th</sup>** percentile for age
- The prevalence of HT in childhood: **5%**

# Insulin resistance and HT

Possible mechanisms through which insulin may influence blood pressure

- 1. Insulin increased renal sodium retention while increasing free water clearance
  - 2. **Insulin resistance** is associated with **increased sympathetic nerve system activity** (increased salt sensitivity, or plasma volume expansion) and **stimulation of vascular smooth muscle growth** (reduced nitric oxide- mediated vasodilation).
- 
- Insulin levels have been found to be **significantly higher in adult patients with essential hypertension and borderline hypertension.**
  - A confounding factor in the Insulin-HT link is **obesity.**
  - Bloods pressure is directly correlated with body weight.
  - The association between **weight gain and insulin resistance** and **percent body fat and waist/hip ratio** are correlated significantly with insulin resistance.

# Dyslipidemia

\*Abnormal blood lipids occur frequently among obese children and adolescents.

“Atherogenic lipoprotein phenotype”-triad

- elevation of VLDL (or triglycerides)
- low HDL
- small dense LDL

■ Elevated levels of cholesterol during childhood were associated with elevation during adulthood

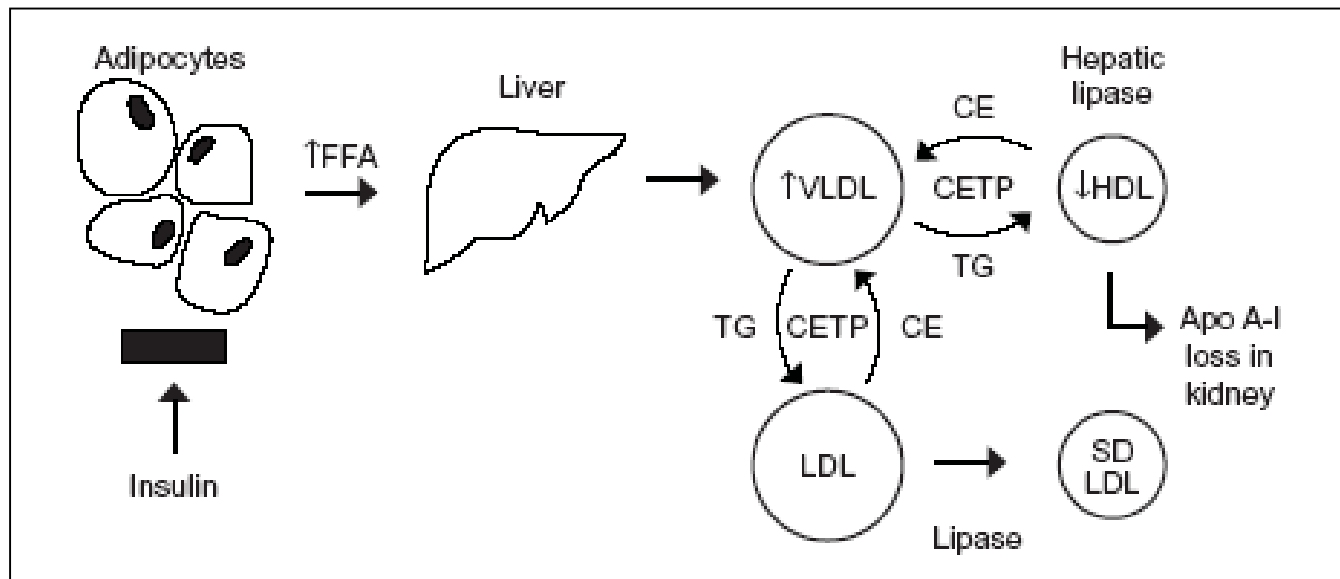
-2446 subjects

-examined : 8-18 years of age-> 20-25 years of age

Lauer et al. Pediatr 1988

- Central fat distribution (abdominal cavity) appears to be related to adverse lipid levels.
- Visceral adiposity associates with insulin resistance.

# Insulin resistance and dyslipidemia



When insulin resistance (bar) blocks the inhibitory effect of insulin on adipocyte lipolysis, adipocytes increase the release of FFAs, which are transported to the liver. The liver incorporates FFAs into TG, which is assembled into VLDL. Via the action of CETP, VLDL exchanges TG for cholesteryl ester from low-density lipoproteins and high-density lipoproteins. Lipases then act on TG-rich LDL to create SD LDL. Apolipoprotein A-1 is lost from TG-rich HDL in the kidney and at other sites, thus, reducing available HDL. This series of events produces the atherogenic lipoprotein phenotype of high TGs, low HDL, and small dense LDL.

# Type II DM

- There is a **rising prevalence** of Type II diabetes mellitus among children and a **decreasing age of onset**.

Dietz WH. Pediatr 1998

- Type II diabetes accounted for **one-third** of all newly diagnosed cases of diabetes in Cincinnati in 1994.

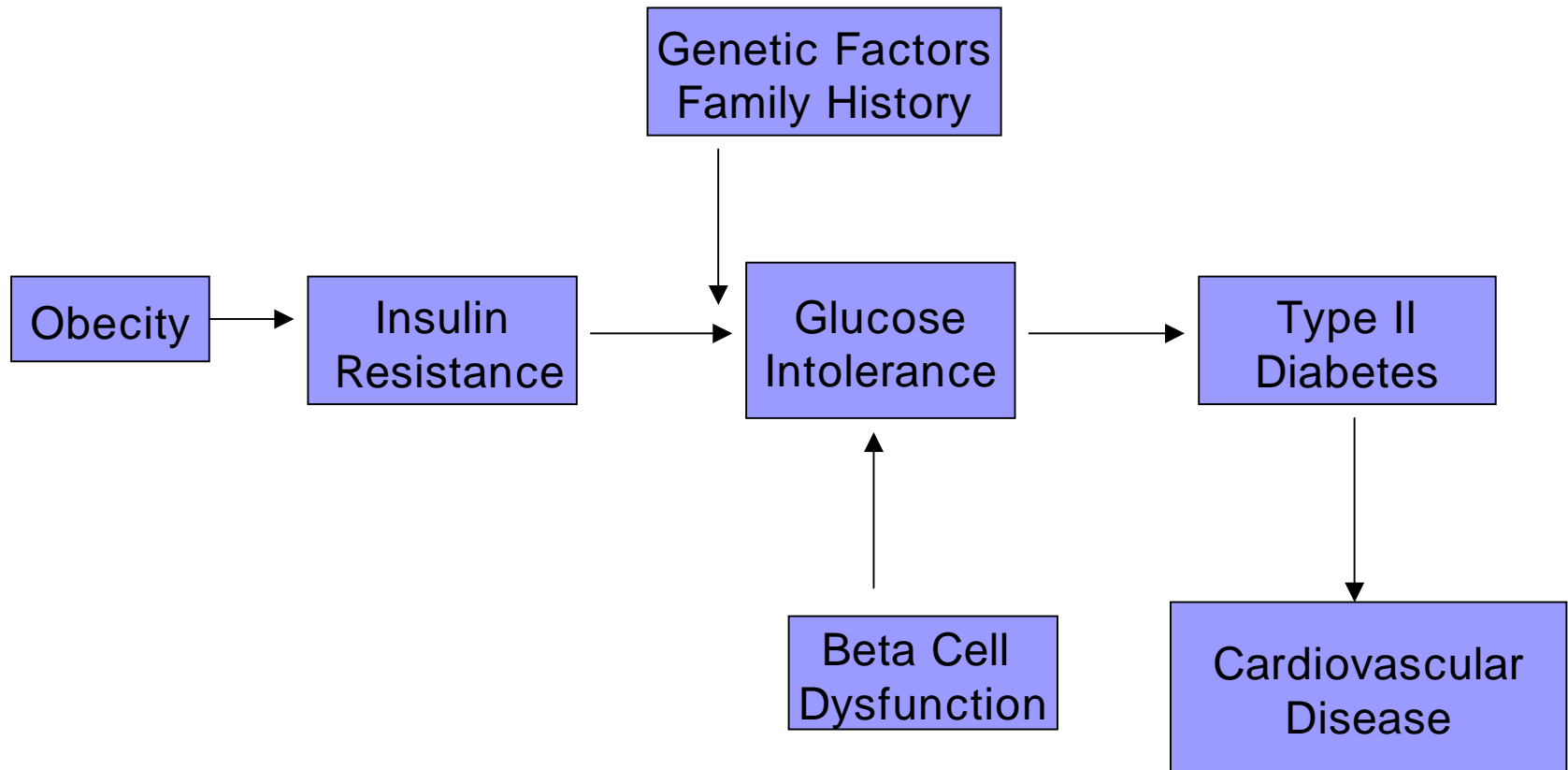
Pinhas-Hamiel et al. J Pediatr 1996

The incidence of type II DM among children and adolescents (< 19 years of age): **increased 10-fold** between 1982 and 1994 (0.7 vs 7.2 per 100,000 per year)

Tamara S et al. Pediatr 2005

- \* **Overweight or obesity** is the most important risk factor for the development of type II DM in youth.

# Insulin resistance and type II diabetes



# Cardiovascular disease

## ■ 1. Left ventricular hypertrophy

\*In adult, left ventricular mass correlates with obesity, advanced age, male sex, and hypertension.

-> strongly implicated in the development of cardiovascular disease

### \*In children,

-322 healthy 13-year-old children

-Left ventricular mass was significantly related to insulin resistance, elevated body mass index, systolic blood pressure, triglycerides, and low HDL-cholesterol in males, and to elevated body mass index only in females.

Steinberger J, circulation 1999

# Insulin resistance and LVH

**Mechanism:** same as the pathogenesis of hypertension.

- **1. Insulin (insulin-like growth factor-I)** may induce cardiac hypertrophy  
\*insulin-like growth factor-I : produce myocardial hypertrophy in animal models.
- **2. Accumulation of complex carbohydrates in the myocardium**  
as seen in individuals with diabetes, and transiently in infants of diabetic mothers could offer additional mechanistic explanation to the development of increased left ventricular mass in insulin resistant states.
- **3. Generalized defect of intracellular calcium and magnesium**  
:related to hyperinsulinemia, hypertension, obesity, left ventricular hypertrophy and type II diabetes.

- **2. Atherosclerosis** is the primary pathological consequence of metabolic syndrome.
  - \* Several key risk factors: Lipoproteins, hypertension, diabetes mellitus, inflammation, endothelial dysfunction

\* Noninvasive imaging technologies for atherosclerosis assessment

- **Carotid intima-media thickness**

:by carotid ultrasound

- **Detection of coronary calcium**

: by fluoroscopy during coronary angiography, conventional CT or electron beam(ultrafast) CT scanning

# Assessment of insulin resistance

## ■ 1. Euglycemic insulin clamp

- continuous intravenous administration of insulin at a constant rate, concomitant with glucose infusion at a variable rate over a period of 3h.
- The amount of glucose required to maintain normal glucose levels(euglycemia)., represents the insulin stimulated whole body glucose uptake : **insulin sensitivity  $M$  value**
- This is determined from the amount of glucose required to maintain euglycemia over the final 40 min of the euglycemic clamp, when it is assumed that steady state has been reached.
- A lower  $M$  value** represents greater **insulin resistance**.

## ■ 2. Measurement of plasma insulin levels (to assessment of hyperinsulinemia )

- not readily accessible estimate of insulin resistance.
- In adolescents, fasting insulin was found to be less sensitive than the  $M$  value in discriminating between differences in insulin sensitivity..

# Therapeutic approaches to metabolic syndrome

## Target:

- 1. Decrease insulin resistance
  - (1). Lifestyle modification  
dietary modification, exercise therapy,
  - (2). Pharmacologic agents
- 2. Control dyslipidemia, hypertension, inflammation, prothrombotic state, and the environmental conditions that promote obesity

# Conclusion

- 1. Metabolic syndrome is a **highly prevalent** but **underrecognized** and **undertreated** condition.
- 2. The concurrence of abdominal obesity, borderline hyperglycemia, atherogenic lipoprotein phenotype, and/or hypertension in a patient constitutes a system of **linked pathogenesis** and **high atherogenicity**.
- 3. Despite its etiologic complexities, regulatory hurdles, and clinical uncertainties, metabolic syndrome **must be recognized as a looming danger to public health**.