Diabetes Mellitus type II

-Pathophysiology & risk factors-

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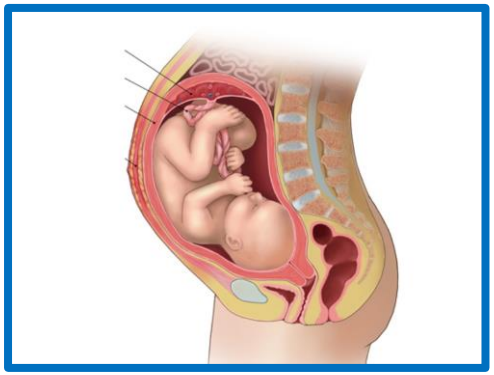
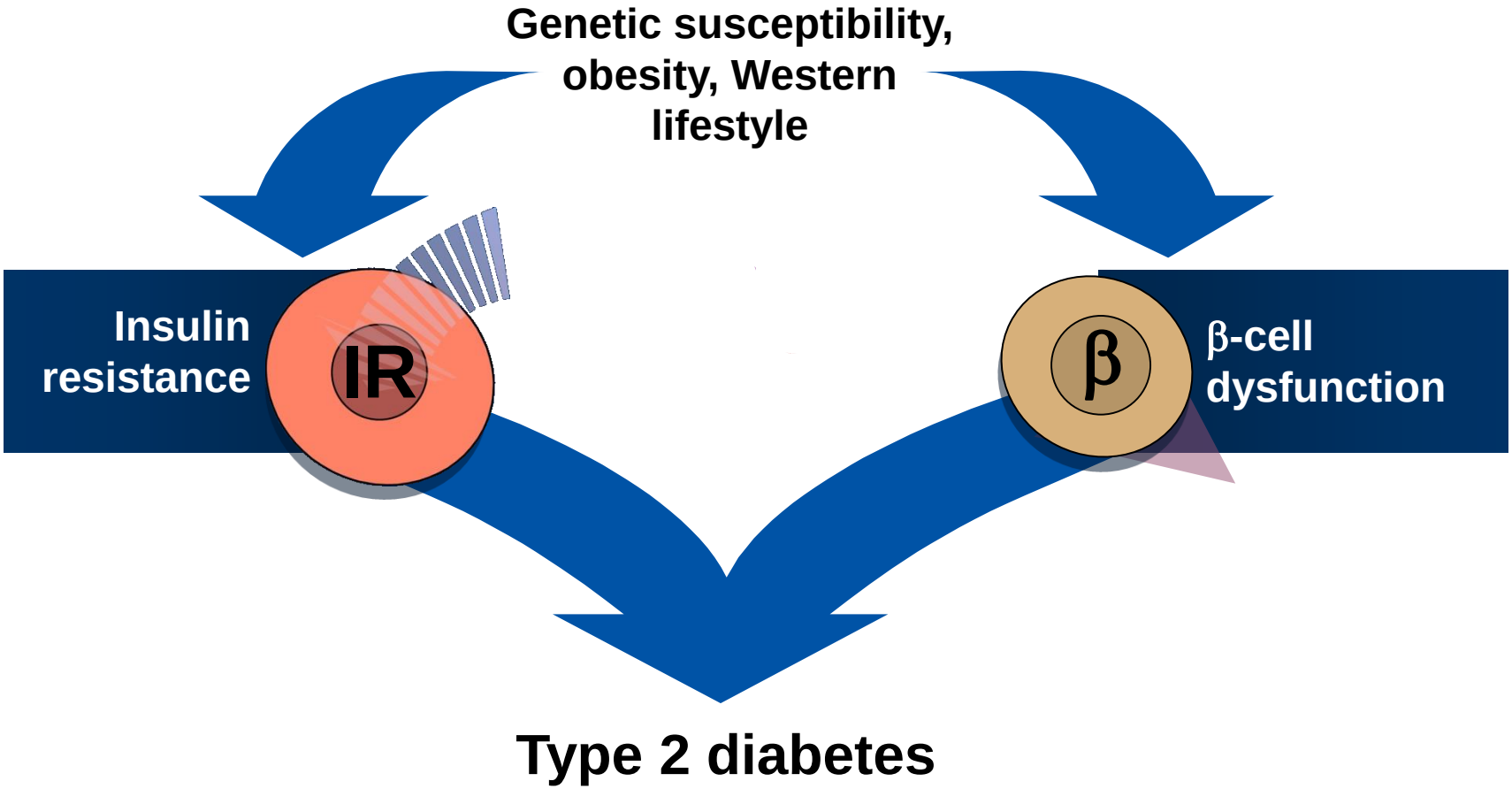


Main features of DM II

- 85-95% of diabetes cases are type II.
- Characterized by **chronic hyperglycemia**.
- Generally arises from a combination of **insulin resistance** and **B-cell dysfunction**.
- Associated with microvascular and macrovascular complications.

Insulin resistance and β-cell dysfunction are core defects of type 2 diabetes

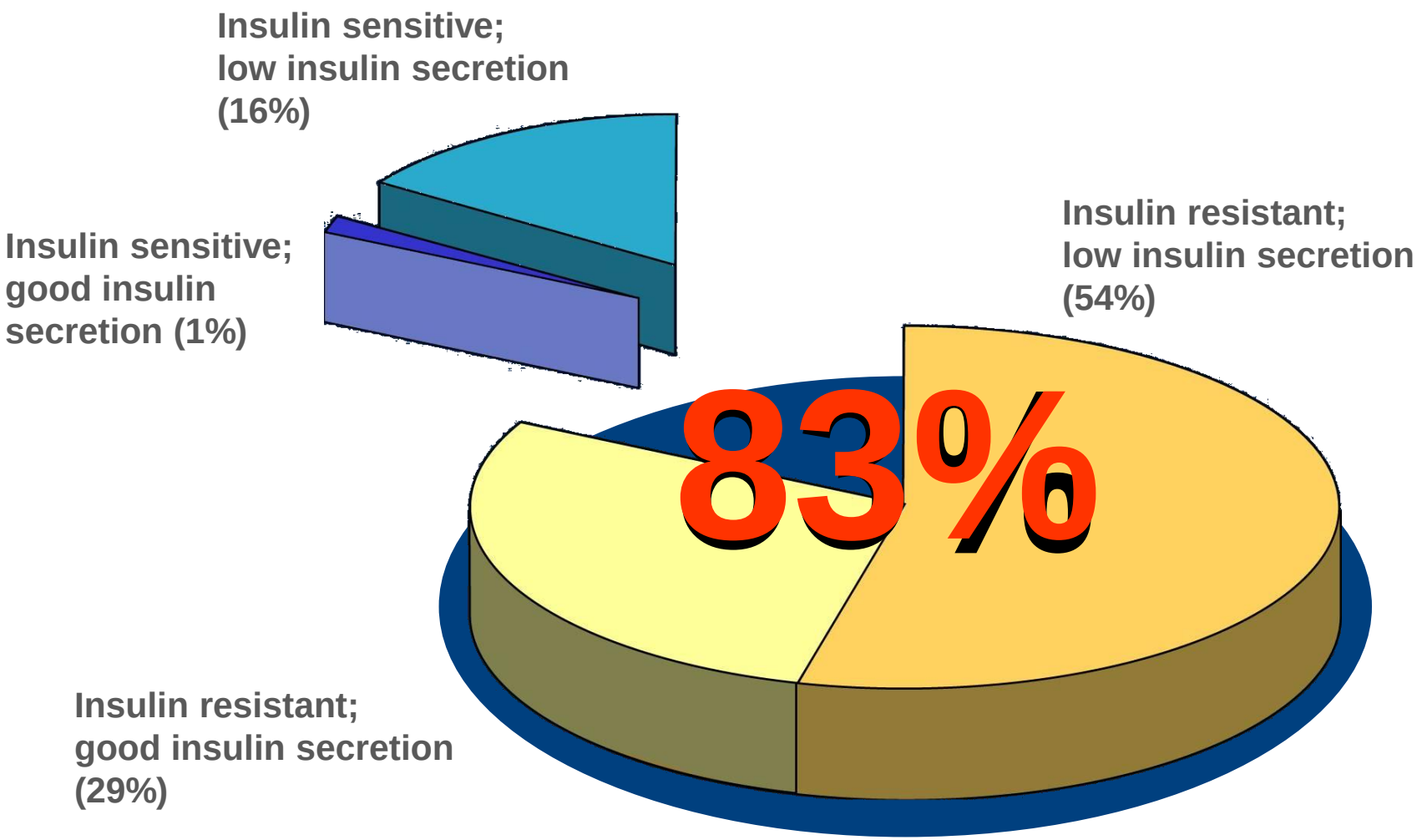


Rhodes CJ & White MF. *Eur J Clin Invest* 2002; 32 (Suppl. 3):3–13.

Pathophysiology of DM II (1): Insulin resistance

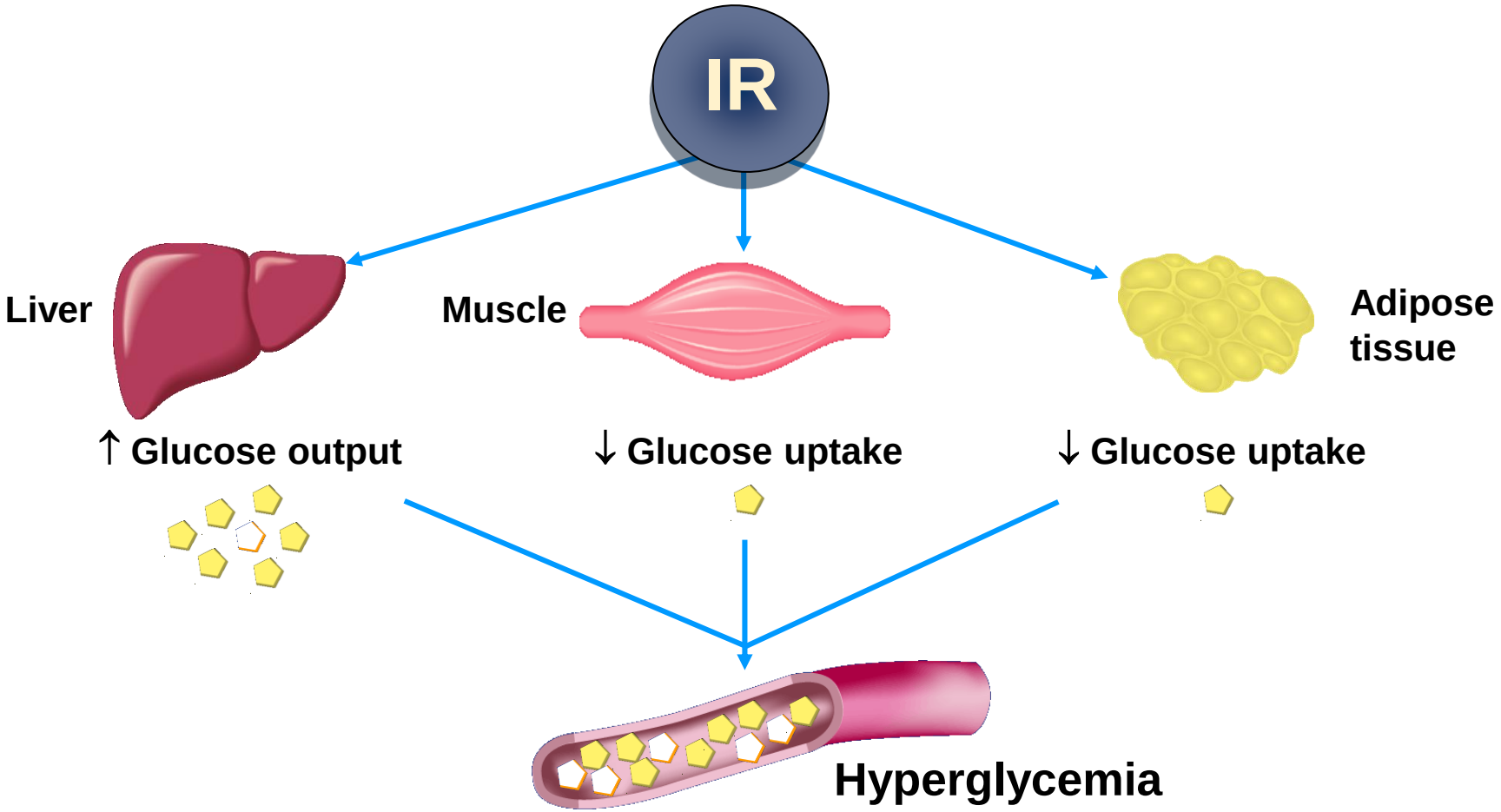
- Subnormal biological response to normal insulin concentrations.
- **Strong predictor of DM II.**
- Closely associated with obesity.
- Found in the general population in a varying degree.
- Can arise from genetic and environmental influences.
- Some inflammatory mediators (e.g. adipokines) may play a role.

More than 80% of patients progressing to DM II are insulin resistant



Haffner SM, *et al. Circulation* 2000; 101:975–980.

Insulin resistance – reduced response to circulating insulin



How is Insulin resistance measured ?

Two methods are available:

1) **The clamp method:**

- The amount of glucose that is infused intravenously in order to maintain constant blood glucose during a simultaneous intravenous insulin infusion.

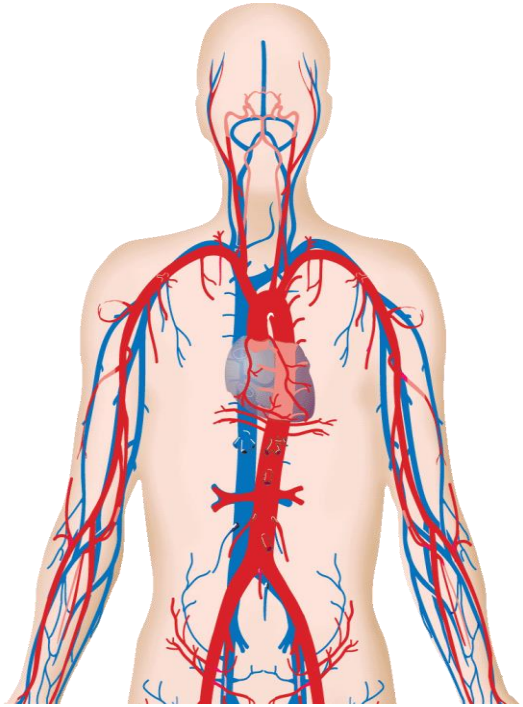
- Gold- standard but impractical for large-scale use.

How is Insulin resistance measured ?

- **2) The HOMA method** (homeostasis model assessment):
  - Estimate of insulin sensitivity and β-cell function from fasting plasma insulin and glucose concentrations using equations.

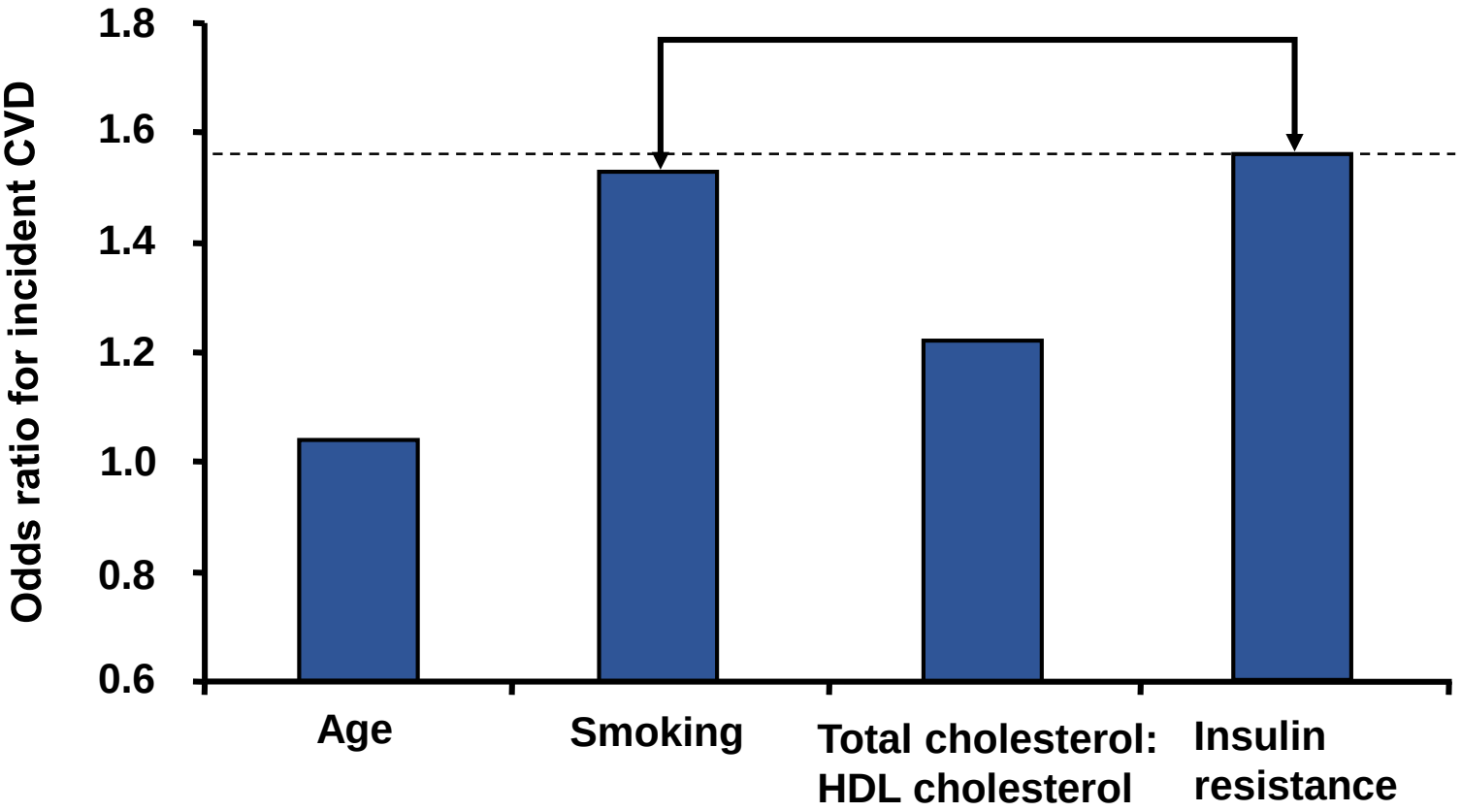
  - More appropriate where rapid or repeated assessment of insulin sensitivity

“ However, both are impractical in clinical practice”



Insulin resistance
&
Cardiovascular diseases

Insulin resistance is as strong a risk factor for cardiovascular disease as smoking



Bonora E, *et al. Diabetes Care* 2002; 25:1135–1141.

Insulin resistance & CVD

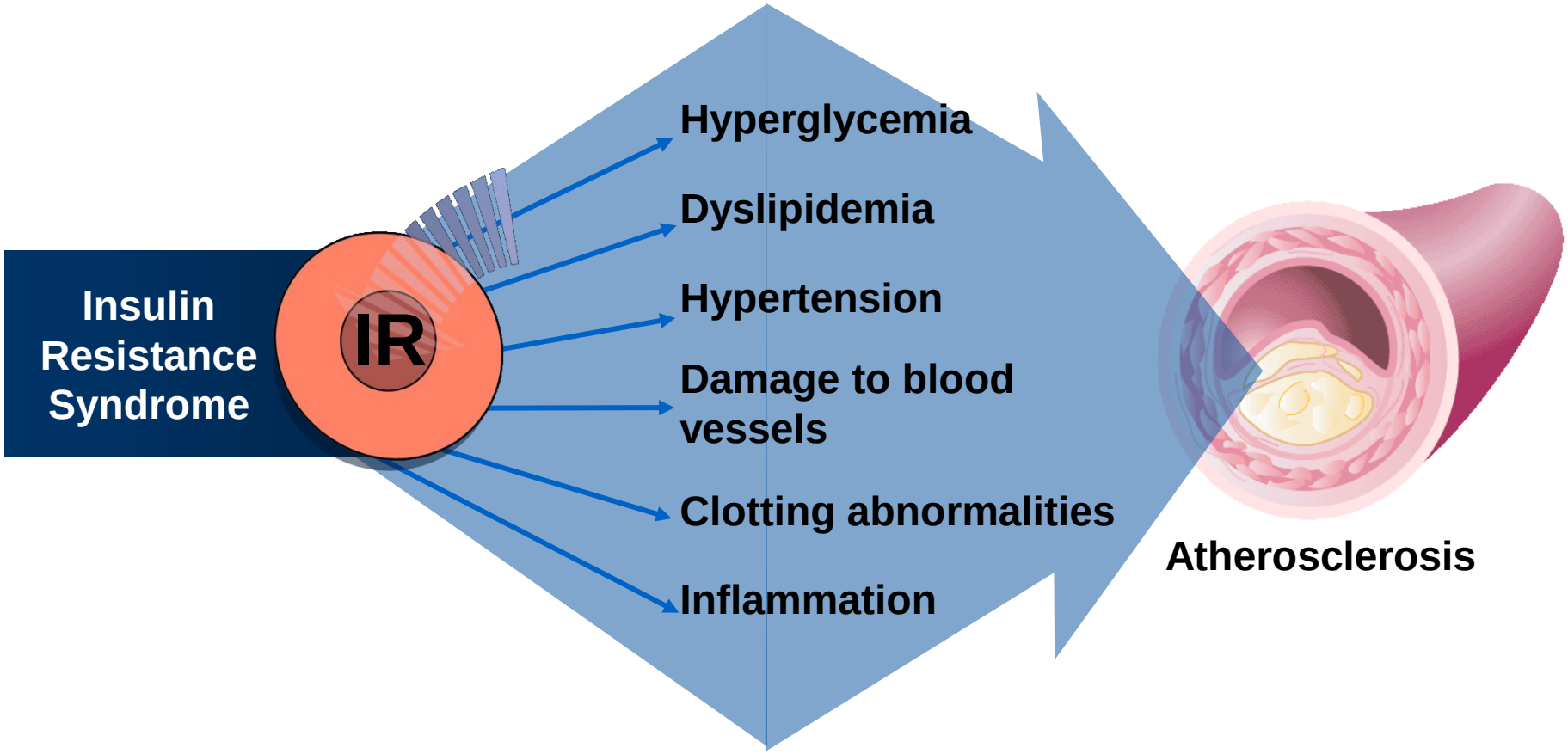
Present in **> 80%** of people with type 2 diabetes[1]

Approximately **doubles** the risk of a cardiac event[2]

Implicated in almost **half** of CHD events in individuals with type 2 diabetes[2]

[1]Haffner SM, *et al. Circulation* 2000; 101:975–980.
[2]Strutton D, *et al. Am J Man Care* 2001; 7:765–773.

Insulin resistance is linked to a range of CVD risk factors



Zimmet P. *Trends Cardiovasc Med* 2002; 12:354–362.

Insulin resistance: Clinical manifestations

- Abnormal glucose metabolism.
- **Cutaneous abnormalities** — Acanthosis nigricans
- **reproductive abnormalities-** ovarian hyperandrogenism
- **Linear and acral growth**
- **Musculoskeletal changes**
- **Adipose tissue – Obesity, lipodystrophy.**
- **Metabolic syndrome**
- **Autoimmunity- Antibodies.**

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Pathophysiology of DM II (2): B-cell dysfunction

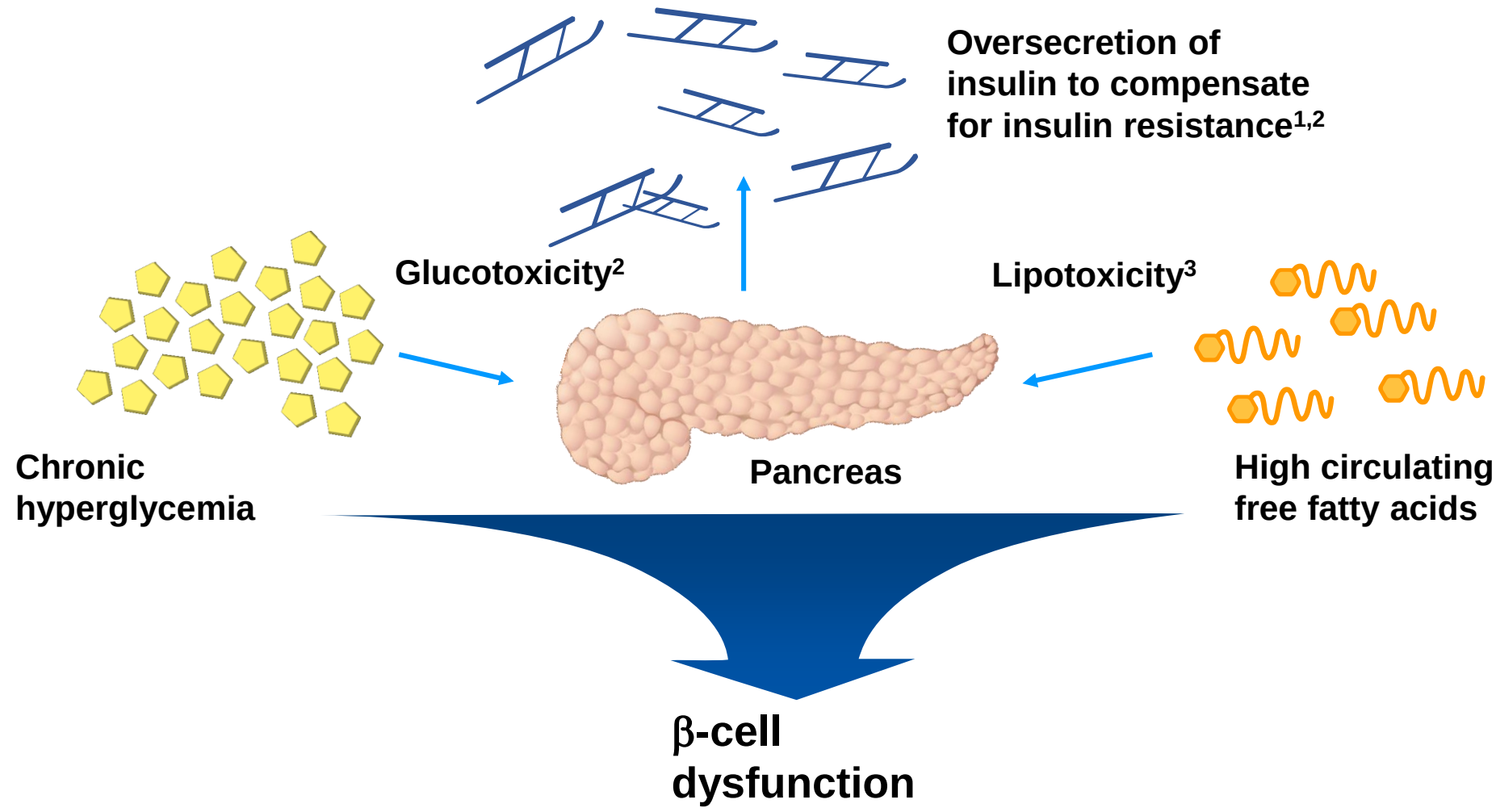
- Reduced ability of B-cells to secret insulin in case of hyperglycemia.
- Has genetic factors involved.
- May result from insulin resistance or occur primarily in insulin-sensitive individuals.

How does insulin resistance lead to B-cell dysfunction ?

How is β-cell function measured?

- β-cell function is difficult to measure and most methods are impractical for large-scale use.
- Homeostasis model assessment (HOMA) provides a simple estimate of β-cell function.
- **Proinsulin:insulin ratio is sometimes used as a marker of β-cell dysfunction.**

Why does the β-cell fail?



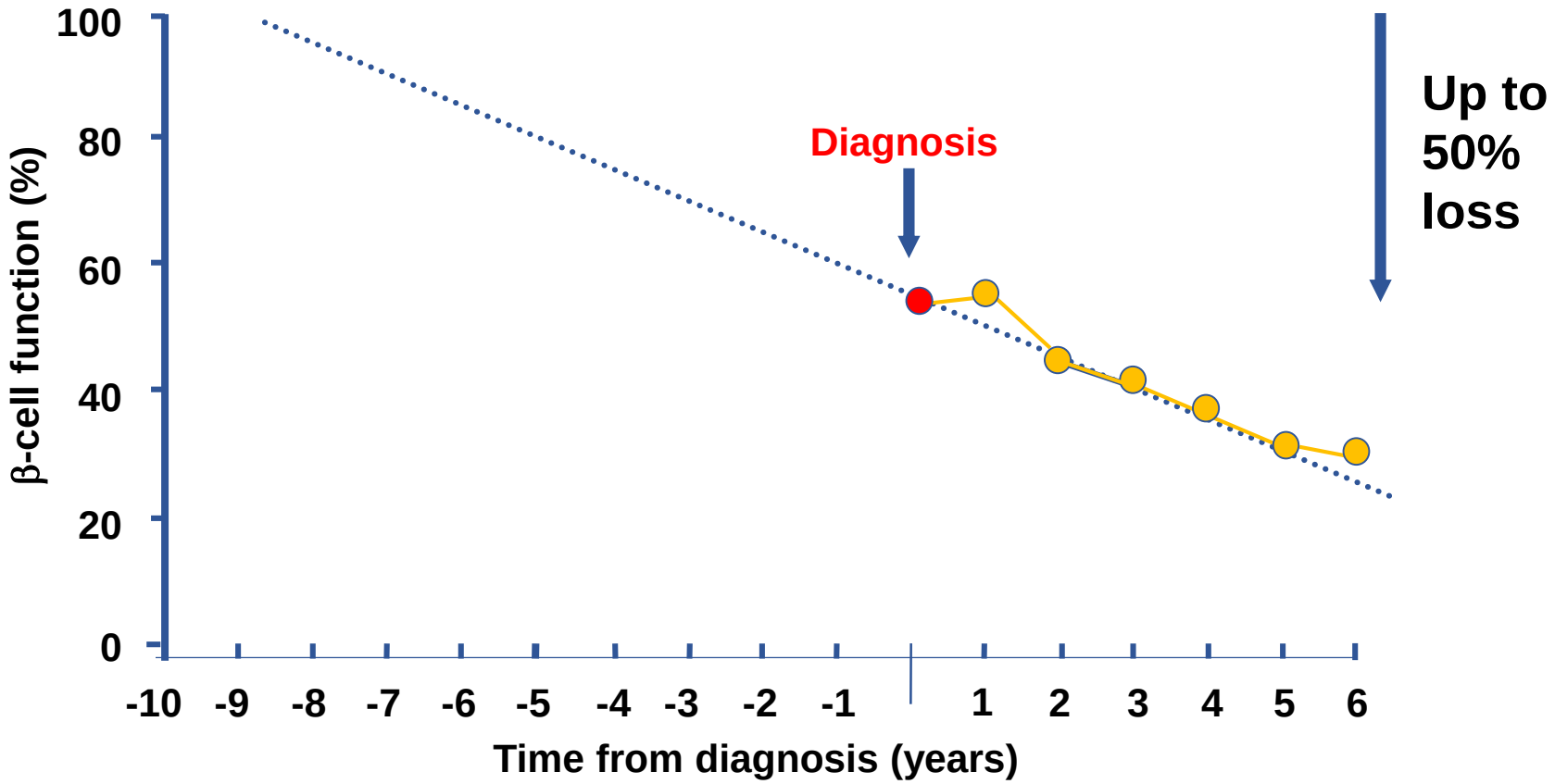
[1]Boden G & Shulman GI. *Eur J Clin Invest* 2002; 32:14–23.

[2]Kaiser N, *et al. J Pediatr Endocrinol Metab* 2003; 16:5–22.

[3]Finegood DT & Topp B. *Diabetes Obes Metab* 2001; 3 (Suppl. 1):S20–S27.

UKPDS

→ Loss of β-cell function occurs before diagnosis



Holman RR. *Diabetes Res Clin Pract* 1998; 40 (Suppl.):S21–S25.

Risk Factors of DM II

DM II risk factors – Obesity

- Almost 80% of people with type II DM are overweight or obese.

- The risk of developing diabetes increases progressively as the BMI increases.

- Latest data from the NHANES survey in the USA confirm a **6 – 10 - fold** increased lifetime risk of DM II of 18 year olds with a **BMI > 35 kg/m2** compared to those < 18.5 kg/m2.

→ 6-7 years reduction of life expectancy.

DM II risk factors – Obesity

- Fat distribution play a role in the risk; Visceral Vs. gluteofemoral.

→ **Central obesity (indicated by, for example, high waist:hip ratio; > 0.90 for men & > 0.85 for women) is a strong risk factor for insulin resistance.**

DM II risk factors – Obesity

- Obesity, for example, causes **peripheral resistance** to insulin-mediated glucose uptake and may also **decrease the sensitivity of the beta-cells** to glucose.

→ These defects are largely reversed by weight loss.

- Several metabolic mechanisms have been subjected in the process.

→ Fat distribution, genetics , inflammation, FFA.

DM II risk factors – Obesity / inflammation

The incidence of DM II has been correlated with increased levels of inflammatory markers:

- **C reactive protein,**
- **IL-6**
- **plasminogen activator inhibitor-1 (PAI-1)**
- **Tumor necrosis factor (TNF)-alpha.**

Adipose Tissue: A Secretory Organ

- Leptin
- Angiotensinogen
- Resistin
- Adiponectin (ACRP-30)

- TNF-α
- PAI-1
- Serum amyloid-A
- IL-6
- CRP

- Estrogens
- Cortisol
- RBP4

Modified from: Kahn BB, Flier JS. *J Clin Invest.* 2000;106:473-481; Lau DCW et al. *Am J Physiol Heart Circ Physiol.* 2005;288:H2031-2041; Wellen KE, Hotamisligil GS. *J Clin Invest.* 2005;115:1111-1119.

DM II risk factors – Obesity / inflammation

- TNF - α and IL – 6 have been shown experimentally to interfere with insulin action.

- TNF - α has been shown to inhibit tyrosine kinase activity at the insulin receptor and decrease expression of the glucose transporter GLUT - 4.

DM II risk factors – Obesity / inflammation

- Adipokines, released from adipose tissue, stimulate **inflammatory activity** which correlates with insulin resistance.

- These markers have also been found to be elevated in patients with atherosclerosis.

DM II risk factors – Obesity / Hormones

1) Adiponectin :

A hormone with anti - inflammatory and insulin - sensitizing properties that is secreted solely by fat cells.

- –It suppresses hepatic gluconeogenesis
- –Stimulates fatty acid oxidation in the liver and skeletal muscles.
- – Increasing muscle glucose uptake and insulin release from the β cells.

→ Circulating adiponectin is reduced in obesity ; a recent meta - analysis showed that the relative risk for diabetes was 0.72 for every 1 - log μ g/mL increment in adiponectin level.

DM II risk factors – Obesity / Hormones

2) Resistin:

An adipocyte - secreted hormone that increases insulin resistance

- First described in rodents
- Found in increased levels in experimental obesity and diabetes.

→ In humans, it appears to be derived largely from macrophages, however, its precise role in human DM is uncertain, although higher circulating levels have been found in some people with DM II.

DM II risk factors – Obesity / Adipokines

3) Leptin:

- An adipokine.

- It suppresses appetite, thus providing a candidate mechanism linking weight gain and appetite control.

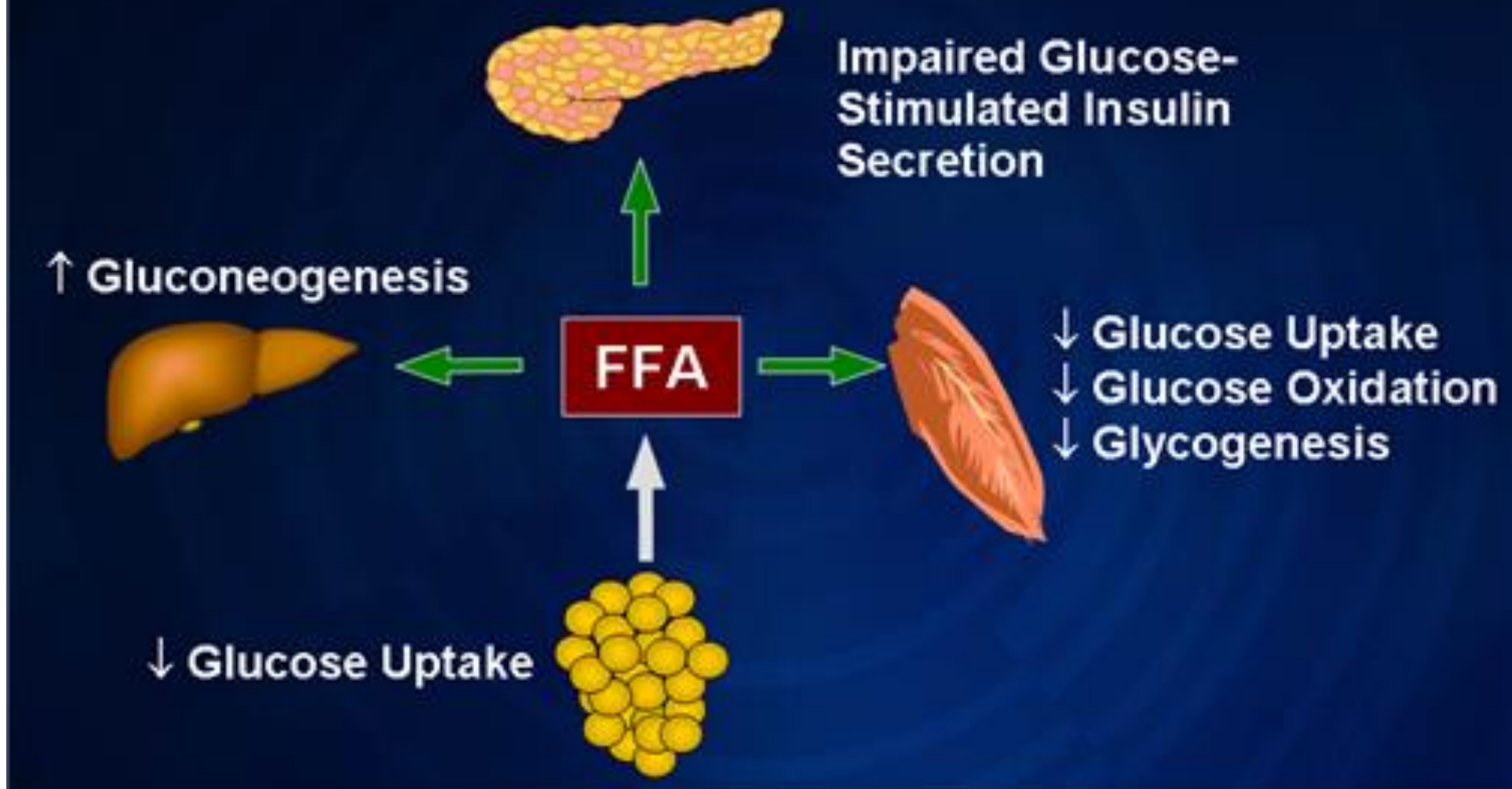
- Although abnormal leptin function has been described in humans, these defects are very rare and paradoxically high levels have been found in type 2 diabetes.

DM II risk factors – Obesity / Other factors

- **Free fatty acids**

→Concentrations are high in obese patients and is correlated with both B-cell dysfunction & insulin resistance.

Elevated FFAs May Play a Key Role in Insulin Resistance



Adapted from Tan MH. *Exp Clin Endocrinol Diabetes.* 2000;113(suppl):54-62.

DM II risk factors – Diet & lifestyle

- Low levels of **physical exercise** predict the development of type 2 diabetes

- possibly because exercise increases insulin sensitivity and helps prevent obesity.

- Subjects who exercise the most have a 25 – 60% lower risk of developing type 2 diabetes regardless of other risk factors such as obesity and family history.

DM II risk factors – Diet & lifestyle

- Physical activity of moderate intensity reduces the incidence of new cases of type 2 diabetes, regardless of the presence or absence of **impaired glucose tolerance.**

DM II risk factors – Diet & lifestyle

- Dietary patterns affect the risk of type 2 diabetes mellitus.
- A healthy diet (high in cereal fiber and polyunsaturated fat, and low in trans fat and glycemic load) had more impact on diabetes risk in minorities than among whites (RR 0.54 versus 0.77) in a large 20 year prospective study.

- Mediterranean diet Vs. Western diet.

DM II risk factors – Diet & lifestyle

- The Diabetes Prevention Programme and Diabetes Prevention Study in the USA and Finland have shown that :

–Lifestyle modifications

–moderate exercise

–modest weight loss

Can dramatically reduce the number progressing from IGT to type 2 diabetes.

DM II risk factors – Genetics

Observations which demonstrate a genetic influence on the development of type 2 diabetes include:

- The prevalence of type 2 diabetes varies remarkably between ethnic groups living in the same environment .
- 39% of patients with type 2 diabetes have at least one parent with the disease.
- Among monozygotic twin pairs with one affected twin, almost 90% of unaffected twins eventually develop the disease.

DM II risk factors – Genetics

- First-degree relatives of patients with type 2 diabetes frequently have impaired glucose metabolism long before they develop type 2 diabetes.

- In addition, they may have beta cell dysfunction, as evidenced by decreases in insulin release in response to glucose stimulation.

- The lifetime risk for a first-degree relative of a patient with type 2 diabetes is 5 to 10 times higher than that of age- and weight-matched subjects without a family history of diabetes.

DM II risk factors – Metabolic syndrome

- Also called insulin **resistance syndrome, syndrome X, the deadly quartet, or the obesity dyslipidemia syndrome .**

- Strongly associated with DM II and CVD.
- Share same risk factors of DM II and CVD.

- Also associated with other disorders: Fatty liver disease, Polycystic ovary syndrome, gout, CKD, Cholangiocarcinoma.. etc.

DM II risk factors – Metabolic syndrome

Definition by **2001 National Cholesterol Education Program/ATP III** :

Risk factor	Defining level
Central obesity	Waist circumference
• Men	> 102 cm (> 40 in)
• Women	> 88 cm (> 35 in)
Triglycerides	≥ 150 mg/dL (1.7 mmol/L)
HDL cholesterol	
• Men	< 40 mg/dL (1.03 mmol/L)
• Women	< 50 mg/dL (1.29 mmol/L)
Blood pressure	≥ 130/≥ 85 mm Hg
Fasting glucose	≥ 110 mg/dL (6.1 mmol/L)

DM II risk factors – Metabolic syndrome/ Definitions comparison

	WHO (1999)	NCEP (2001)	IDF (2005)
Required	Insulin resistance*		WC† ≥ 94 cm in men or ≥ 80 cm in women
No. of abnormalities	≥ 2 of:	≥ 3 of:	≥ 2 of:
Obesity	WHR > 0.9 in men or > 0.85 in women; BMI ≥ 30 kg/m^2	WC ≥ 102 cm in men or ≥ 88 cm in women	
Triglycerides	≥ 150 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL
HDL cholesterol	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women
Hypertension	≥ 140/90 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg
Glucose		≥ 110 mg/dL‡	≥ 100 mg/dL
Microalbuminuria	Albumin/creatinine ratio > 30 mg/g; Albumin excretion rate > 20 mcg/min		

DM II risk factors – Metabolic syndrome/ other factors

- The metabolic syndrome has been recognized as a proinflammatory, prothrombotic state, associated with elevated levels of :

- C-reactive protein.
- Interleukin (IL)-6.
- Plasminogen activator inhibitor.

→ **No causal association, not essential**

DM II risk factors – Metabolic syndrome/ Prevalence

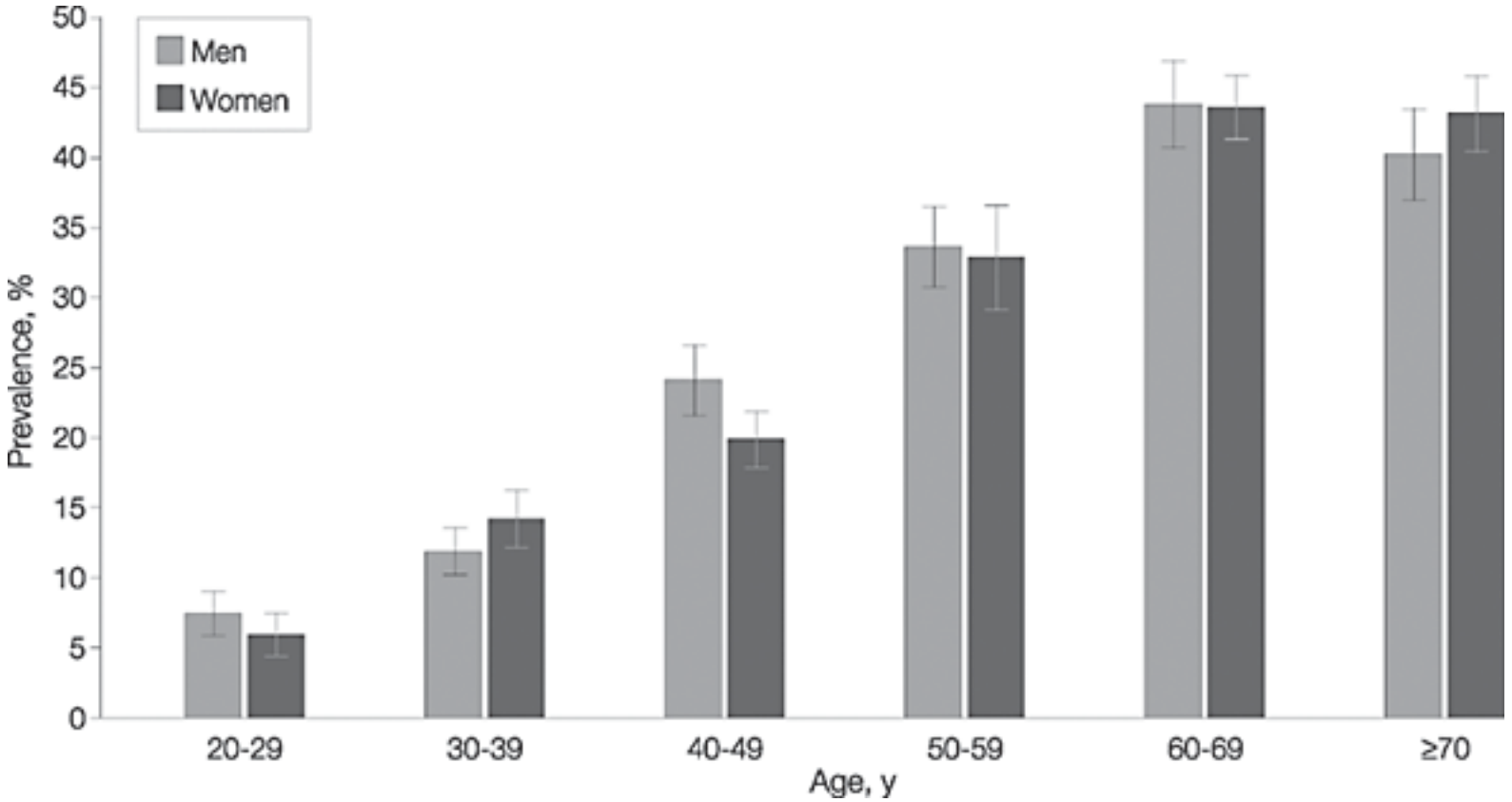


Figure 1. Age-Specific Prevalence of the Metabolic Syndrome Among 8814 US Adults Aged at Least 20 Years, by Sex, National Health and Nutrition Examination Survey III, 1988-1994

DM II risk factors – Metabolic syndrome

- In a meta-analysis of **16 multi-ethnic** cohort studies, the relative risk of developing diabetes ranged from **3.53 to 5.17;** depending upon the definition of metabolic syndrome and the population studied.

- As an example, in an analysis of 890 nondiabetic Pima Indians, **144** developed diabetes over four years of follow-up.

- The metabolic syndrome increased the relative risk (RR) for incident diabetes by 2.1-fold with the ATP III definition and 3.6-fold using the WHO definition.

Hanson RL, Imperatore G, Bennett PH, Knowler WC. Components of the "metabolic syndrome" and incidence of type 2 diabetes. Diabetes 2002; 51:3120.

DM II and cardiovascular diseases

- Heart failure and myocardial infarction (MI) appear to be associated with an increased risk of type 2 diabetes.

→In one study of 2616 nondiabetic patients with coronary artery disease, those with advanced heart failure had nearly **twice the risk** of developing diabetes during 6 to 12 years of follow-up

(17 versus 8 percent in NYHA class I patients; RR 1.7, 95% CI 1.1-2.6)

DM II risk factors – Intrauterine development

- Intrauterine growth restriction leading to **low birth weight** may be associated with an increased risk in adulthood of → **insulin resistance, glucose intolerance, type 2 diabetes, dyslipidemia, and hypertension.**

- Role of "thrifty genotype" – insulin resistance/caloric intake & survival ?

  → induced by malnutrition in early life ?

DM II risk factors – Intrauterine development

- Nurses' Health Study → confirmed the **inverse association** between birth weight and type 2 diabetes.

- Thinness at birth and in adult life have opposing effects on insulin resistance

→ such that subjects who were **underweight at birth** but who become **overweight in middle age** have the **most severe** insulin resistance and the greatest risk for type 2 diabetes.

DM II risk factors – Intrauterine development

- **High birth weight** was associated with increased risk of diabetes in later life to the same extent as low birth weight (odds ratios 1.36 versus 1.47).

- May be related to maternal hyperglycemia during pregnancy – mothers with DM II, regardless of genetics.
- U-shaped relationship.

- **Prematurity** – infants born <32 weeks has high risk regardless of weight.

  → reduced insulin sensitivity – till adulthood.

DM II risk factors – DRUG-INDUCED HYPERGLYCEMIA

Drugs that can impair glucose tolerance or cause overt diabetes mellitus

Glucocorticoids
Oral contraceptives
Tacrolimus, sirolimus, and cyclosporine
Nicotinic acid (niacin)
HIV protease inhibitors
Thiazide diuretics (primarily at doses above 25 mg/day of hydrochlorothiazide or its equivalent)
Atypical antipsychotics (clozapine, and some conventional antipsychotics)
Gonadotropin releasing hormone agonists
Other
Beta blockers
Clonidine
Pentamidine
Alcohol

DM II- Other risk factors

- **Family history-** DM II or DM I.
- **Ethnicity**- Asians, Hispanics, and blacks > whites.
- **Smoking** – USA about 10 % of the incidence of type 2 diabetes .
- **Sleep duration** - Quantity and quality of sleep, melatonin secretion ?

Up To date, 2013

DM II- Other risk factors

- **Hyperuricemia** - endothelial dysfunction, oxidative stress, and insulin resistance
- **Irregular menstrual cycles** - long intermenstrual intervals
- **Breastfeeding** - decreased risk for women of DM II.

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DM II- Other risk factors/less common

- **Serum ferritin levels & high iron intake-** not well understood.
- **Magnesium intake**- protective ? Sources ?
- **Moderate alcohol intake** - ↓ risk ?
- **Exposure to environmental toxins**- inorganic arsenic in drinking water, organophosphate and chlorinated pesticides.

Up To date, 2013