DEFINIZIONE

- Il Diabete Mellito è una sindrome caratterizzata da iperglicemia secondaria ad un difetto di secrezione o di attività dell'insulina o più spesso da entrambi.

- L'iperglicemia a lungo termine provoca danni a vari organi: occhio, rene, sistema nervoso periferico, apparato cardiovascolare.

Diabete mellito

Entità del problema

Prevalenza nella popolazione adulta:

Nel Mondo

- **1997: 124 milioni**
- **2003: 140 milioni**
- **previsione 2010: 230 milioni**

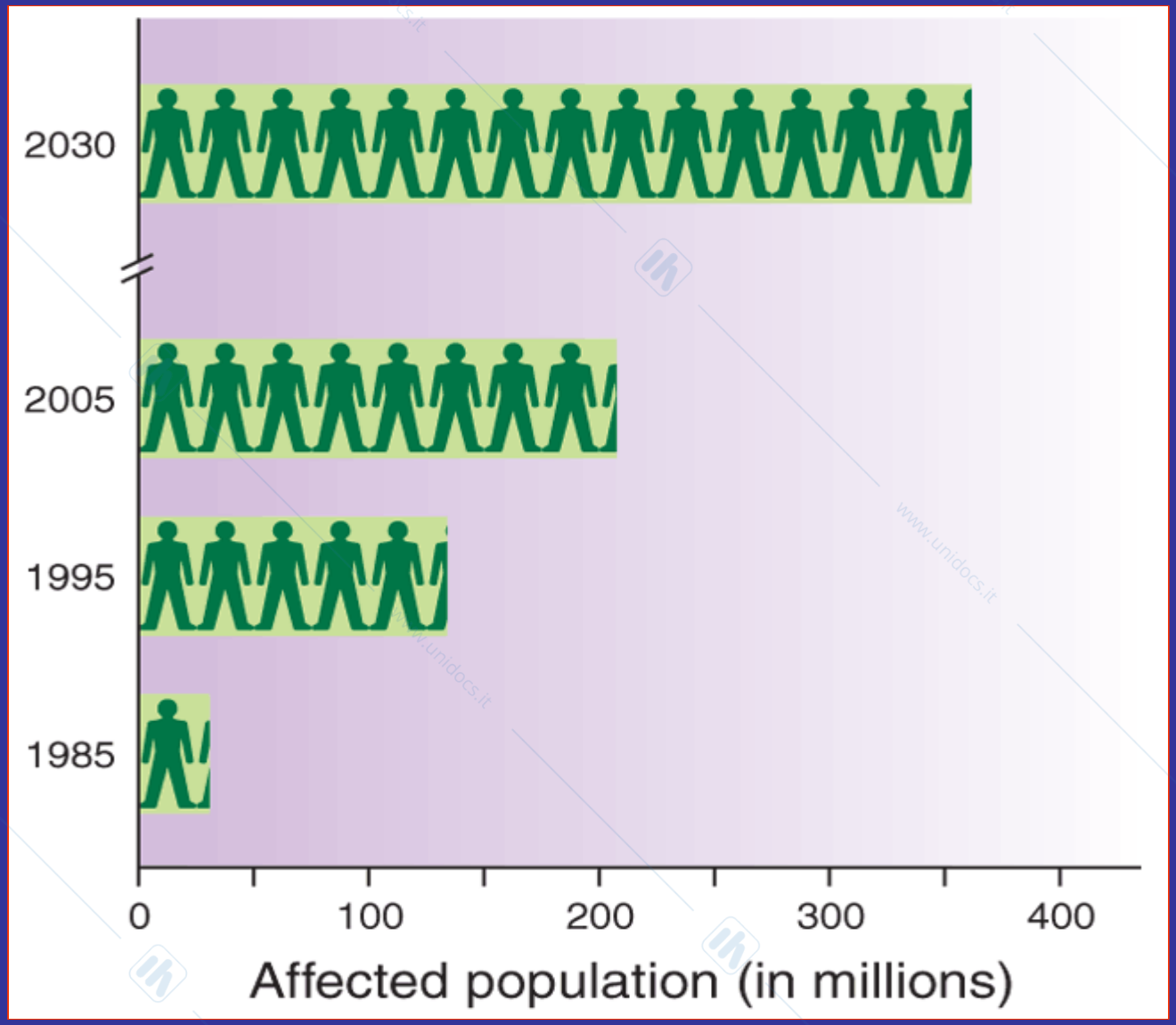
In Italia

- **6 - 9 % (circa 2.5 milioni di soggetti affetti)**

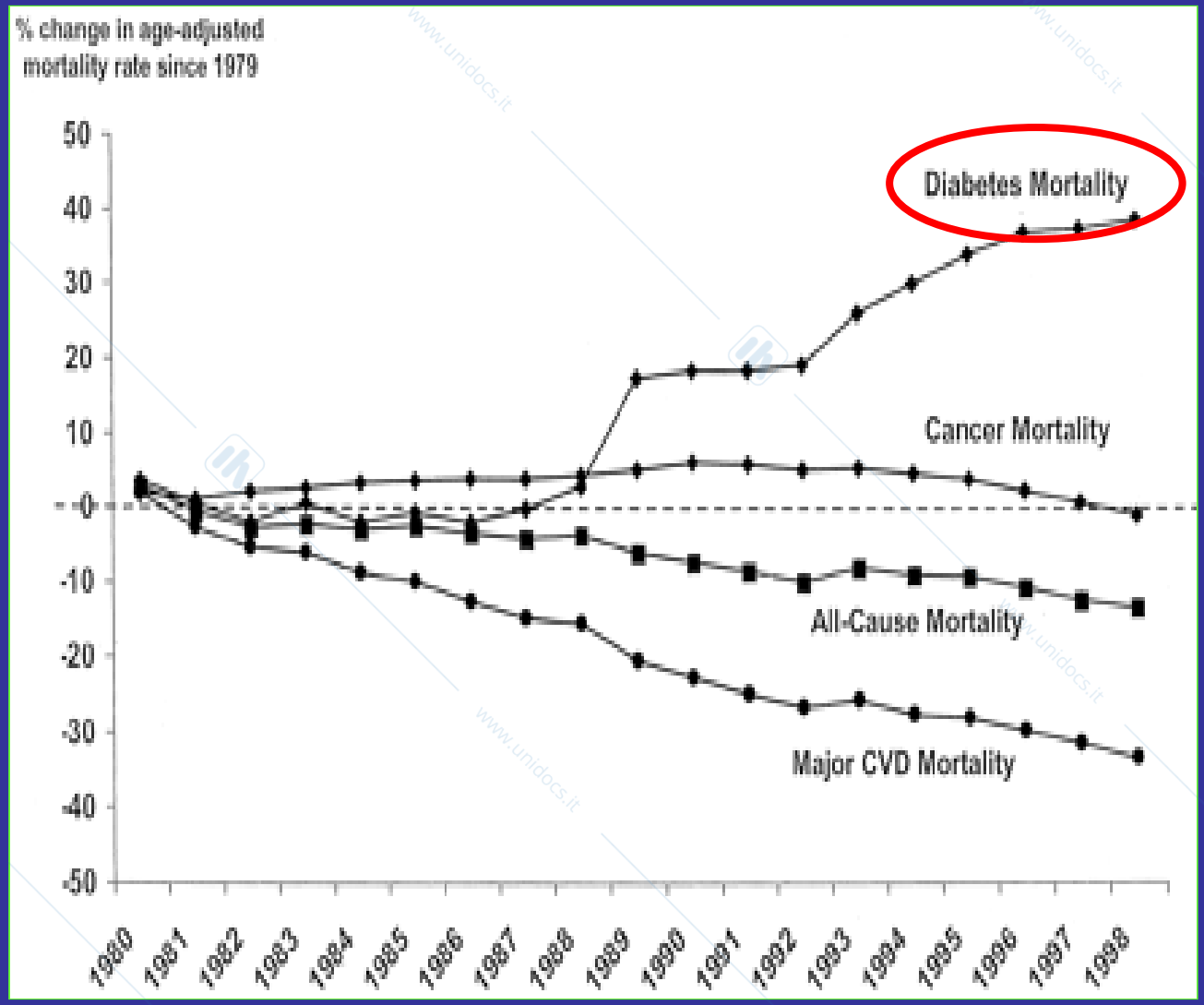
American Diabetes Association.
Cure • Care • Commitment®

nature medicine
12, 75 - 80, 2006

La prevalenza del diabete mellito tipo 2 nel mondo aumenterà del 60% passando dal 4 al 6,4% nei prossimi 25 anni



Diabete e cause di morte



Sobel et Circulation 107:636,2003

DiabetesCare

The Burden of Mortality Attributable to Diabetes

Realistic estimates for the year 2000

Gojka Roglic, MD[1]
Nigel Unwin, DSC, MFPH[1]
Peter H. Bennett, MB, FRCP[2]
Colin Mathers, DSC, PHD[3]
Jaakko Tuomilehto, MD, PHD[4,5,6]
Sayaji Nag, MRCP[7]
Vincent Connolly, MD, FRCP[7]
Hilary King, MD, DSC[1]

The excess global mortality attributable to diabetes in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths.

Diabetes Care 28:2130-2135, 2005

Classificazione Etiologica del Diabete Mellito

Diabete Tipo 1: (da distruzione della β-cellula con deficit insulinico assoluto)

Diabete Tipo 2: (da insulino resistenza con deficit relativo di secrezione o da prevalente deficit di secrezione insulinica)

Altri tipi di Diabete :

a) difetti genetici della β-cellula
b) difetti genetici dell'azione insulinica
c) malattie del pancreas esocrino
d) endocrinopatie
e) farmaci
f) infezioni
g) da forme rare di malattie immunitarie
h) da malattie genetiche associate al diabete

Diabete Gestazionale

CRITERI DI DIAGNOSI

	Glucosio nel plasma *venoso** *mg/dl*	Glucosio da sangue intero *venoso* *mg/dl*	Glucosio da sangue intero *capillare* *mg/dl*
Digiuno			
"Diabete"	≥126	≥110	≥110
"IFG"	≥110 e <126	≥100 e <110	≥100 e <110
OGTT 2-h			
"Diabete"	≥200	≥180	≥200
"IGT"	≥140 e <200	>120 e <180	>140 e <200

* valore *da preferire*

OGTT: 75g di glucosio in 300ml di acqua da ingerire in 3-5 min

Diabete mellito

Nuovi criteri di diagnosi - A.D.A. 2003

Glicemia a digiuno	Vecchi criteri	Nuovi criteri
diabete	> 140 mg/dl	> 126 mg/dl
IGT	139-116 mg/dl	125-111 mg/dl
normale	< 115 mg/dl	< 110 mg/dl

American Diabetes Association.
Cure • Care • Commitment®

ALGORITMO DIAGNOSTICO

1. Sintomi di diabete (poliuria,polidipsia, perdita di peso)

⇒ Controllo casuale della glicemia (vedi oltre per gli equivalenti capillare/venoso)

se ≥ 200 mg/dl ⇨ "Diabete"

se ≥ 100 mg/dl *procedere al passo 2*

2. Glicemia a digiuno o casuale ≥ 100 mg/dl

⇒ Controllo glicemia a digiuno da plasma venoso

se ≥126 mg/dl, ripetere e se confermata ⇨ "Diabete"

se ≥110 mg/dl fare (OGTT)

se >90 mg/dl, considerare controllo annuale dei fattori di rischio cardiovascolare, inclusa la glicemia

Curva da carico di glucosio (OGTT) (da plasma venoso):

se 2h ≥ 200 mg/dl ⇨ "Diabete"

se 2h < 200 mg/dl e ≥ 140 mg/dl ⇨ "IGT"

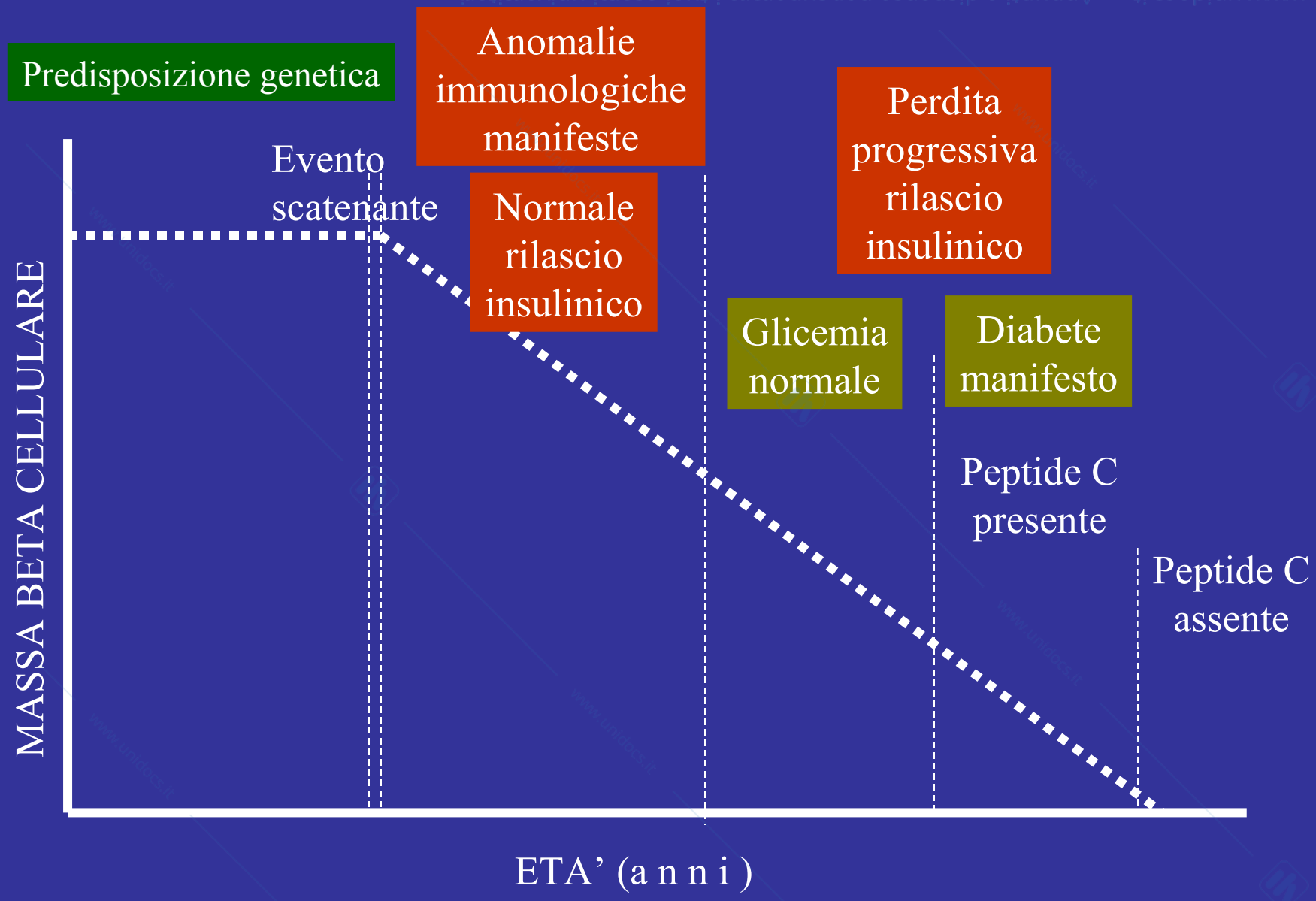
3. *Se* a digiuno ≥110 mg/dl e <126 mg/dl e 2h <140 mg/dl ⇨ "IFG"

CARATTERISTICHE DIFFERENZIALI DEL DIABETE TIPO 1 E TIPO 2

	TIPO 1	TIPO 2
• Livelli di insulina	Assenti o ridotti	Normali o aumentati
• Sintomatologia	Importante	Spesso assente
• Chetosi	Presente	Assente
• Peso	Magro	Obesità o sovrappeso
• Età d'esordio (anni)	< 35	> 35
• Comparsa delle complicanze croniche	Parecchi anni dopo l'esordio	Spesso presenti alla diagnosi
• Prevalenza	0,6%	3-7%
• Familiarità	Modesta	Importante
• Sistema HLA	Correlato	Non correlato
• Autoimmunità	Presente	Assente
• Terapia	Insulina	Dieta, ipoglicemizzanti orali, talora insulina

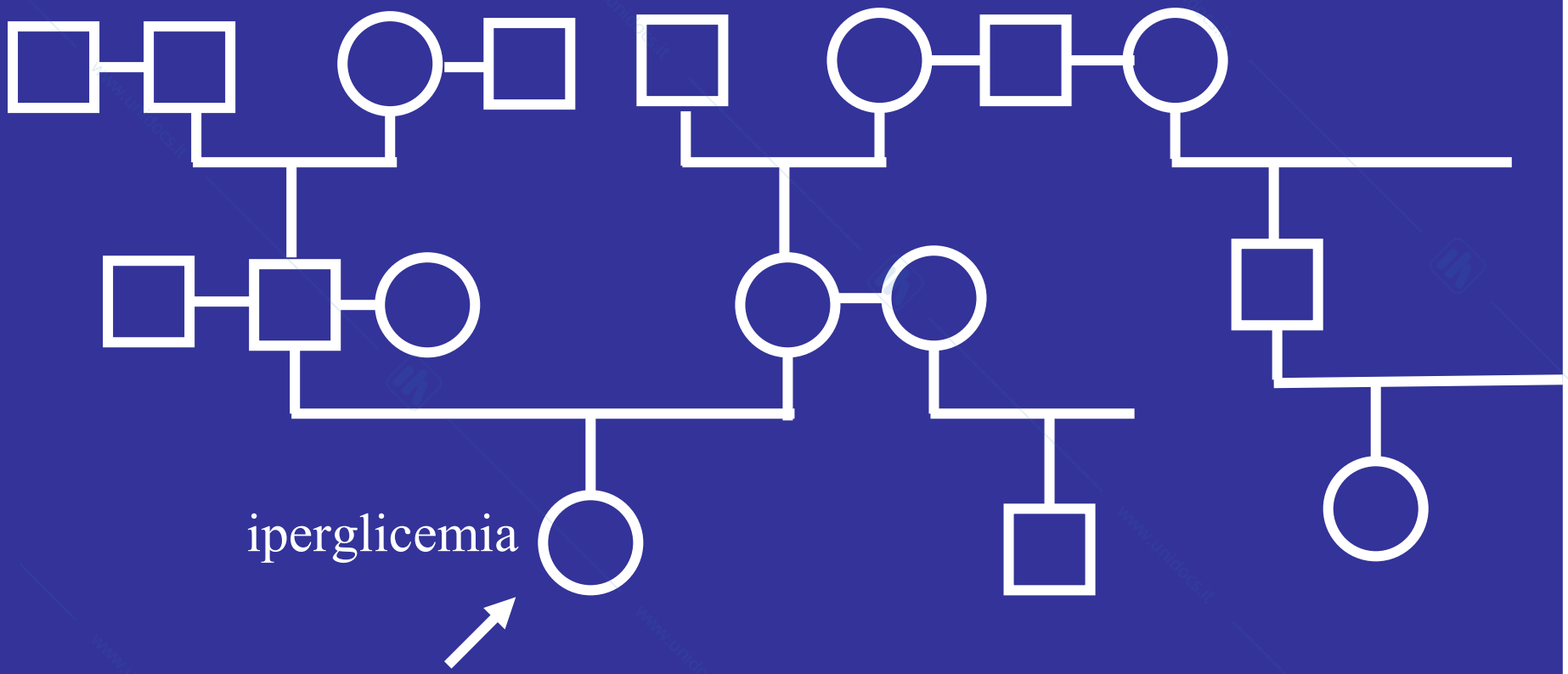
LA STORIA NATURALE DEL DIABETE MELLITO TIPO 1

HLA, Human Leukocyte Antigen leucocitario umano; ICA, Islet-cell Cytoplasmic Antibodies: Anticorpi verso le isole pancreatiche; IAA, Insulin AutoAntibodies: Auto-anticorpi anti-insulina;anticorpi anti-GAD (Glutamic Acid Decarboxylase: decarbossilasi dell'acido glutammico)



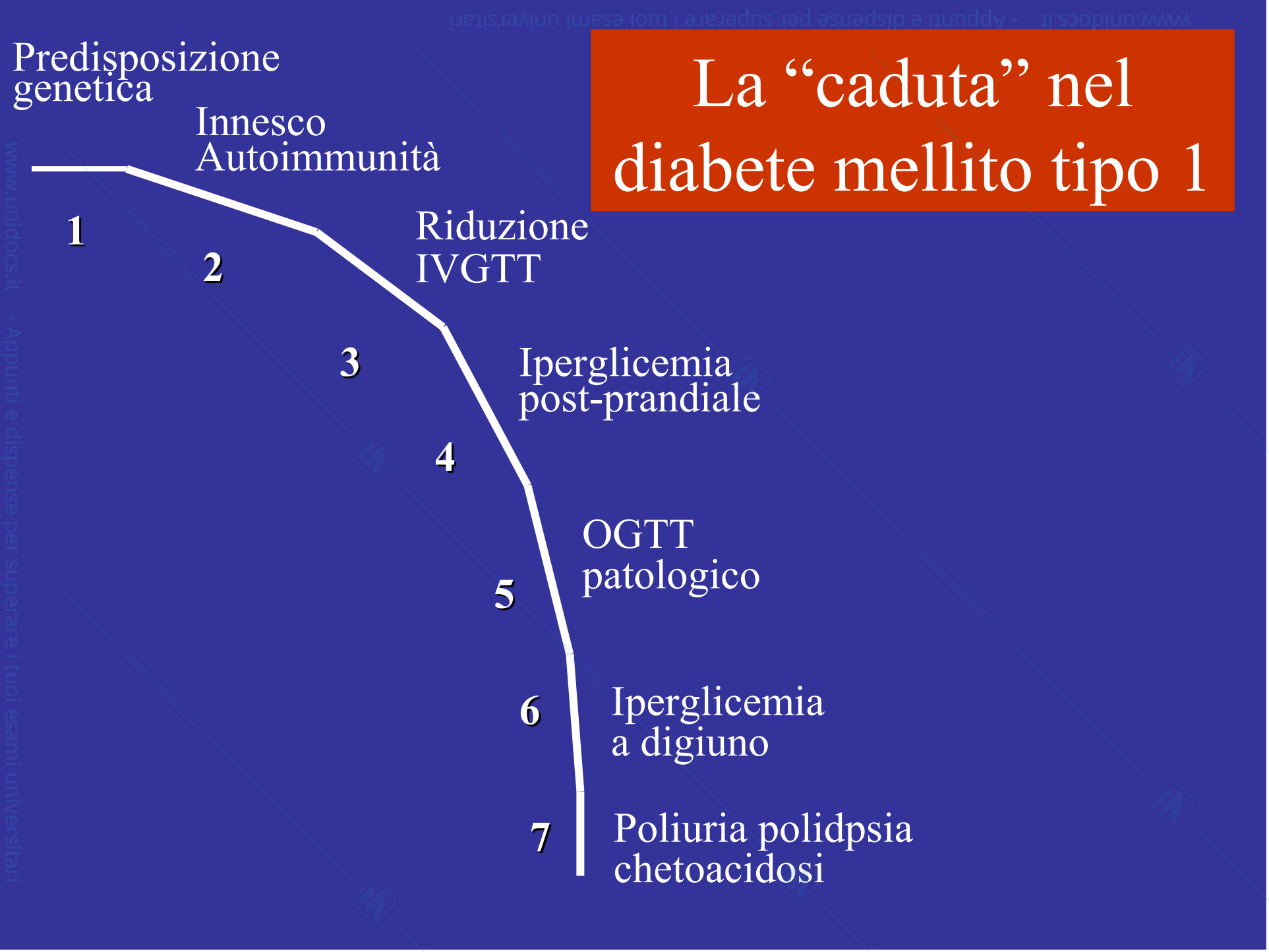
Eisenbarth GS New Engl J Med 1986

Anche importante è la raccolta della anamnesi familiare per malattie autoimmuni



Nel sospetto di diabete autoimmune

La “caduta” nel diabete mellito tipo 1



Rischio di IDDM

Popolazione generale	1/500
HLA a basso rischio	1/5.000
HLA DR3 o DR4	1/400
HLA DR3-DR3 o DR4-DR4	1/150
HLA DR3-DR4	1/40

Predisposizione genetica

La “caduta” nel diabete mellito tipo 1

Fratello con IDDM	1/14
Fratello con diverso HLA	1/100
Fratello DR3 o DR4	1/20
Fratello HLA DR3-DR3 o DR4-DR4	1/6
Fratello HLA DR3-DR4	1/4 - 1/5
Gemello monozigote	1/3 - 2/3

Genitore con IDDM	1/25
Madre con IDDM	1/40 - 1/50
Padre con IDDM	1/20
Entrambi i genitori	1/3 - 1/4

La maggiore suscettibilità genetica è correlata al cromosoma 6 (HLA)

Tipizzazione sierologica predisponente :

HLA DR3-DQ2, DR4-DQ8

Tipizzazione sierologica protettiva :

HLA DR2-DQ6

Lernmark A Diabetes Metabolism Rev 1998, 14,3-29

Linee Guida per lo screening del prediabete nei bambini

RIP 18; 484-5: 1992

748 soggetti (età 1-18 anni)
480 maschi e 268 femmine

TEST IMMUNOLOGICI

ICA, IAA, GAD
IA2 *dal 1996*

TEST GENETICI

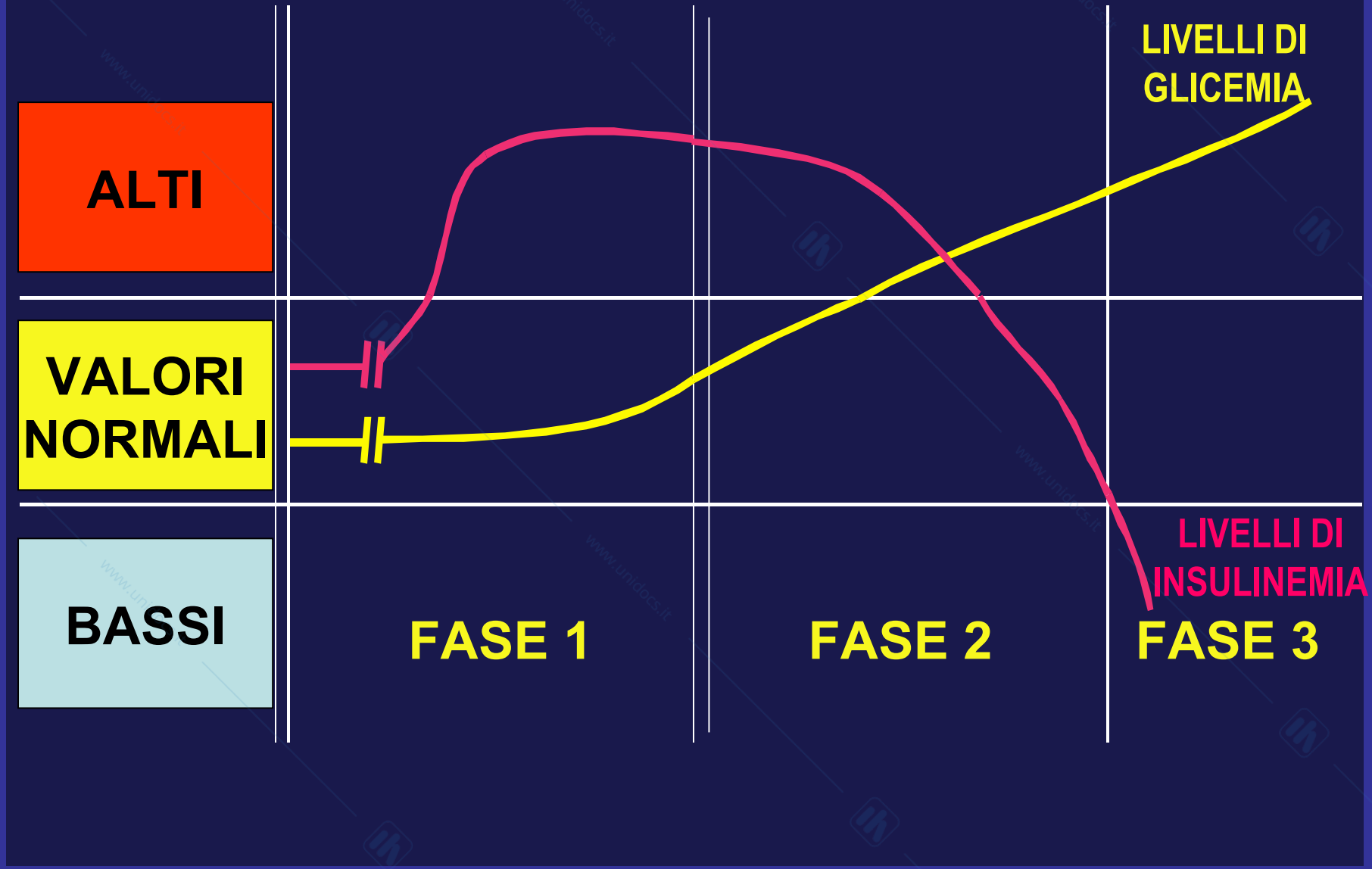
HLA DR
HLA DQ alfa/beta

TEST METABOLICI

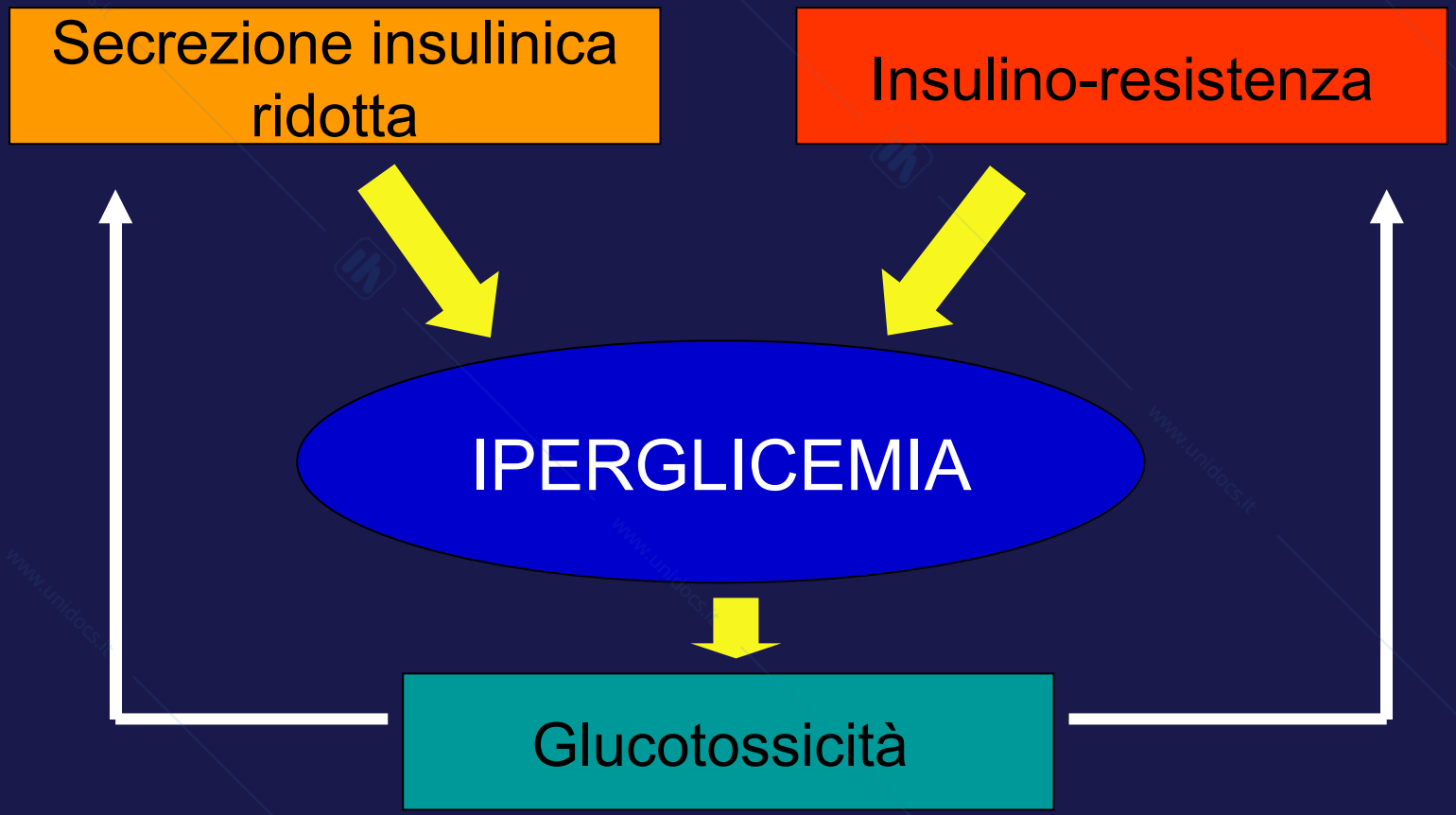
OGTT
IVGTT

LA STORIA NATURALE DEL DIABETE MELLITO TIPO 2

RAPPRESENTAZIONE SCHEMATICA DELLA STORIA NATURALE DEL DIABETE MELLITO TIPO 2



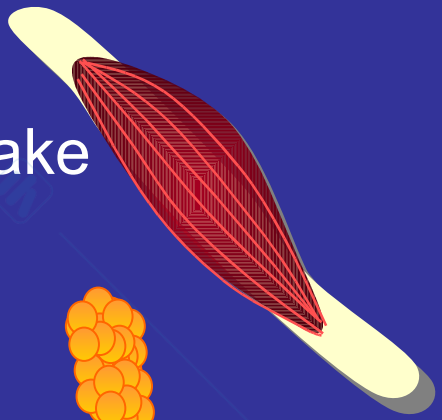
FISIOPATOLOGIA DELL'IPERGLICEMIA NEL DIABETE TIPO 2



Dual Metabolic Abnormalities in Type 2 Diabetes

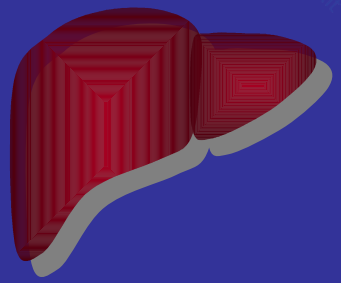
Insulin Resistance

Decreased Glucose Uptake



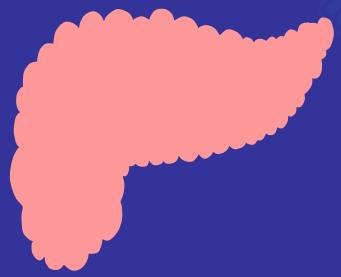
Unrestrained Lipolysis

Excessive Hepatic Glucose Output

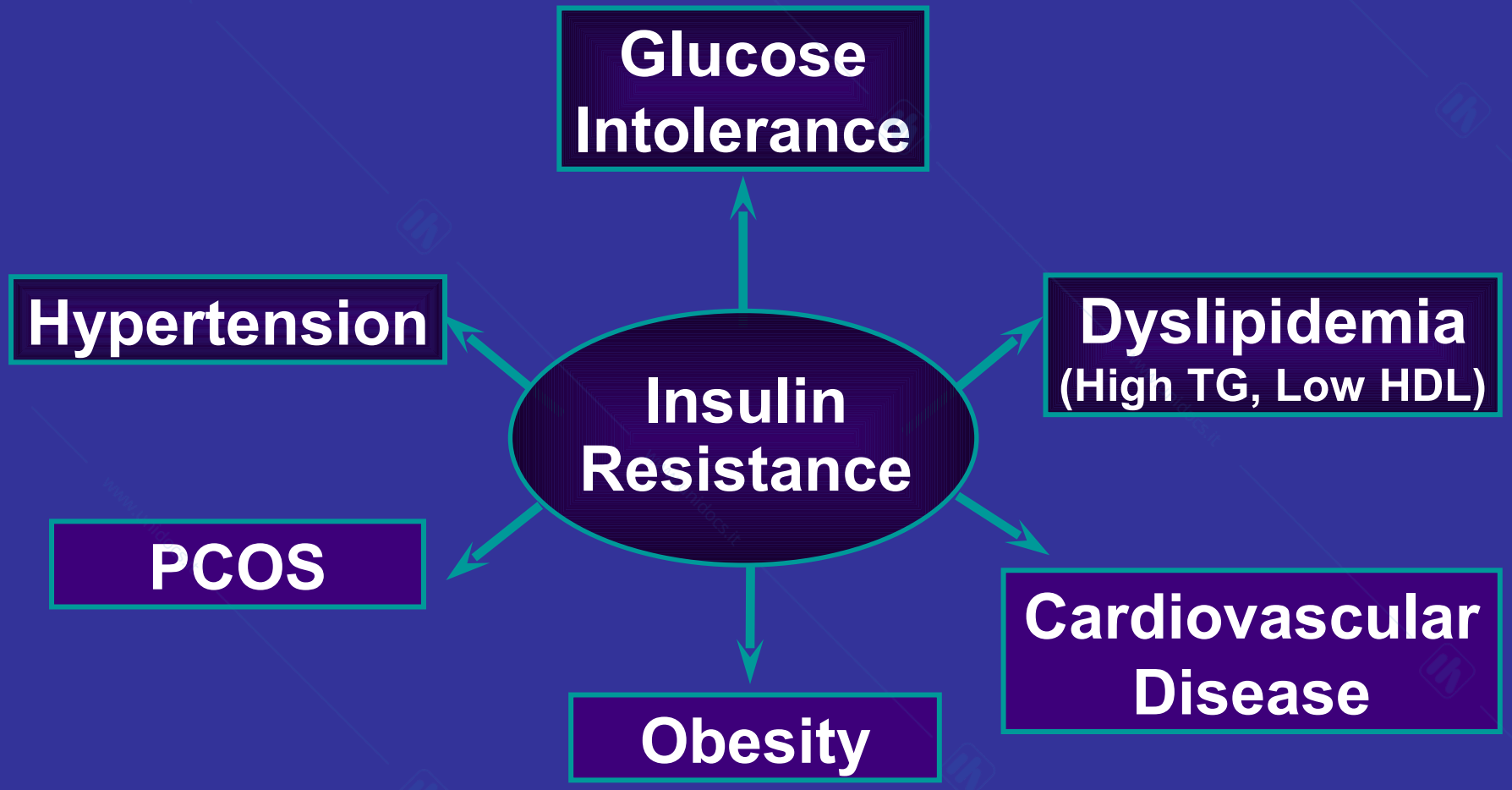


Insulin Deficiency

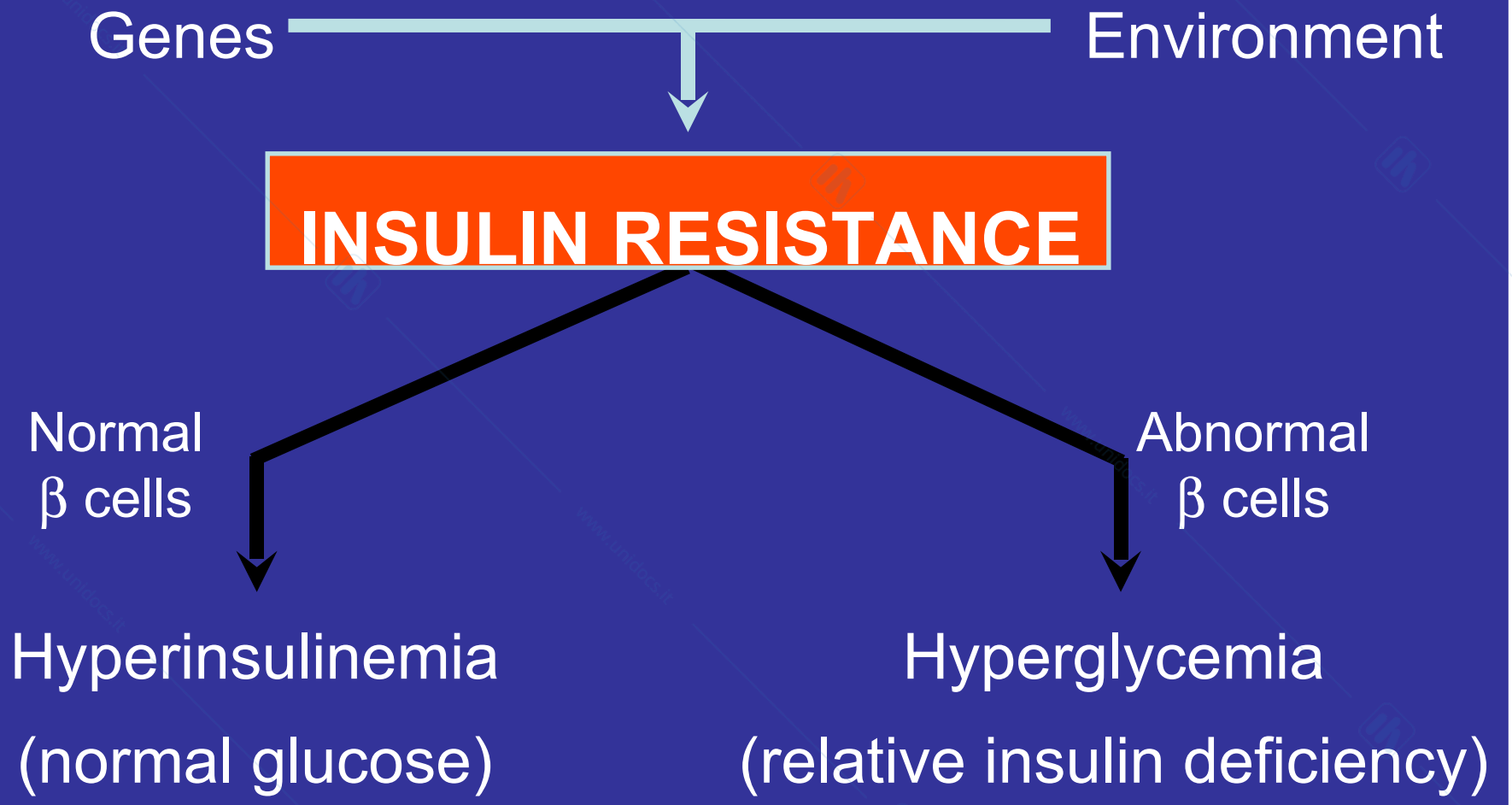
Decreased Insulin Secretion



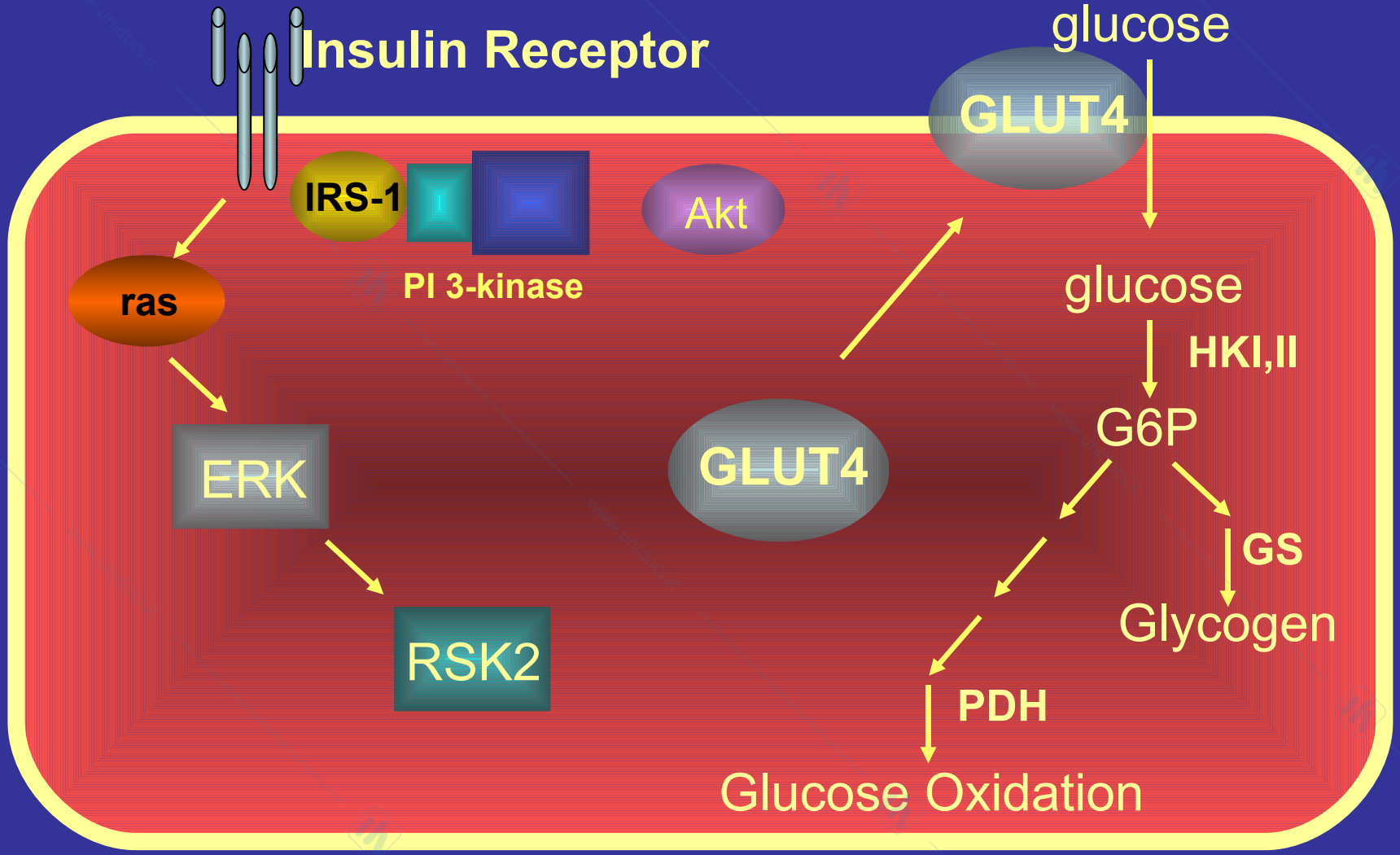
Insulin Resistance Syndrome (Metabolic Syndrome)



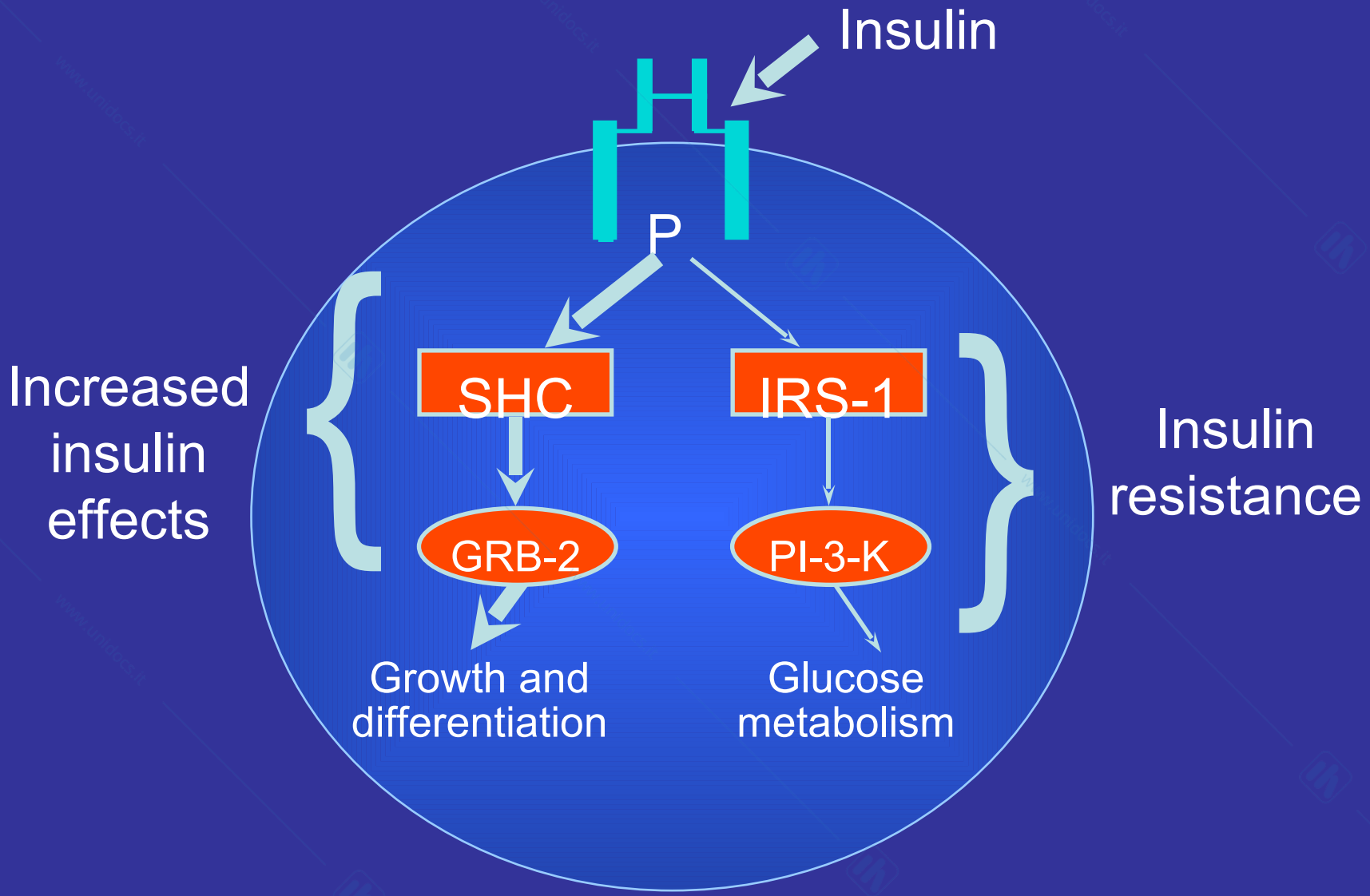
Response to Insulin Resistance: The Pancreatic β Cell



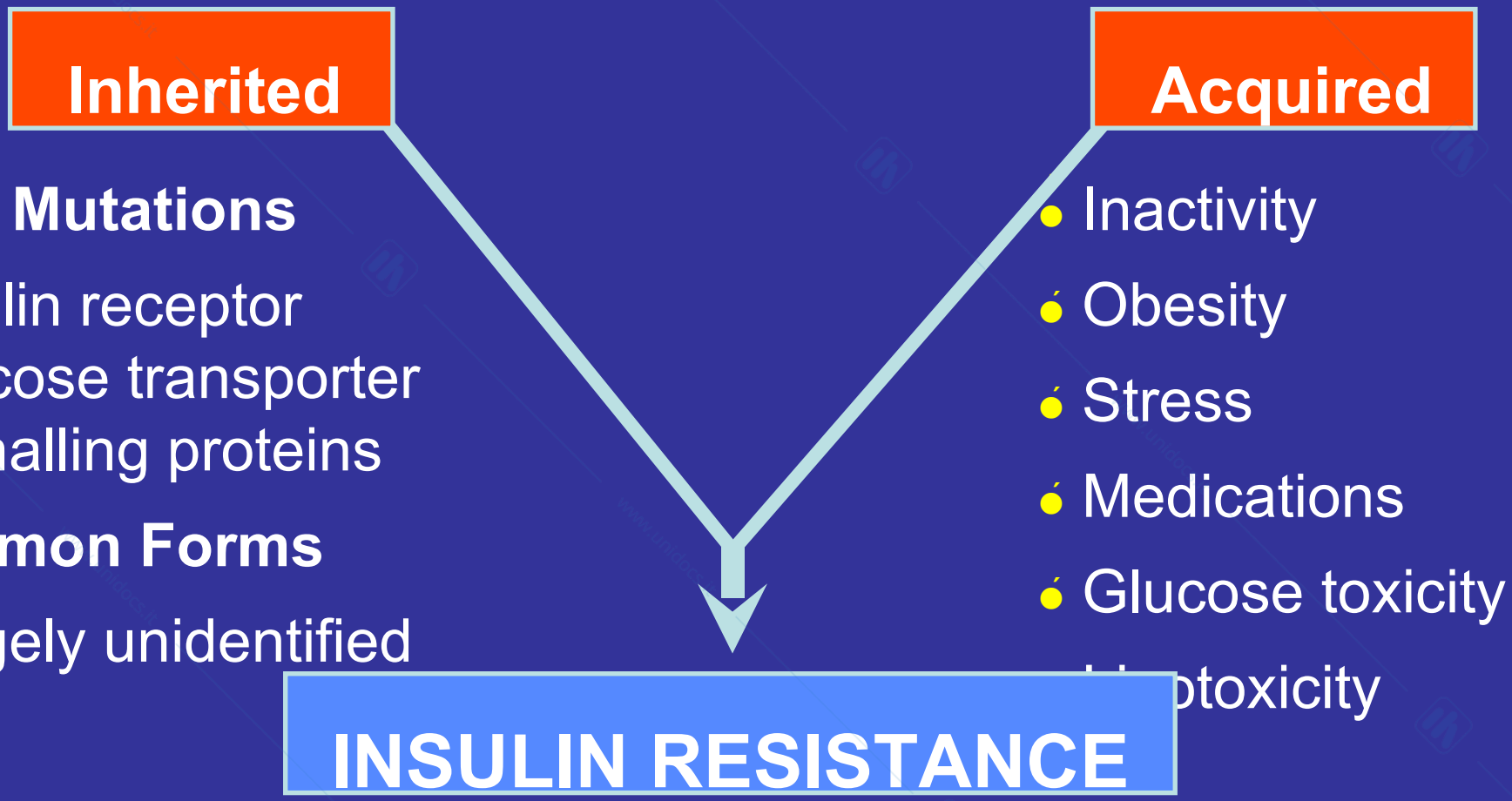
Candidate Molecular Sites of Insulin Resistance in Skeletal Muscle



Differential Insulin Resistance



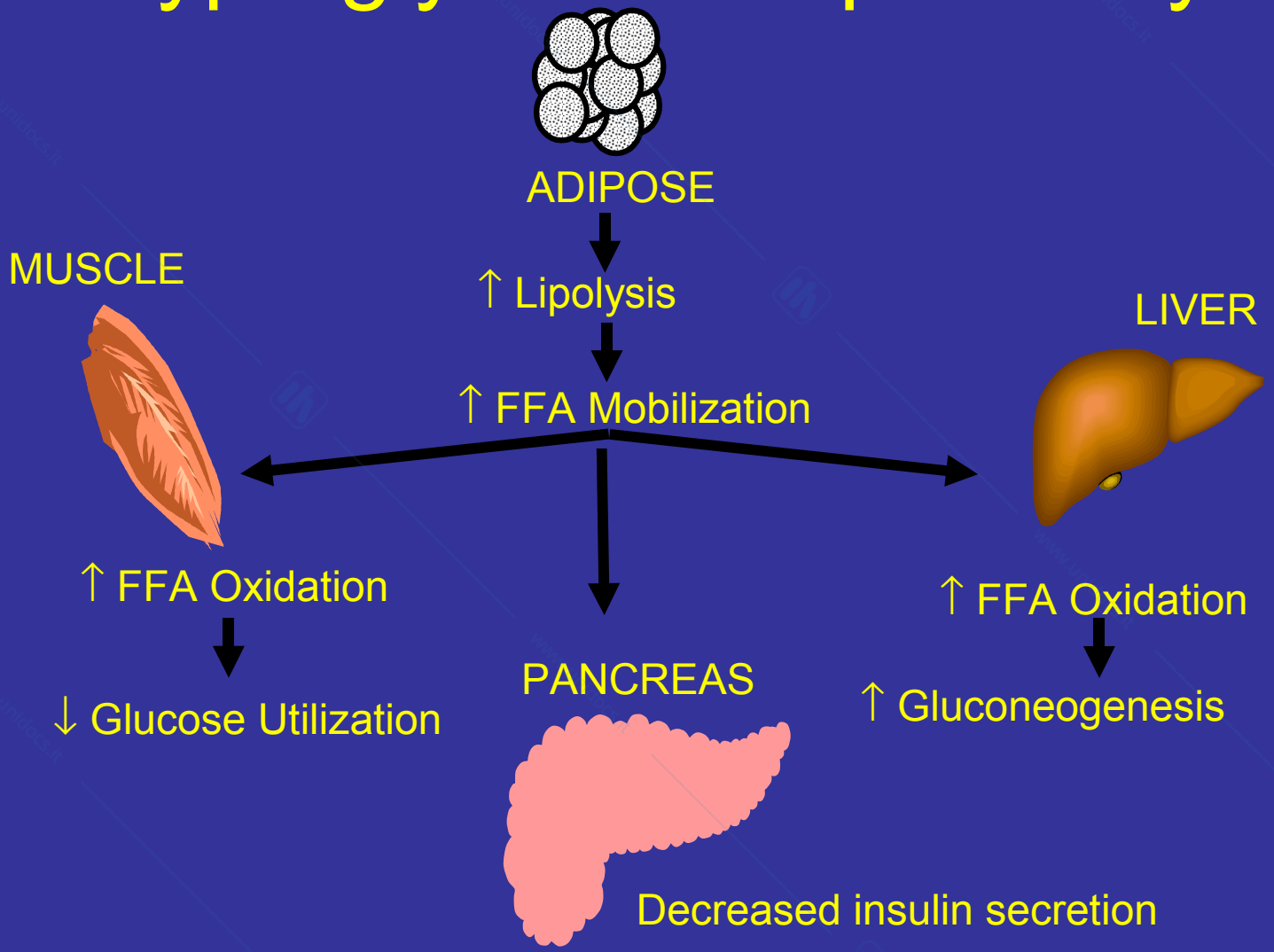
Insulin Resistance: Inherited and Acquired Influences



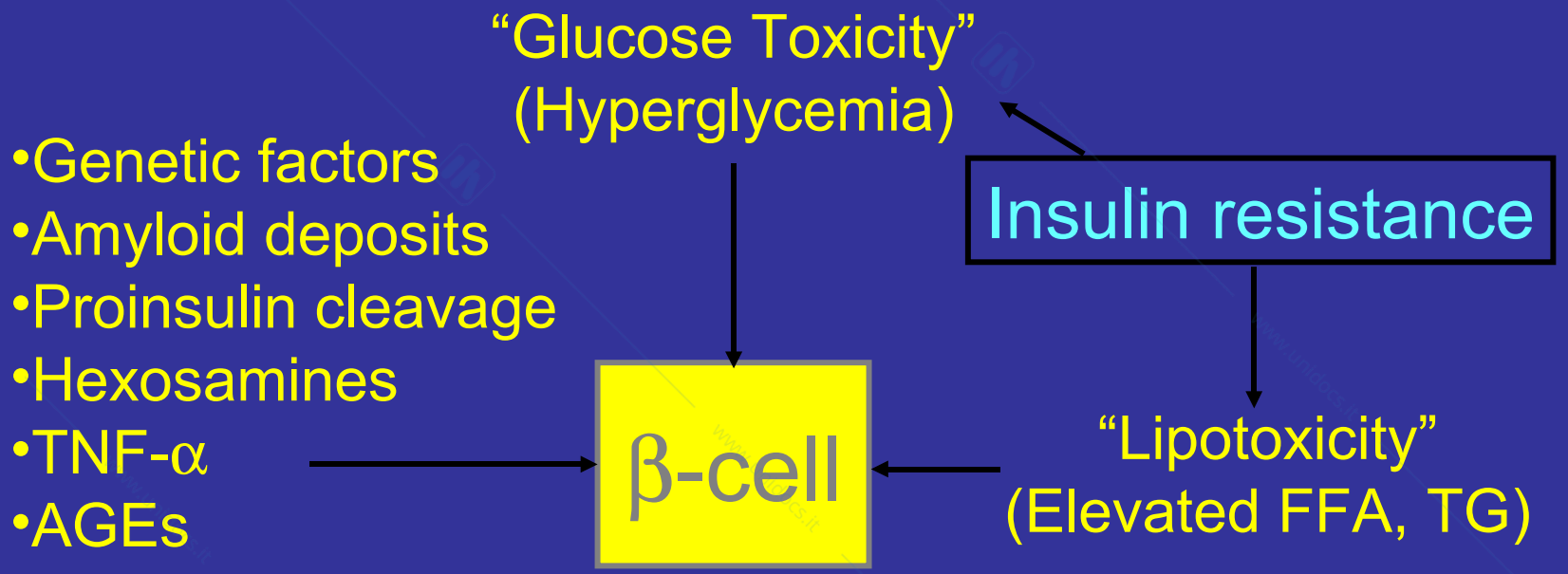
Adipose Cell Products Implicated in Insulin Resistance

- FFA
- Resistin
- Adiponectin
- IL-1
- IL-6
- Leptin
- PAI-1
- TNF-α
- Adipsin
- Angiotensinogen

Role of FFA in Hyperglycemia: Lipotoxcity



Possible Mechanisms for Decline of β-Cell Function



Adapted from Reaven GM. *Physiol Rev* 1995;75:473–486.

Complicanze Acute

- Ipoglicemia
- Coma Ipogligemico
- Chetoacidosi diabetica
- Coma Chetoacidosico
- Coma Iperosmolare

Principali organi bersaglio

- Rene
- Occhio
- Sistema Nervoso Periferico
- Cuore
- arterie
- Piede
- Apparato urogenitale

Altri distretti:
encefalo, cute, apparato muscolo-scheletrico, respiratorio, etc.

Complicanze Croniche

- Retinopatia diabetica
- Nefropatia diabetica
- Neuropatia diabetica
- Macroangiopatia diabetica
- Piede diabetico
- Turbe della vis

Aspetti anatomo-clinici

- ***Microangiopatia*:**
  - ✓ arteriole, venule, capillari
- ***Macroangiopatia*:**
  - ✓ arterie di medio e grosso calibro
- ***Neuropatia*:**
  - ✓ Somatica, Autonomica

DIABETE MELLITO E GLUCOTOSSICITÀ

IPERGLICEMIA

A. Perpetuazione della malattia

L'iperglicemia può peggiorare il deficit di secrezione insulinica e l'insulino resistenza periferica

---

B. Determinismo complicanze croniche

a. Esaltazione della via dei polioli

b. Glicazione non enzimatica delle proteine

Ispessimento della membrana basale dei capillari renali, retinici, nervosi → MICRO-ANGIOPATIA

c. Glicazione dell'emoglobina con ipossia tissutale

d. Glicazione del collageno con alterato trofismo tissutale

e. Glicazione delle LDL

Aterosclerosi → MACRO-ANGIOPATIA

The Pathobiology of Diabetic Complications
A Unifying Mechanism

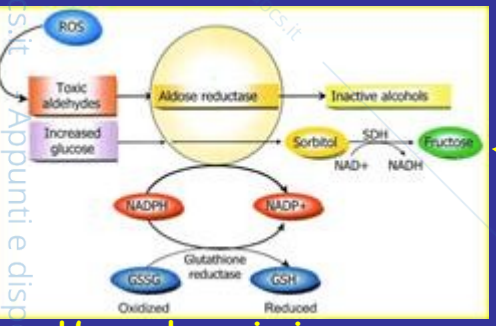
American Diabetes Association. Cure • Care • Commitment

diabetes
A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION.

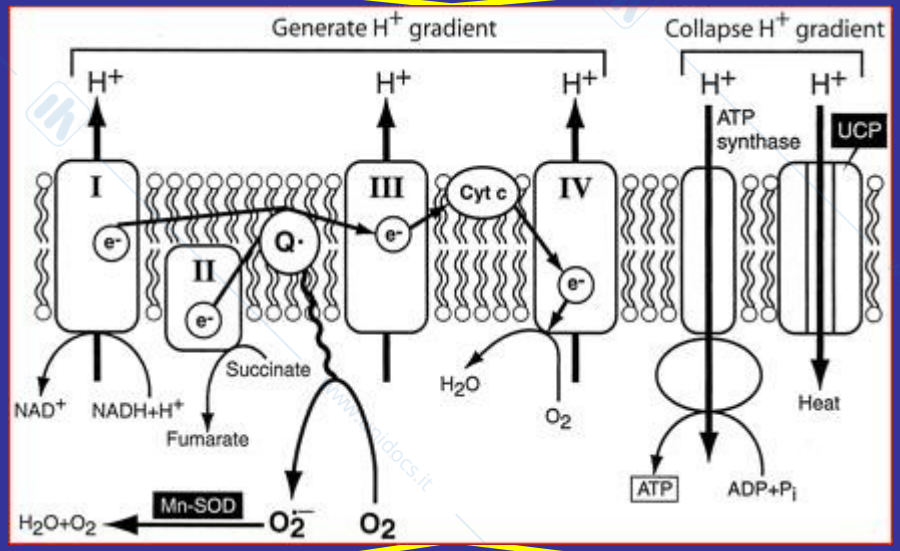
Diabetes 54:1615-1625, 2005

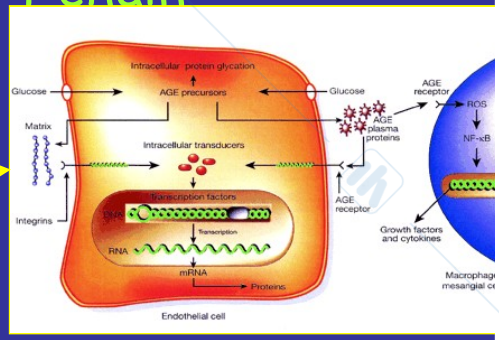
Michael Brownlee

Hyperglycemia-induced ROS production
by the mitochondrial electron transport chain

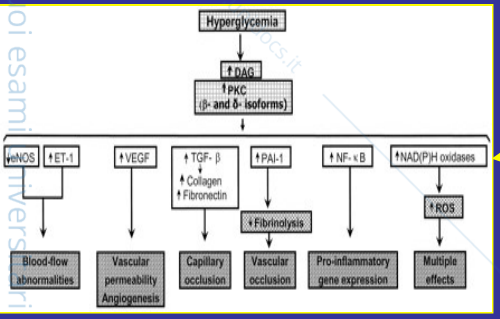


Hyperglycemia increases the polyol pathway

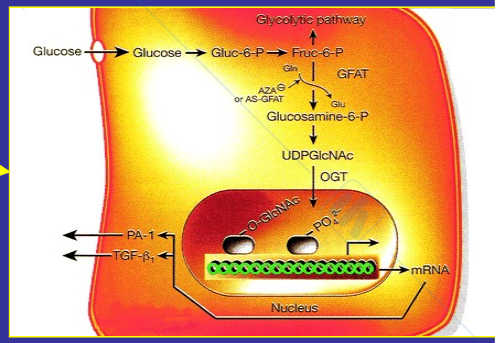




Hyperglycemia increases production of AGE precursors



Hyperglycemia increases activation of PKC



Hyperglycemia increases the hexosamine pathway

Retinopatia diabetica Classificazione

- Assenza di RD

- RD non proliferante: Lieve, Moderata, Avanzata
- RD proliferante

con o senza

- Maculopatia edematosa: edema maculare non clinicamente significativo, edema maculare clinicamente significativo
- Maculopatia ischemica

- OftaImopatia diabetica avanzata

Lesioni retiniche

- *Non retinopatia:* assenza di lesioni.

- *RD non proliferante (lieve o moderata):* Microaneurismi e/o emorragie retiniche; Essudati duri; Noduli cotonosi non associati ad altre lesioni della retinopatia non proliferante grave.

- *RD non proliferante grave (preproliferante):* Emorragie retiniche numerose; Noduli cotonosi numerosi; IRMA (Anomalie Microvascolari Intraretiniche); Irregolarità del calibro venoso; Anse venose.

La Neuropatia Diabetica

E’ la più frequente ed insidiosa complicanza cronica del DM

Definizione

“Diabetic neuropathy is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system”.

(Consensus Conference of San Antonio on diabetic neuropathy, 1988)

Caratteri clinici

- Dolori acuti trafittivi e profondi ad arti inferiori
- Sindromi da intrappolamento agli arti superiori (STC)
- Ipoestesie, disestesie, ridotta sensibilità termo-dolorifica agli arti inferiori (piede diabetico)
- Ipotensione ortostatica, alterata FC, denervazione cardiaca, ischemie cardiache silenti (dead in bed syndrome)
- Deficit della vis, disfunzioni vescicali
- Alterara motilità gastro-esofagea (gastroparesi) e intestinale (incontinenza)
- Alterate risposte oculari alla luce

Epidemiologia

Estremamente variabile perchè solo di recente sono state standardizzate le tecniche di rilevazione

Classificazione (da Dyck)

- Polineuropatia simmetrica distale (>80%)

  (sensitiva, motoria, mista, autonomica)
- Neuropatia simmetrica prossimale:

  a) craniale

  b) truncale (radicolopatia)

  c) mononeuropatia o neuropatia dei plessi

  d) mononeuropatie multiple

  e) neuropatie da intrappolamento (STC)
- Neuropatia asimmetrica

Nefropatia diabetica

- Diagnosi e follow-up: Parametri funzionalità renale, microalbuminuria e proterinuria, PA, ecografia renale

- Evoluzione:

- Assenza di nefropatia
- Iperfiltrazione con assenza di microalbuminuria
- Microalbuminuria con PA normale
- Microalbuminuria con PA alterata
- Proteinuria con PA alterata
- Insufficienza renale end-stage

Nefropatia Diabetica

Classificazione clinica (Mogensen)

***1° STADIO*:** ipertrofia, iperfunzione renale

- Aumento della Creatinina Clearance
- Aumento del volume renale

Nefropatia Diabetica

Classificazione clinica (Mogensen)

2° STADIO: danno anatomico glomerulare

- Membrana basale ispessita
- Filtrato glomerulare aumentato
- Microalbuminuria (20-200 ug/min)

Può durare tutta la vita

Nefropatia Diabetica

Classificazione clinica (Mogensen)

***3° STADIO*:** Nefropatia Diabetica incipiente

- Filtrato normale
- Macroalbuminuria
- Aumento della PA

Può durare diversi anni

Nefropatia Diabetica

Classificazione clinica (Mogensen)

***4° STADIO*:** Nefropatia Diabetica conclamata

- Filtrato glomerulare ridotto
- Macroalbuminuria
- Ipertensione

Nefropatia Diabetica

Classificazione clinica (Mogensen)

***5° STADIO*:** Insufficienza Renale Terminale

- Filtrato glomerulare < 10 ml/min
- Glomerulosclerosi
- Riduzione della proteinuria
- Ipertensione

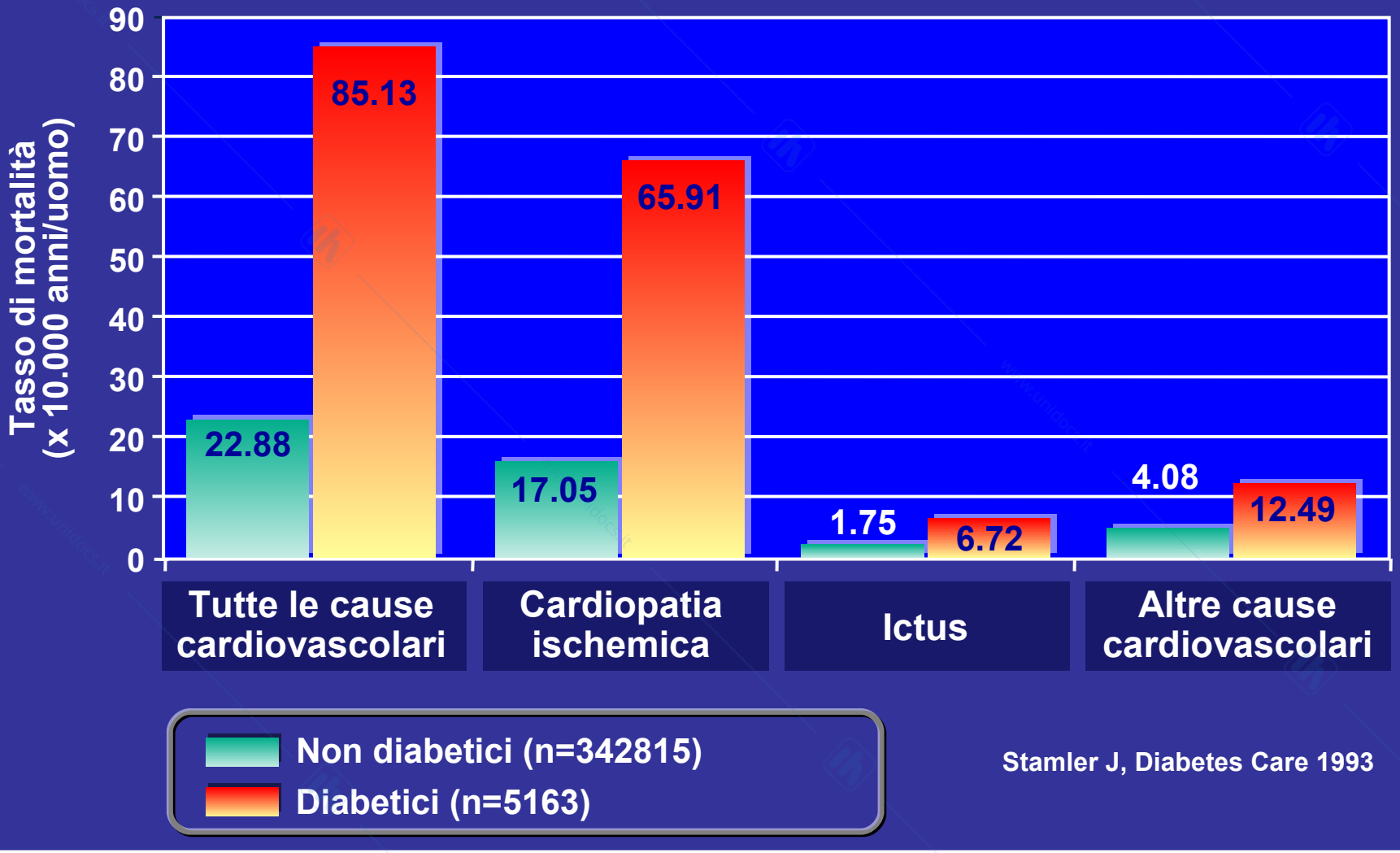
Diabete Mellito e Macroangiopatia

- Lesione di carattere aterosclerotico, che interessa i vasi arteriosi di medio e grosso calibro

- Ne sono espressione quadri clinici variabili, a seconda del distretto colpito:
  - coronaropatia ⇒ miocardiopatia ischemica e infarto miocardico
  - vasculopatia cerebrale ⇒ ictus ischemico
  - vasculopatia periferica ⇒ arteriopatia obliterante degli arti inferiori

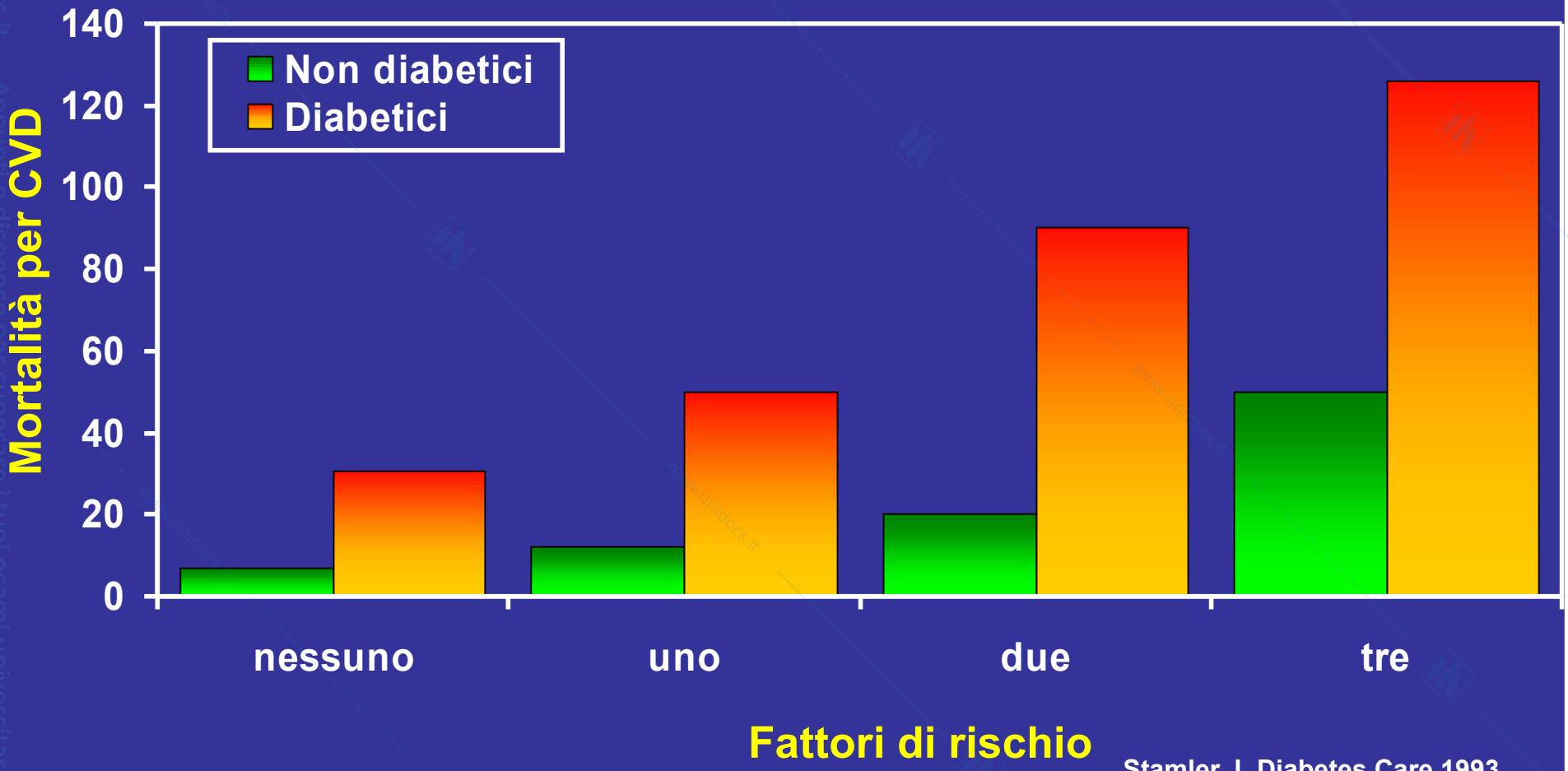
STUDIO MRFIT

Tasso di mortalità da causa cardiovascolare in pazienti di sesso maschile non diabetici e con diabete noto al momento dell'arruolamento



Stamler J, Diabetes Care 1993

Mortalità da malattia cardiovascolare in individui di sesso maschile diabetici e non diabetici in funzione della consistenza di fattori di rischio



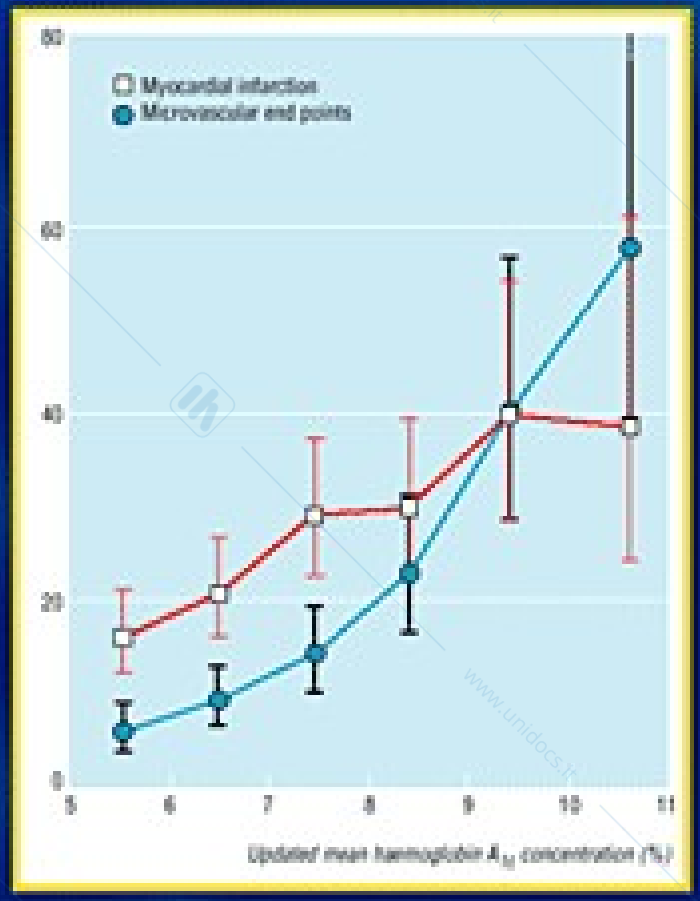
Stamler J, Diabetes Care 1993

Table 2: Factors Underlying Accelerated Atherogenesis In Diabetes

- Diabetic dyslipidemia
  - ↑ TG-rich LP's, ↓ HDL-chol, ↑ small, dense LDL
- Hyperglycemia
  - Glyco-oxidation, sorbitol/myoinositol pathway, Diacylglycerol/PKC activation
- Hypertension
- Oxidative stress
- Hemorrheological alterations:
  ↑ platelet aggregation, ↑ fibrinogen, ↓ fibrinolysis,↑ PAI-1
- Endothelial dysfunction
- Insulin resistance
- Others

Per each 1% increment in HbA_{1c}, there was an 10% increase in the risk of coronary heart disease

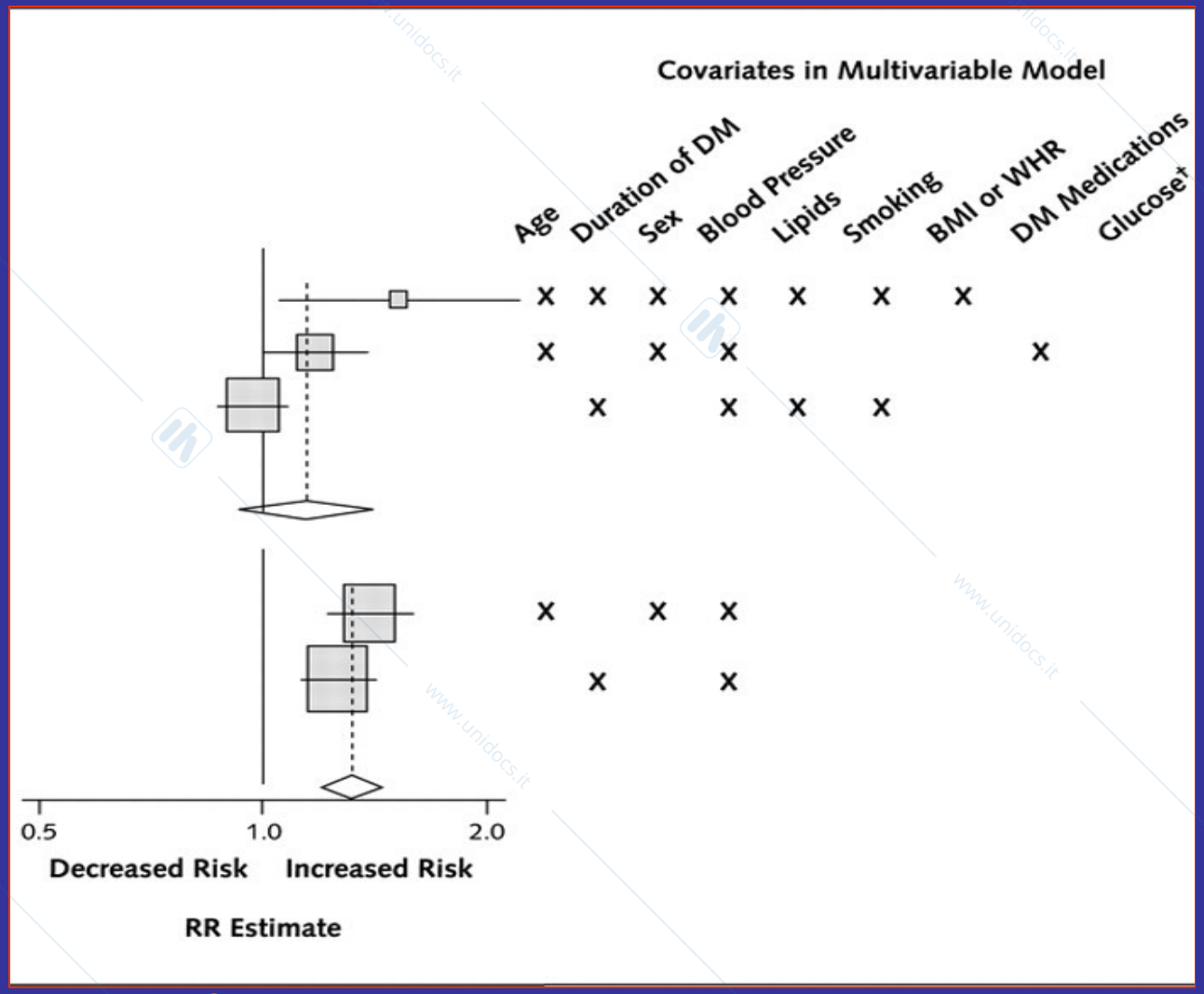
UKPDS: A1C and Diabetic Complications



Incidence rates and 95% confidence intervals for myocardial infarction and microvascular complications by category of updated mean haemoglobin A1C concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years.

Stratton JM, et al. *BMJ*. 2000;321:405-12.

Relative risk for HbA1c (per 1-percentage point increase) and incident coronary heart disease in persons with diabetes



Selvin, E. et. al. Ann Intern Med 2004;141:421-431

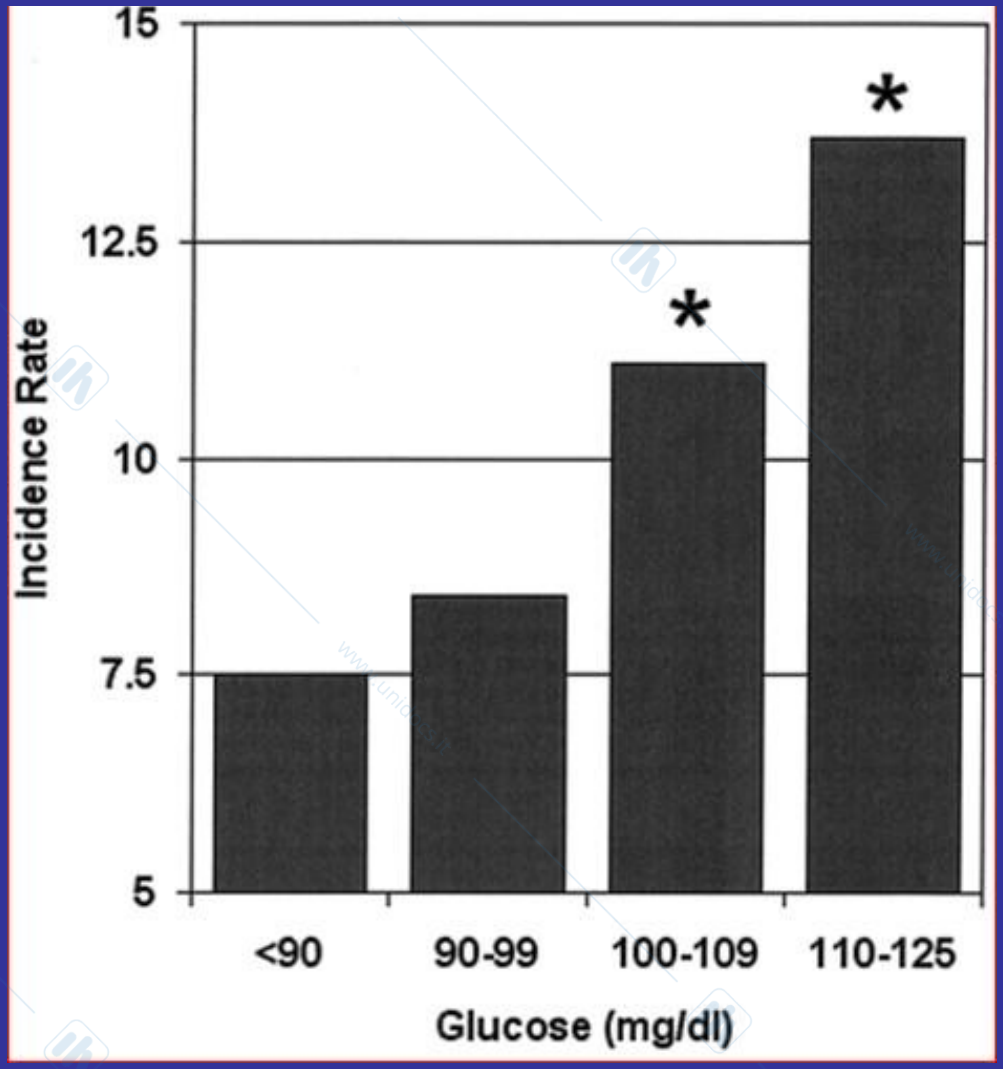
Annals of Internal Medicine

DiabetesCare

Epidemiology/Health Services/Psychosocial Research
ORIGINAL ARTICLE

Blood Glucose and Heart Diseases in Nondiabetic Patients

CHRISTOPHER NIELSON, MD[1,2,3]
THEODORE LANGE, MD[2,3]



Diabetes Care 28:607-611, 2005

American Heart Association®

Learn and Live℠

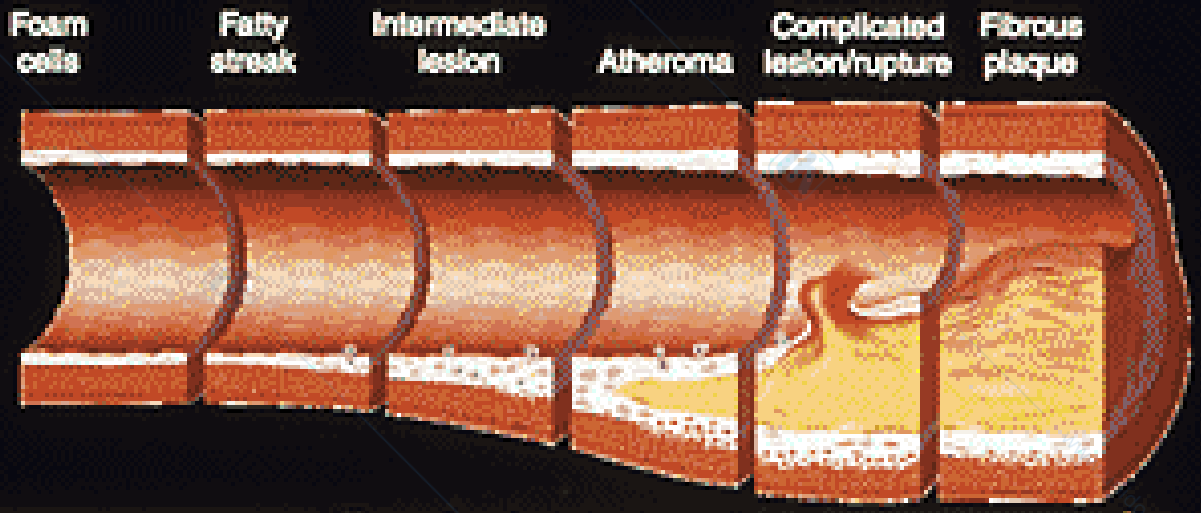
Diabetes is a cardiovascular disease

Diagnosed by measuring glycemia

In che modo l'iperglicemia
può condizionare
l'inizio dell'aterosclerosi?

Atherosclerosis timeline

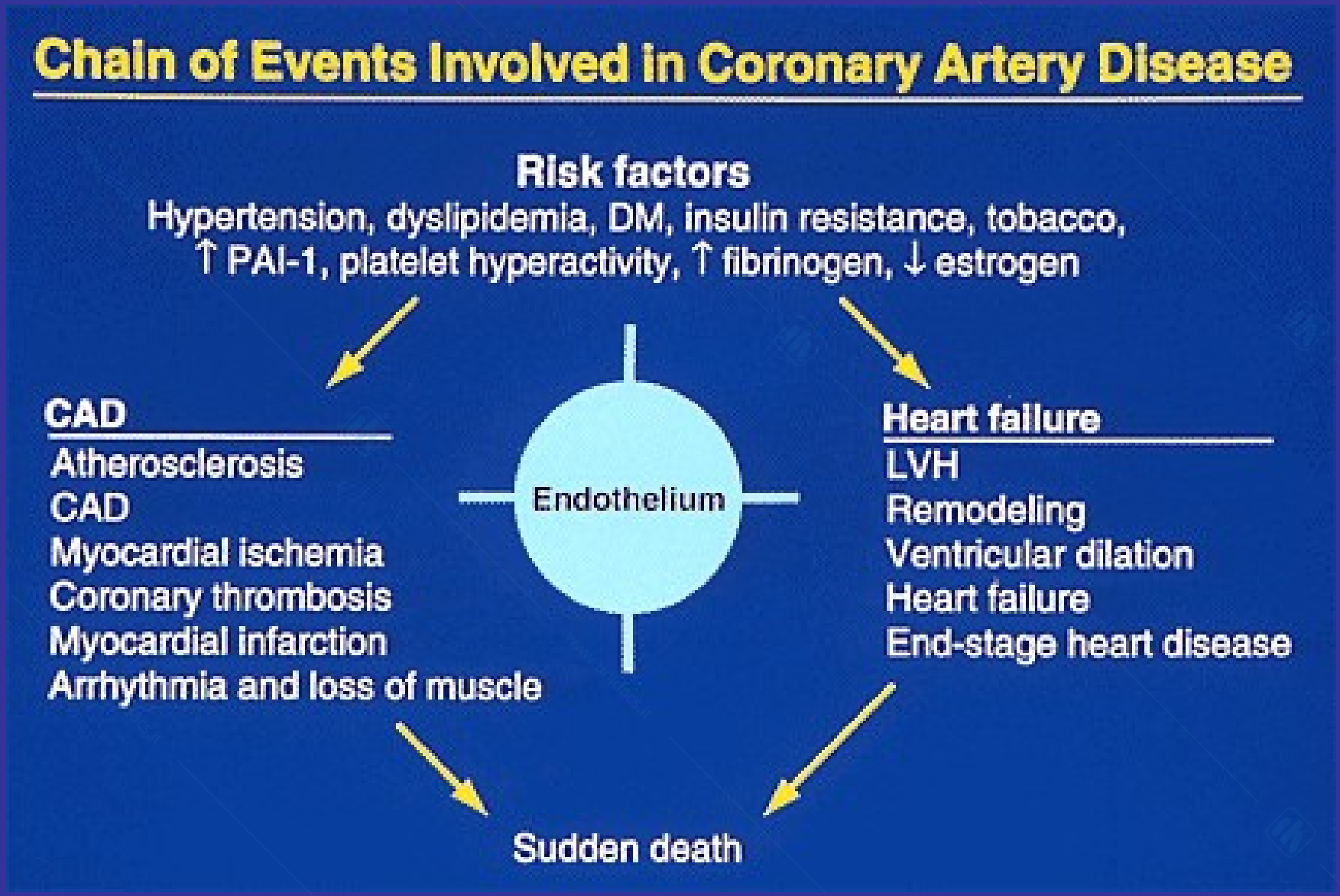
VBWG



Endothelial dysfunction

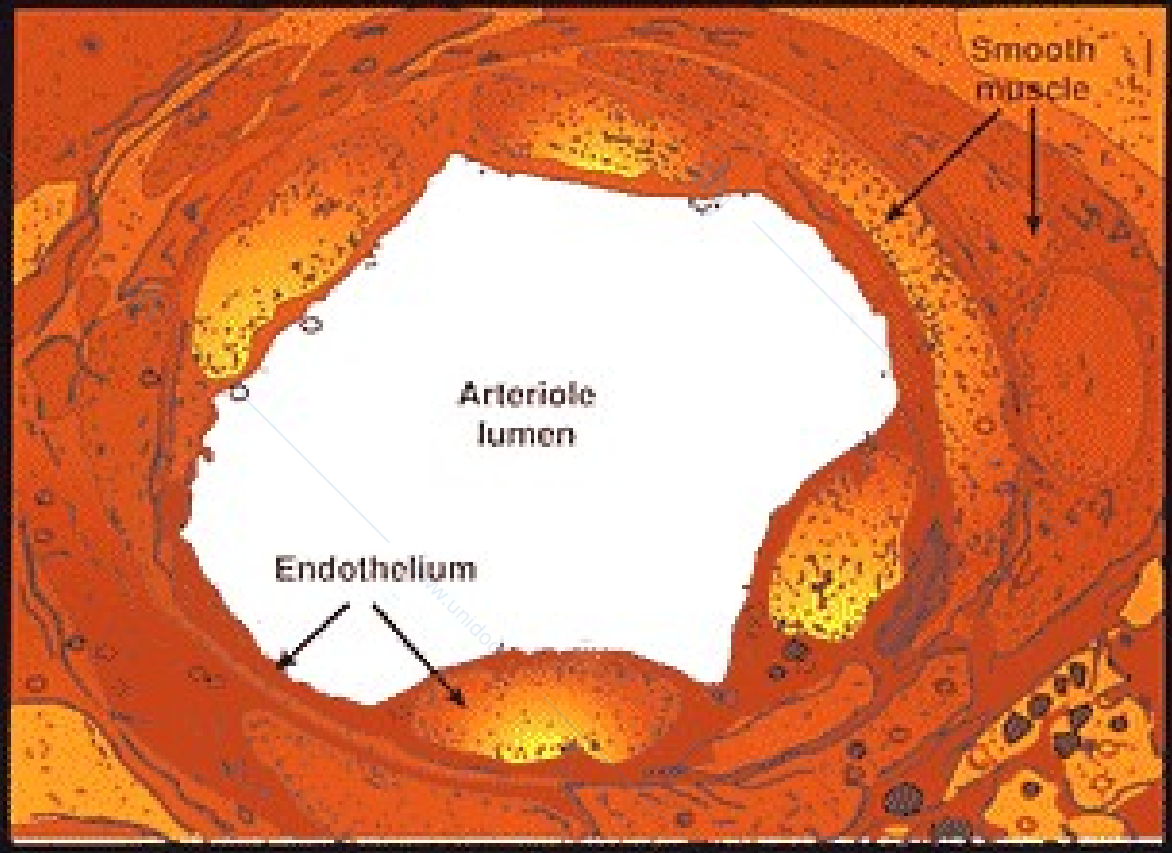
From first decade	From third decade	From fourth decade	
Growth mainly by lipid accumulation		Thrombosis, hematoma	Smooth muscle and collagen

Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 10A:23S-27S).



The endothelium: A living organ

VBWG



Multiple Functions of Endothelium

- Provide selectively permeable barrier between blood and vessel wall
- Maintain nonthrombogenic surface (lumen)
- Produce/release vasoactive substances (luminal and abluminal)
  - Vasodilators/vasoconstrictors
  - Growth inhibitors/growth promoters
- Modulate smooth muscle cell growth and migration
- Modulate coagulation and fibrinolytic pathways

Lüscher. J Myocard Ischemia. 1995;7(suppl 1):15-20.

Substances Released by Endothelium

Vasoactive Substances

- **Vasodilators**
  - — Nitric oxide/EDRF
  - — EDHF
  - — Prostacyclin (PGI_2)
  - — Bradykinin
  - — Acetylcholine, serotonin, histamine, substance P, etc
- **Vasoconstrictors**
  - — Endothelin
  - — Angiotensin II
  - — Thromboxane A_2, acetylcholine, arachidonic acid, prostaglandin H_2, etc

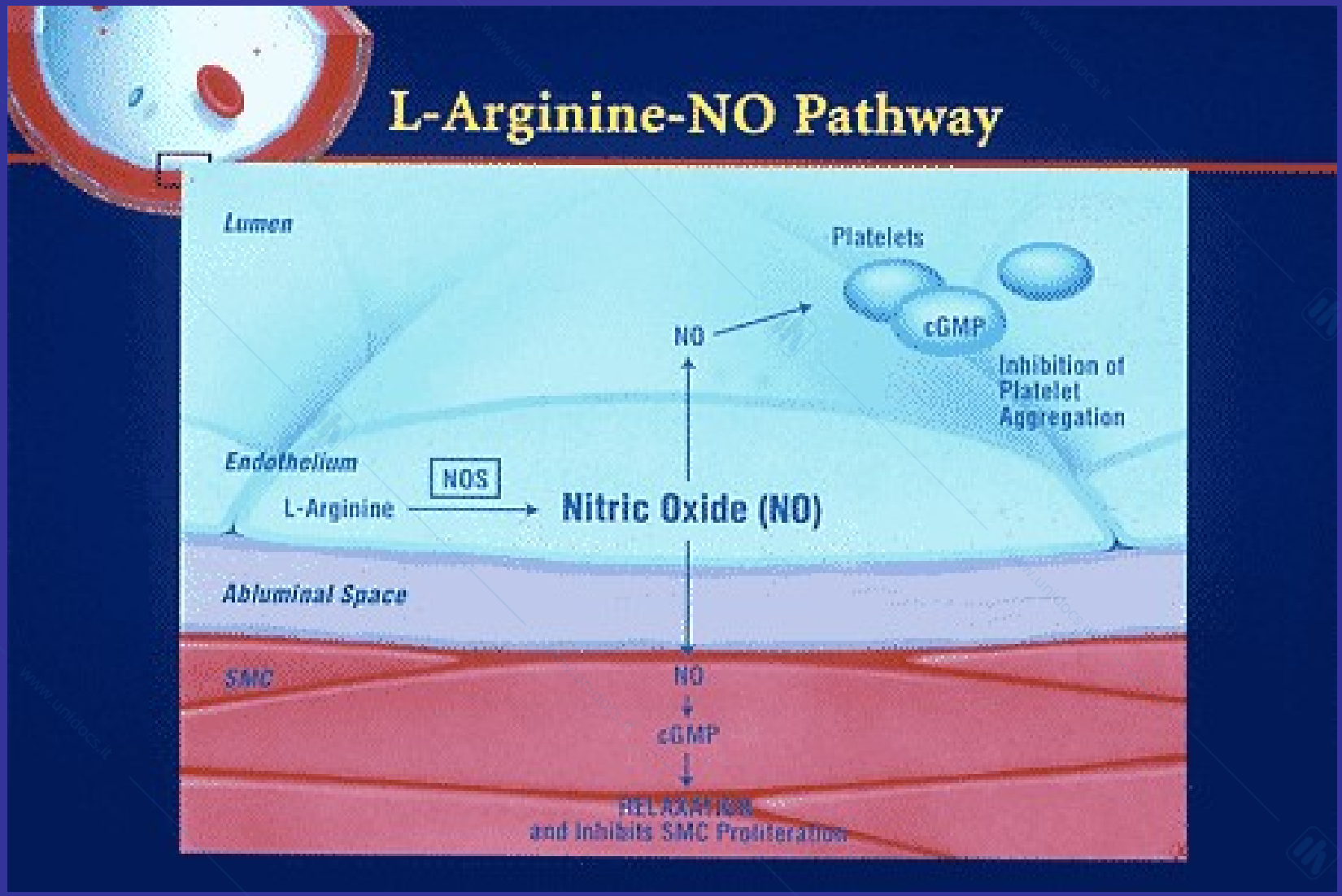
Growth Mediators/Modulators

- Growth promotors
- Growth inhibitors

Inflammatory Mediators/ Modulators

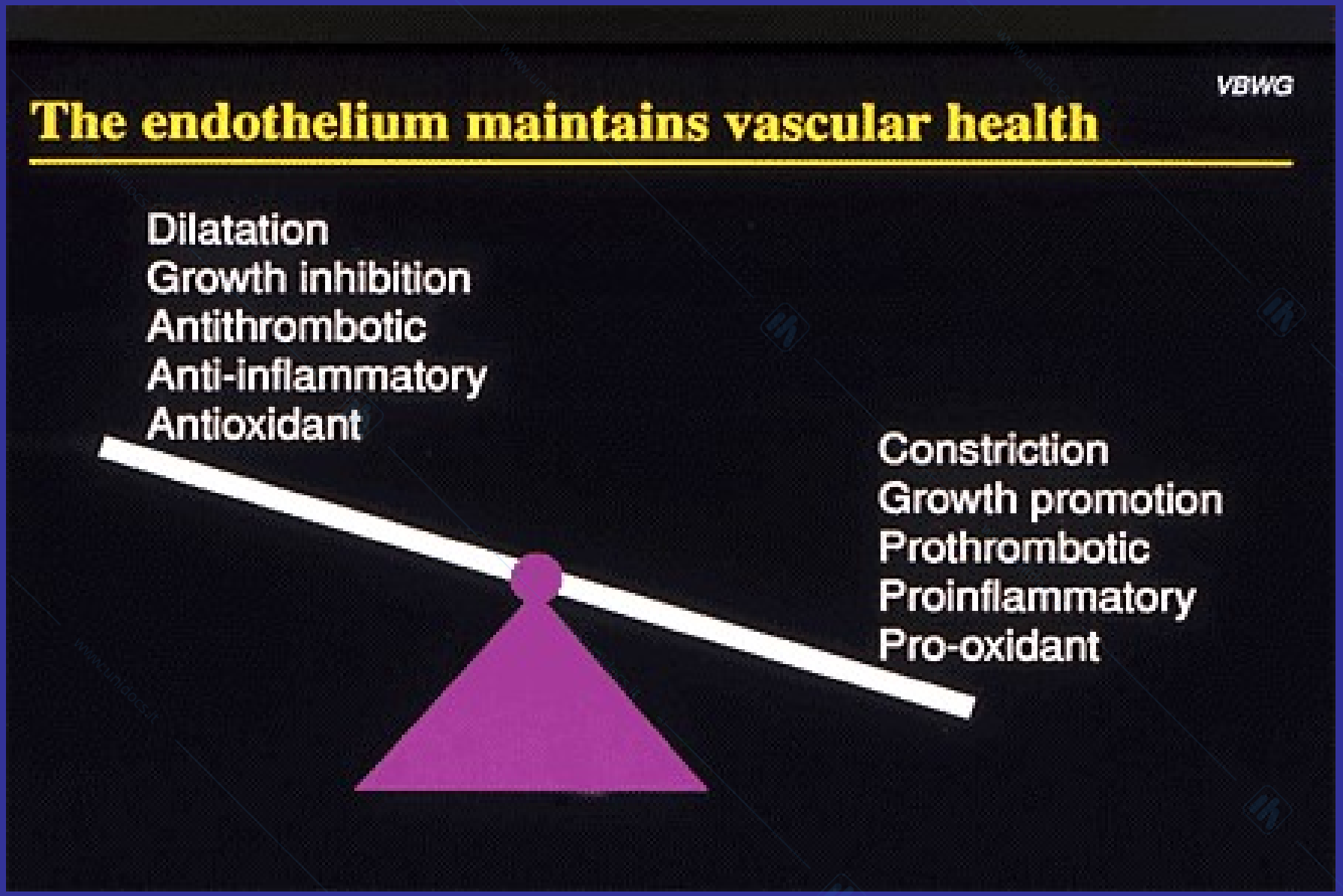
Hemostasis and Thrombosis

Redox State

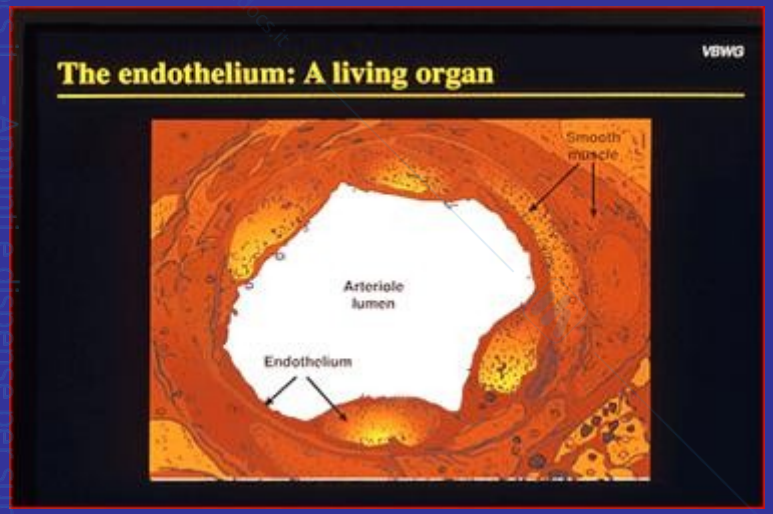


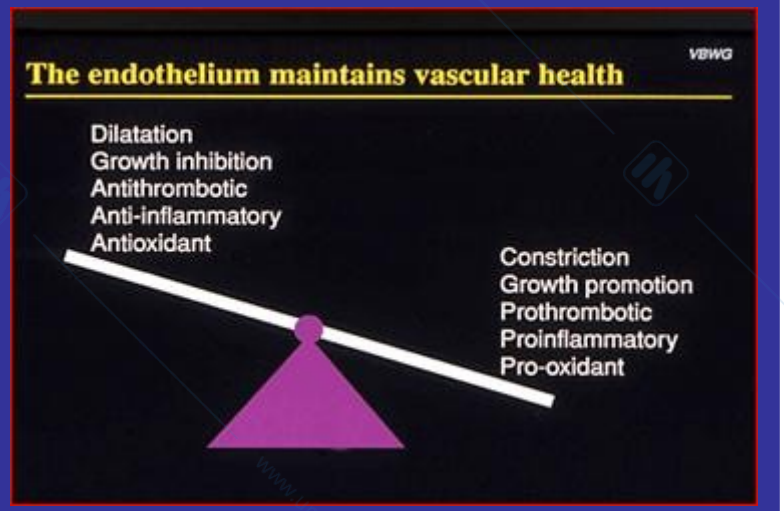
Vasculoprotective Effects of NO

- Vasodilator (via relaxation of SMCs)
- Growth inhibitor (via actions on SMCs)
- Inhibitor of platelet adherence/aggregation
- Inhibitor of endothelial/leukocyte interactions
- ? Counterbalance effects of superoxide anion



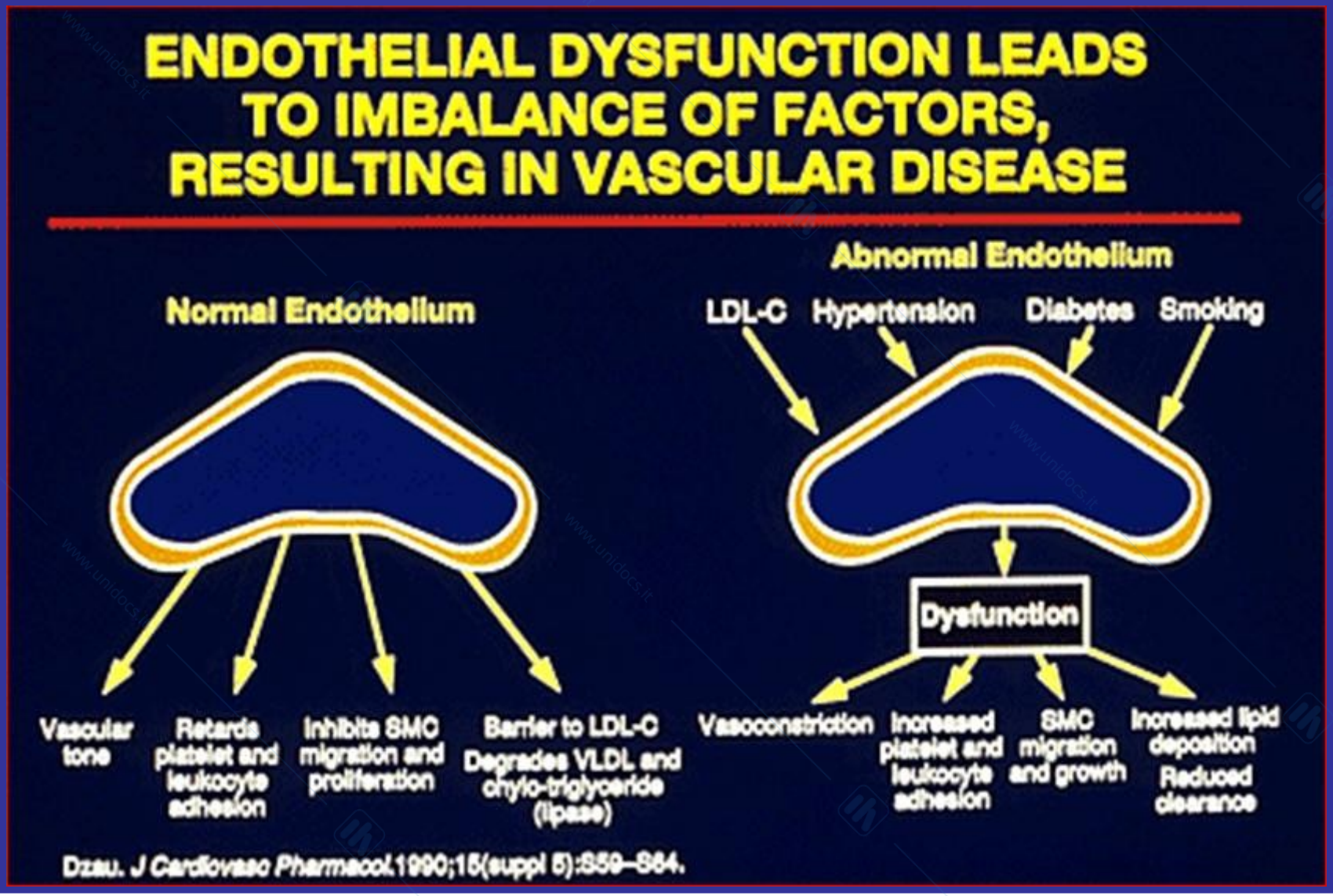
La produzione di ossido nitrico (NO) regola la funzione endoteliale





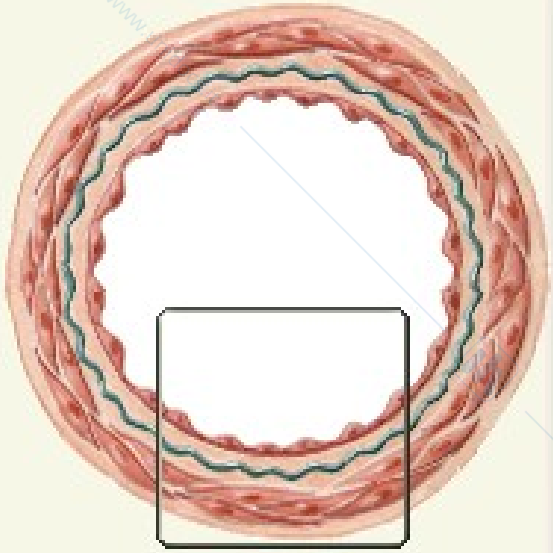
Deficient NO generation contributes:

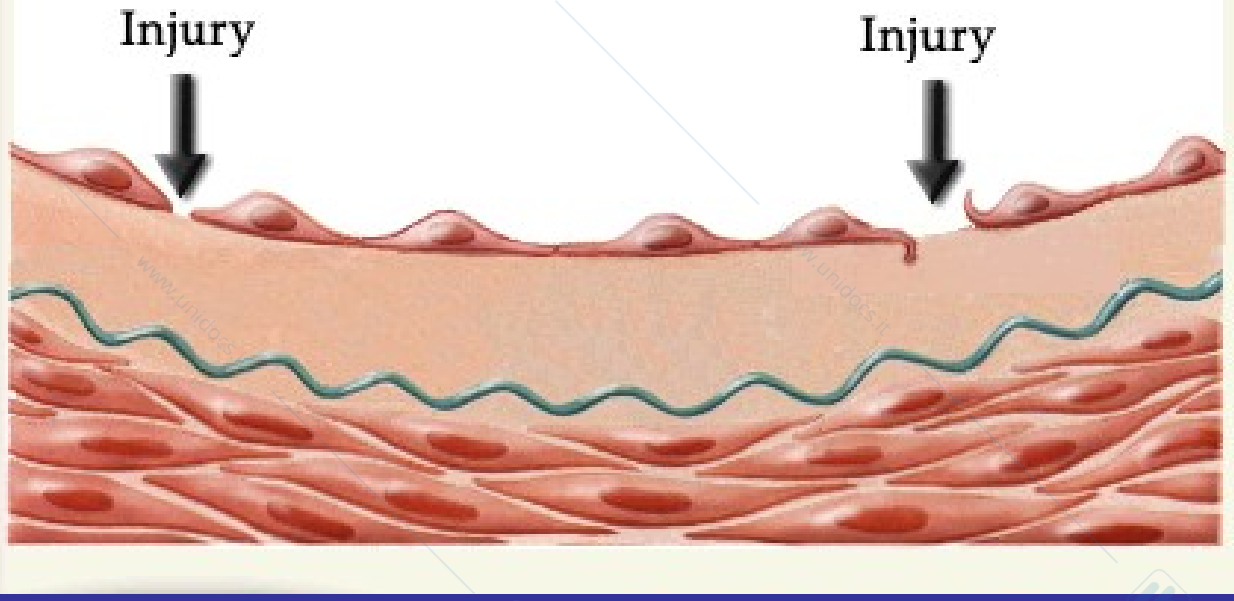
- to impaired vascular relaxation
- enhanced platelet aggregation
- increased inflammation

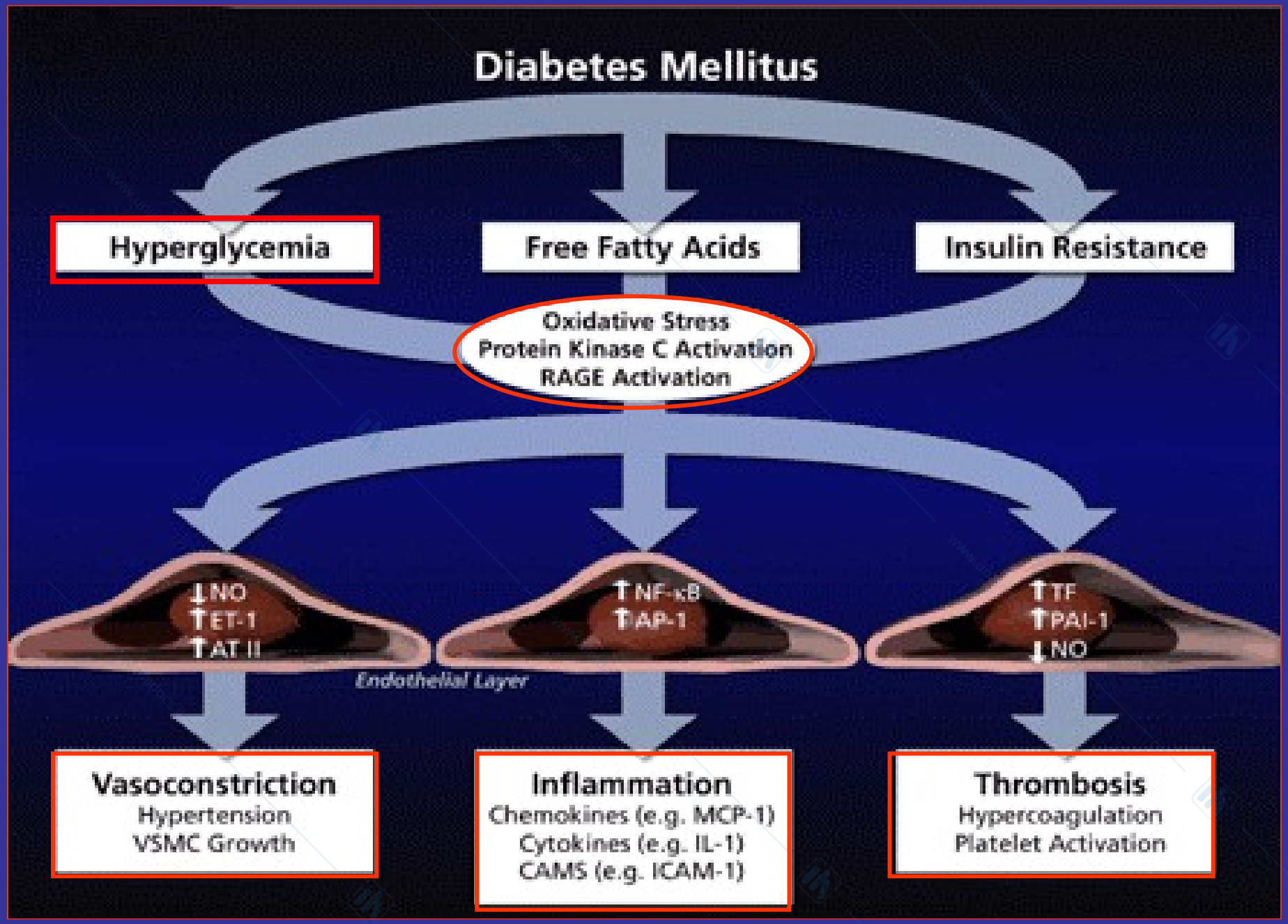


The key event in the development of macrovascular complications of diabetes appears to be injury to the endothelium

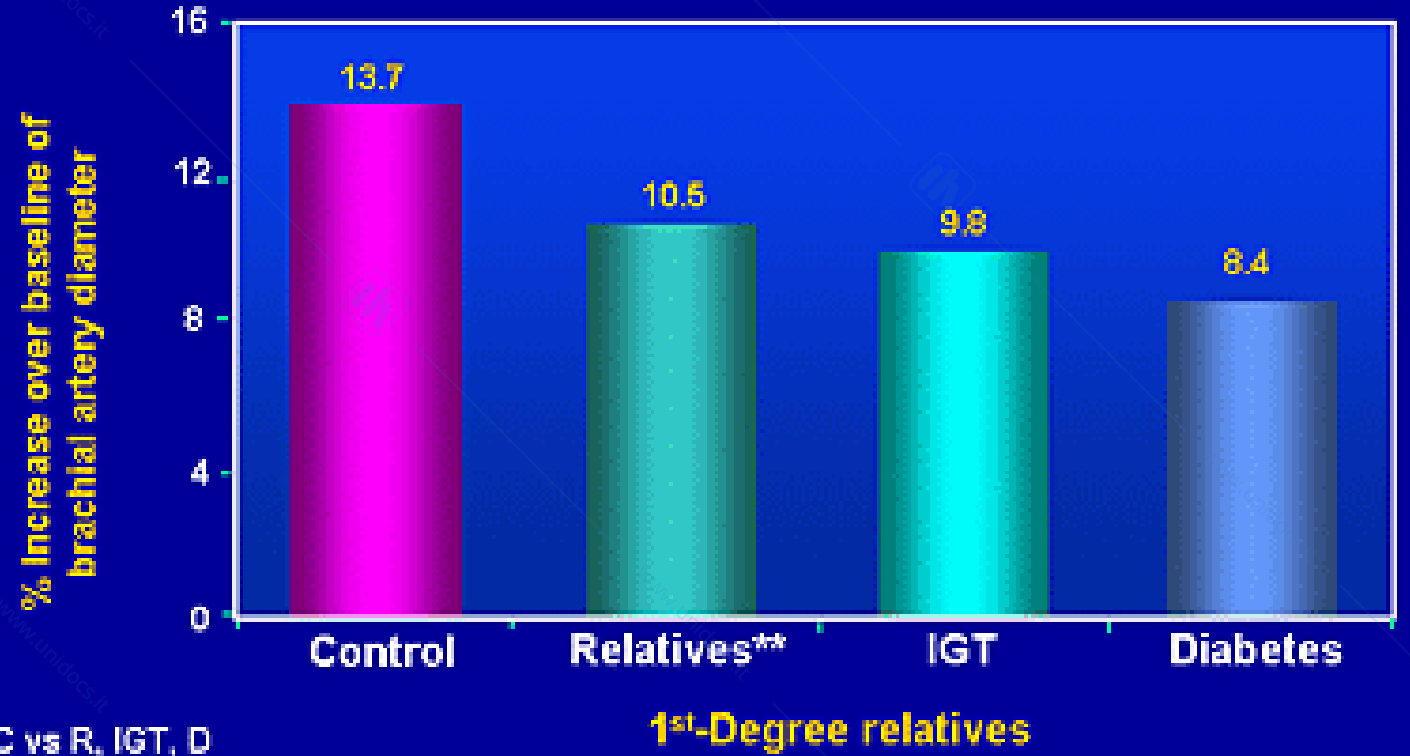
Diabetes





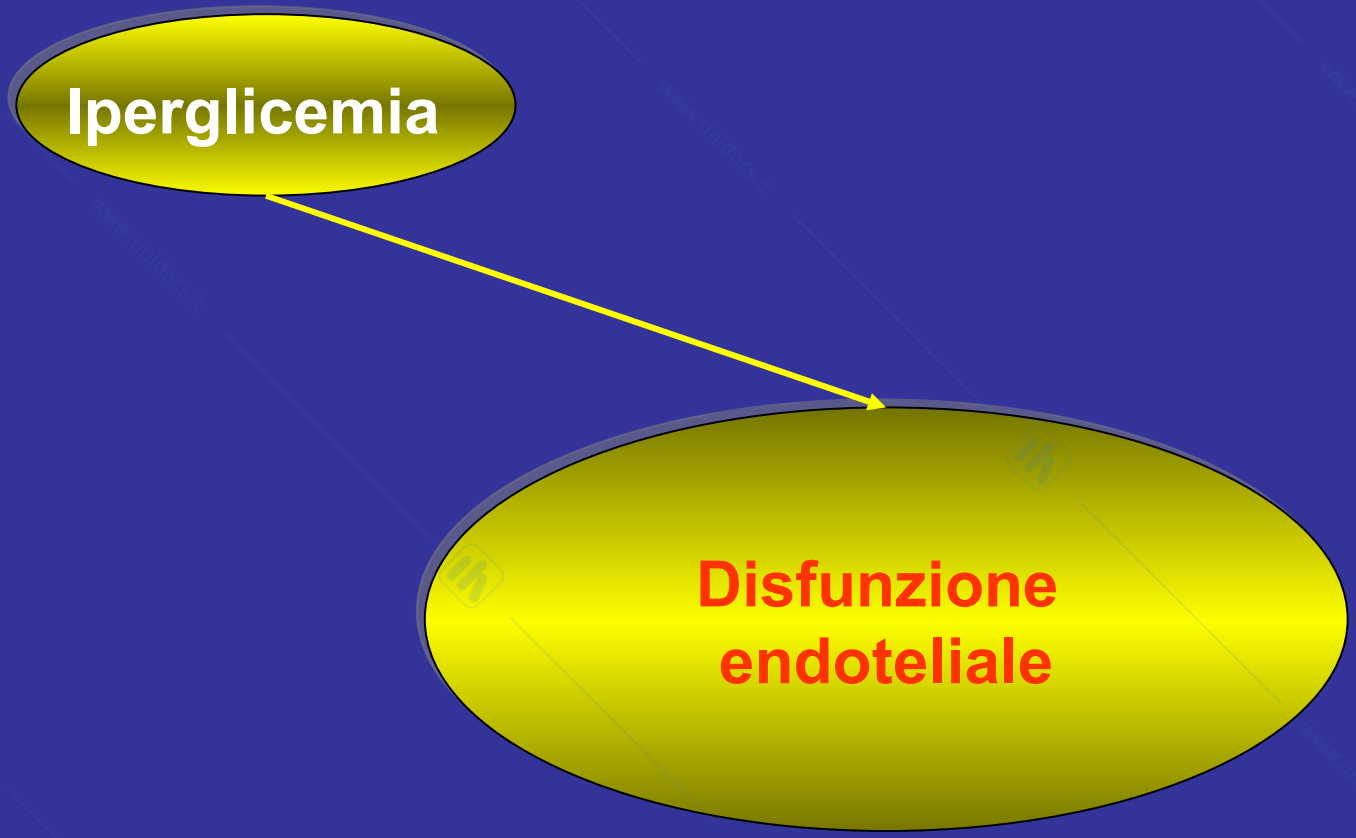


Impaired Endothelium-Dependent Vasodilation in People at Risk for Type 2 Diabetes

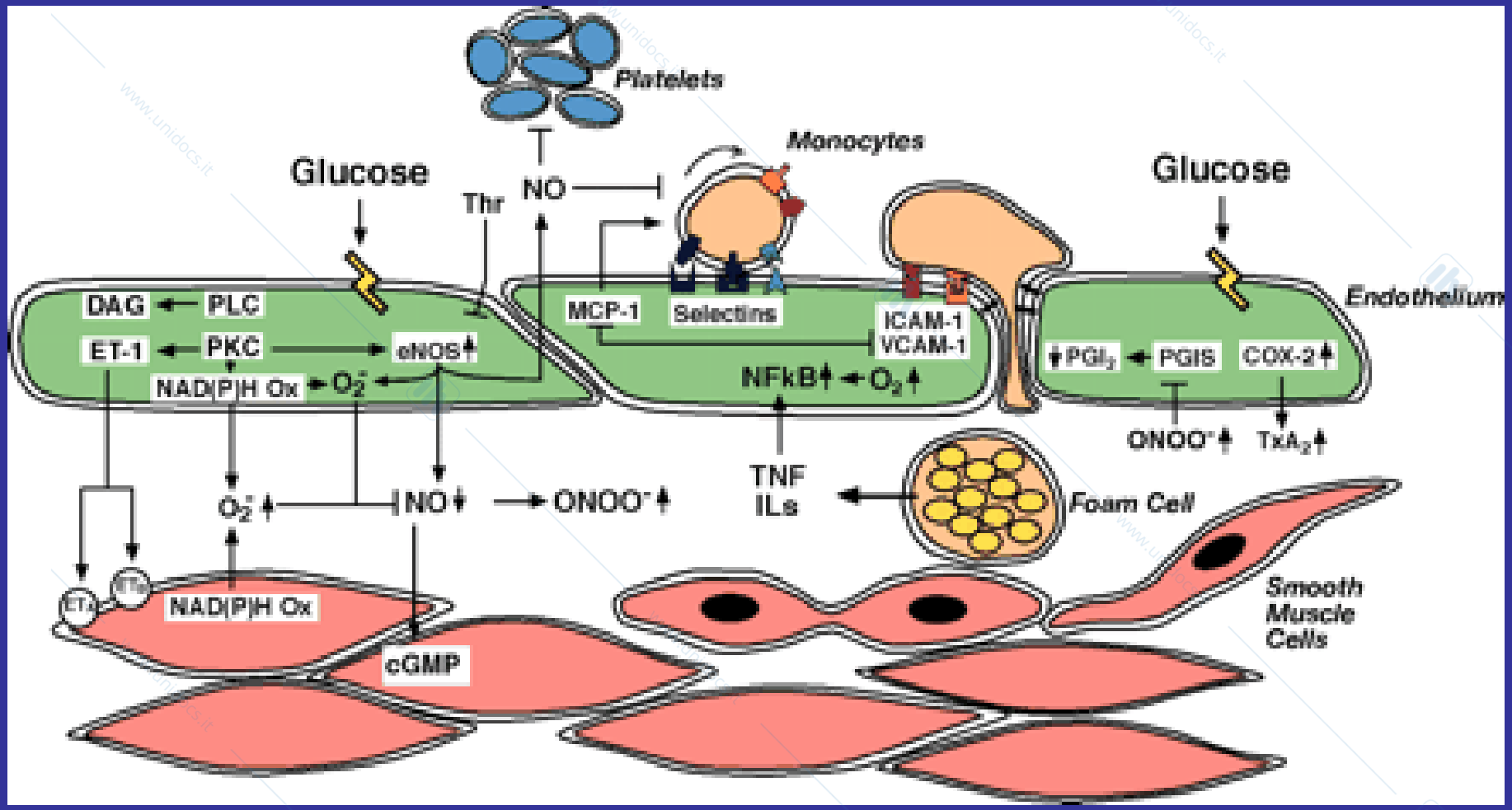


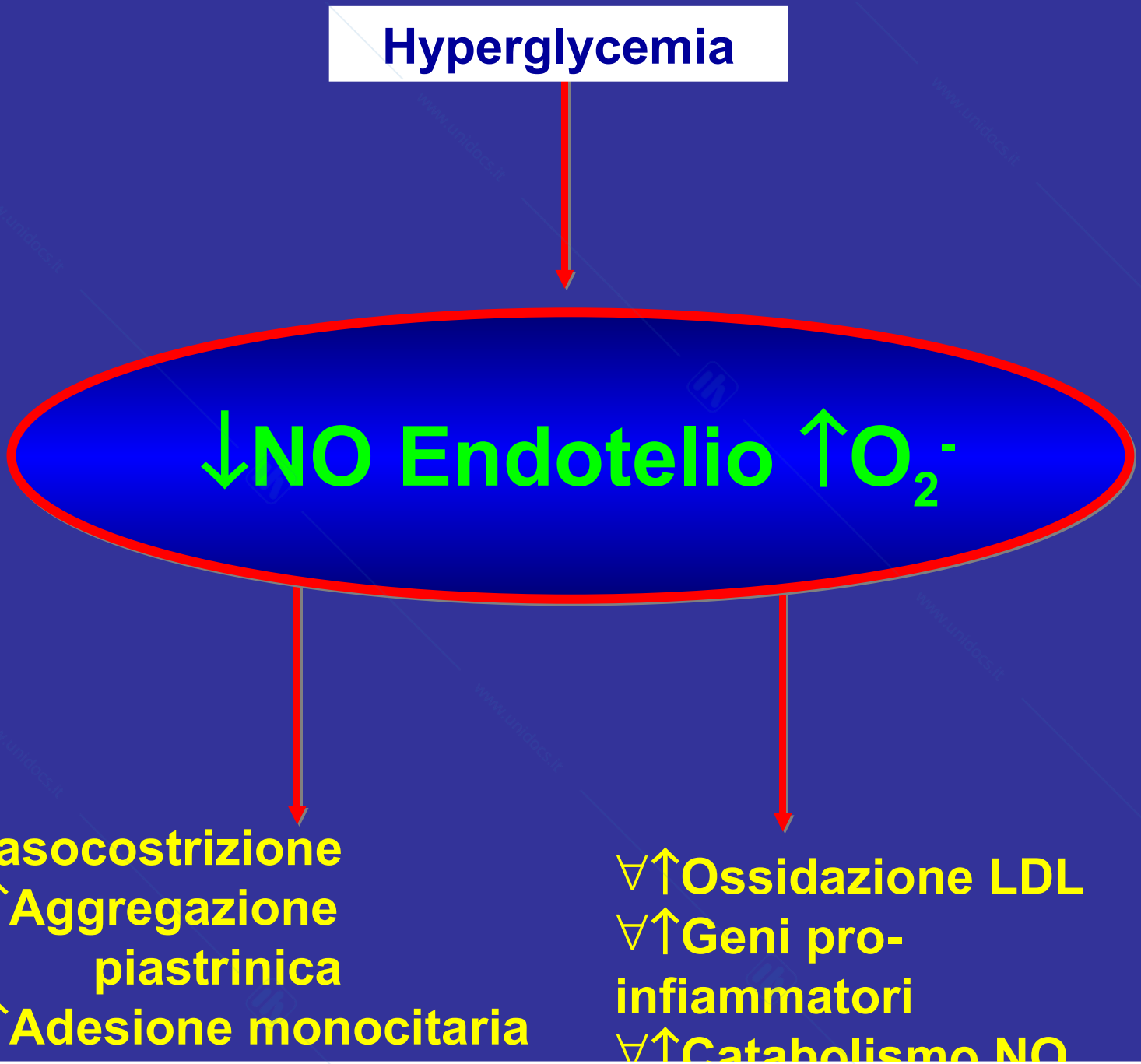
*C vs R, IGT, D
**1 or both parents

Caballero AE et al. *Diabetes*. 1999; 48: 1856-1862.



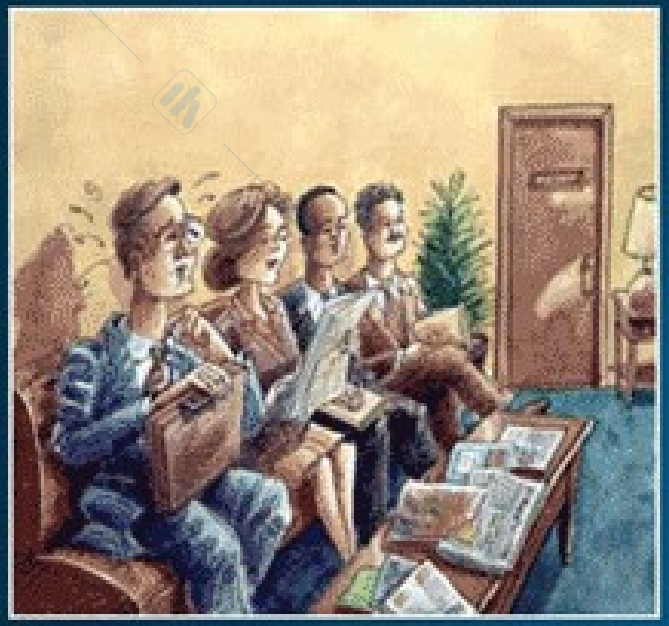
Hyperglycemia





Atherosclerosis is worsened by hyperglycemia but is also related to several other risk factors, all of which are, as it turns out, related to insulin resistance

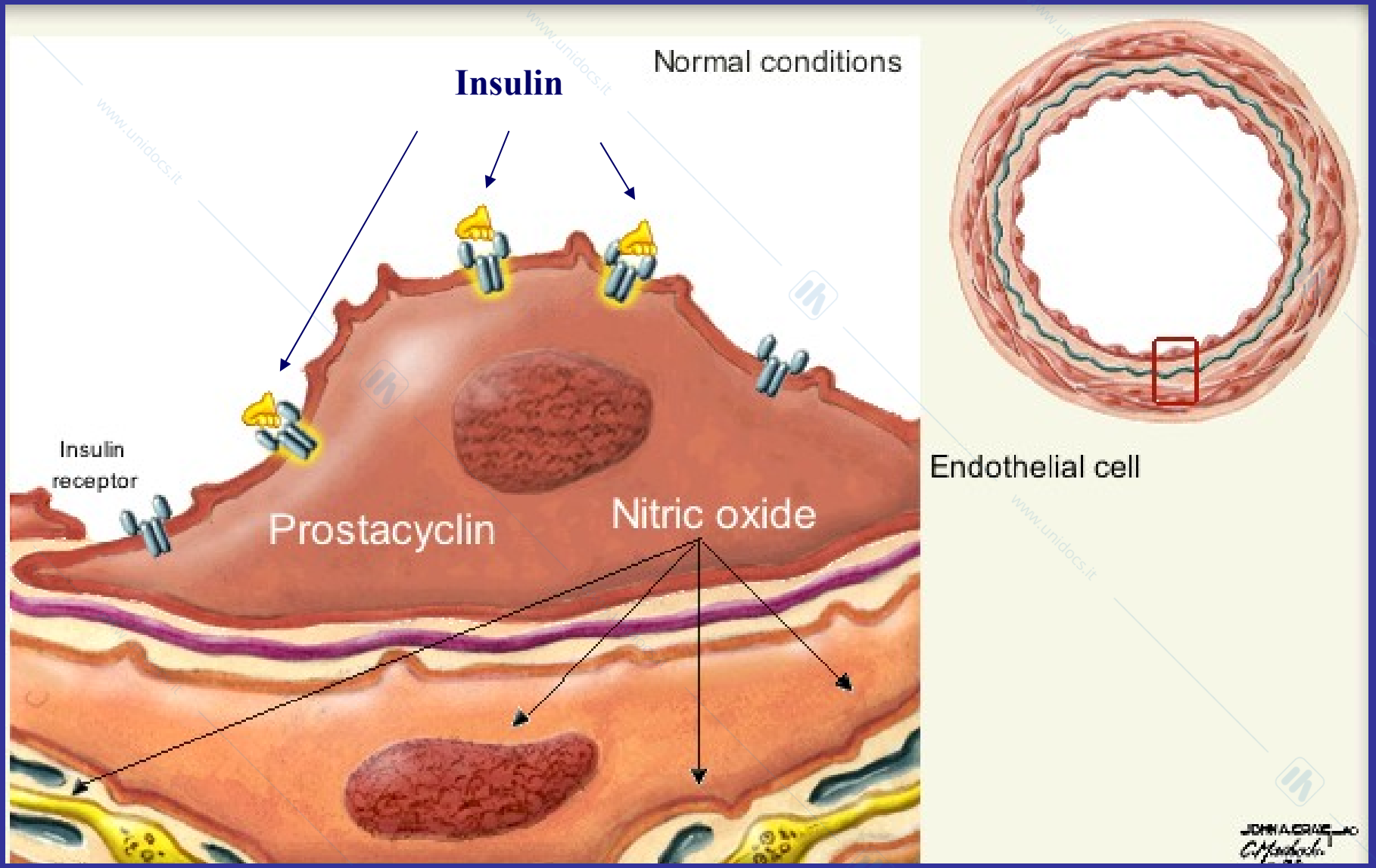
Who Is Insulin Resistant?



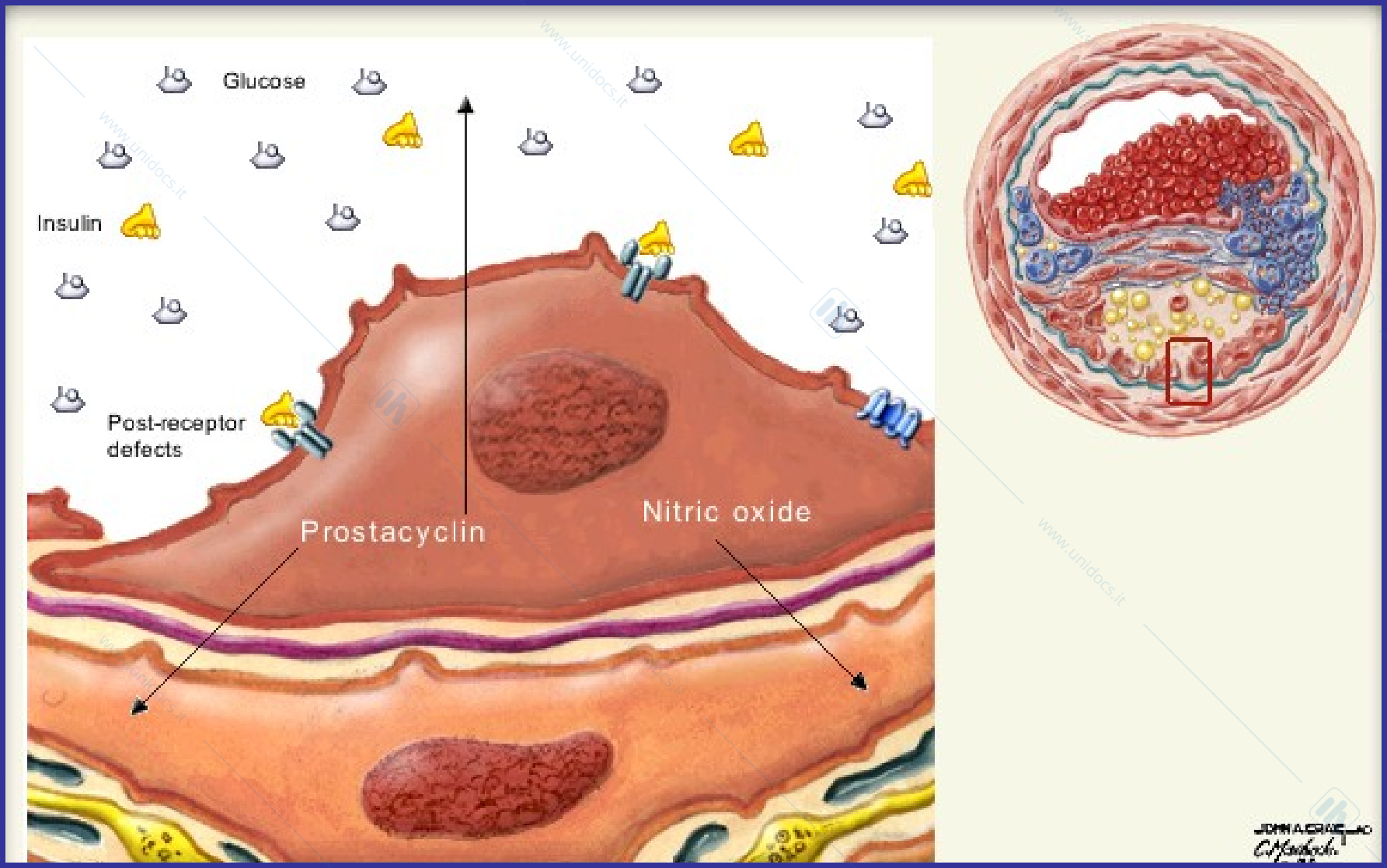
- 30% of the US population, aged 40–74 years
- 60% of all patients with CVD
- 50% of patients with confirmed coronary heart disease (CHD) and no prior history of diabetes
- 92% of patients with type 2 diabetes

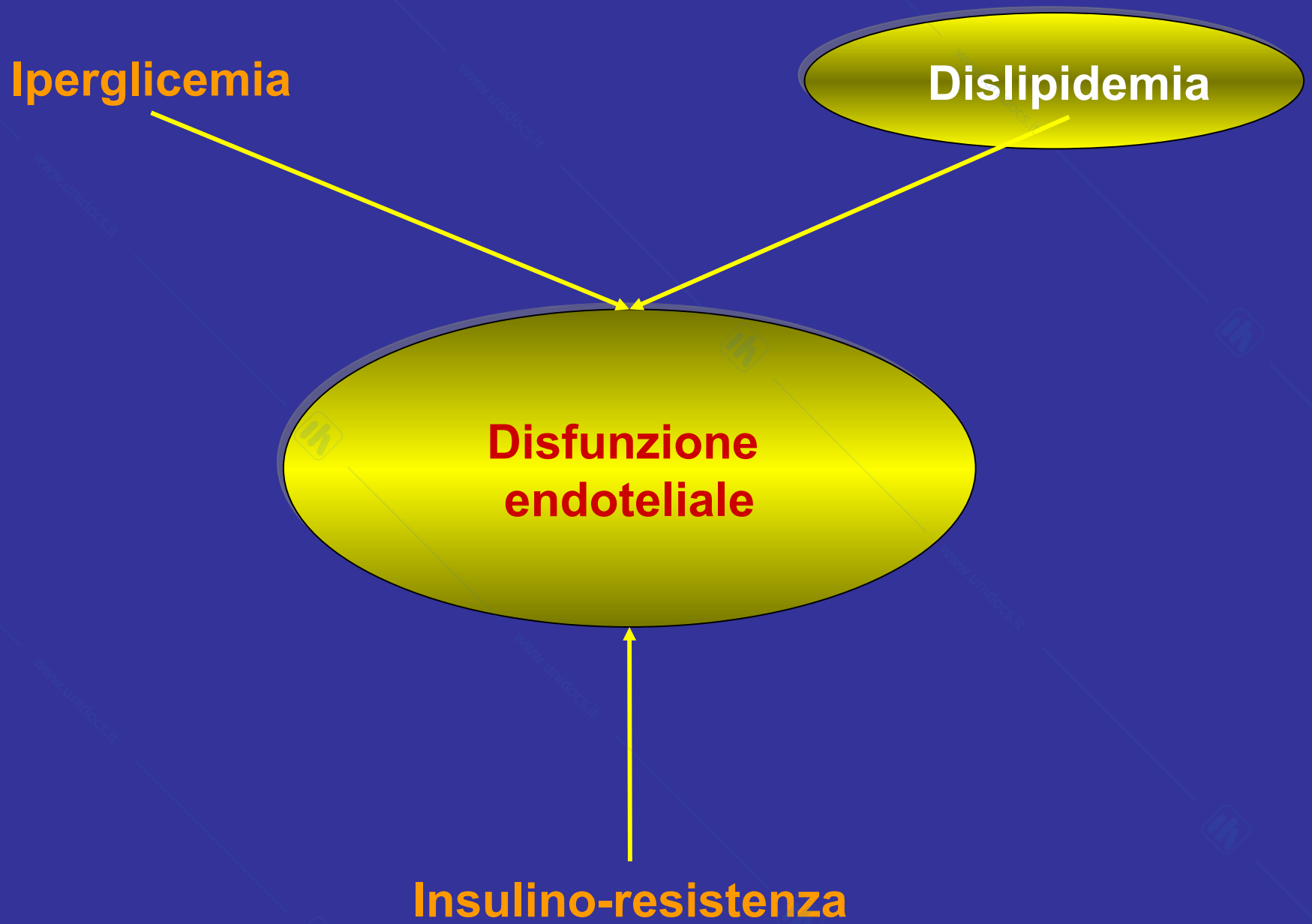
1. Harris M et al. *Diabetes Care.* 1998;21:518-524. 2. Haffner SM et al. *Circulation.* 2000;101:975-980.
3. Kowalska I et al. *Diabetes Care.* 2001;24:897-901.4. Haffner SM, Miettinen H. *Am J Med.* 1997;103:152-162.

Normal Condition



Insulin Resistance





Common Pattern of Dyslipidemia in People with Type 2 Diabetes

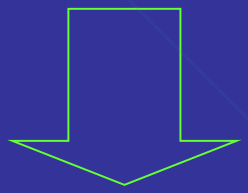
- ↑ Triglyceride
- ↓ HDL-cholesterol
- ↔ LDL-cholesterol
- ↑ VLDL
- ↑ Small, dense LDL-cholesterol

American Diabetes Association. *Diabetes Care*. 2001;24(suppl1):S33-S43.

In che modo il diabete condiziona l'insorgenza della dislipidemia ?

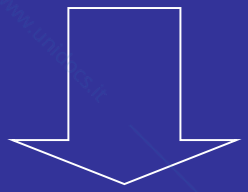
Insulino-resistenza

diabete tipo 2 e stati di insulino-resistenza in generale

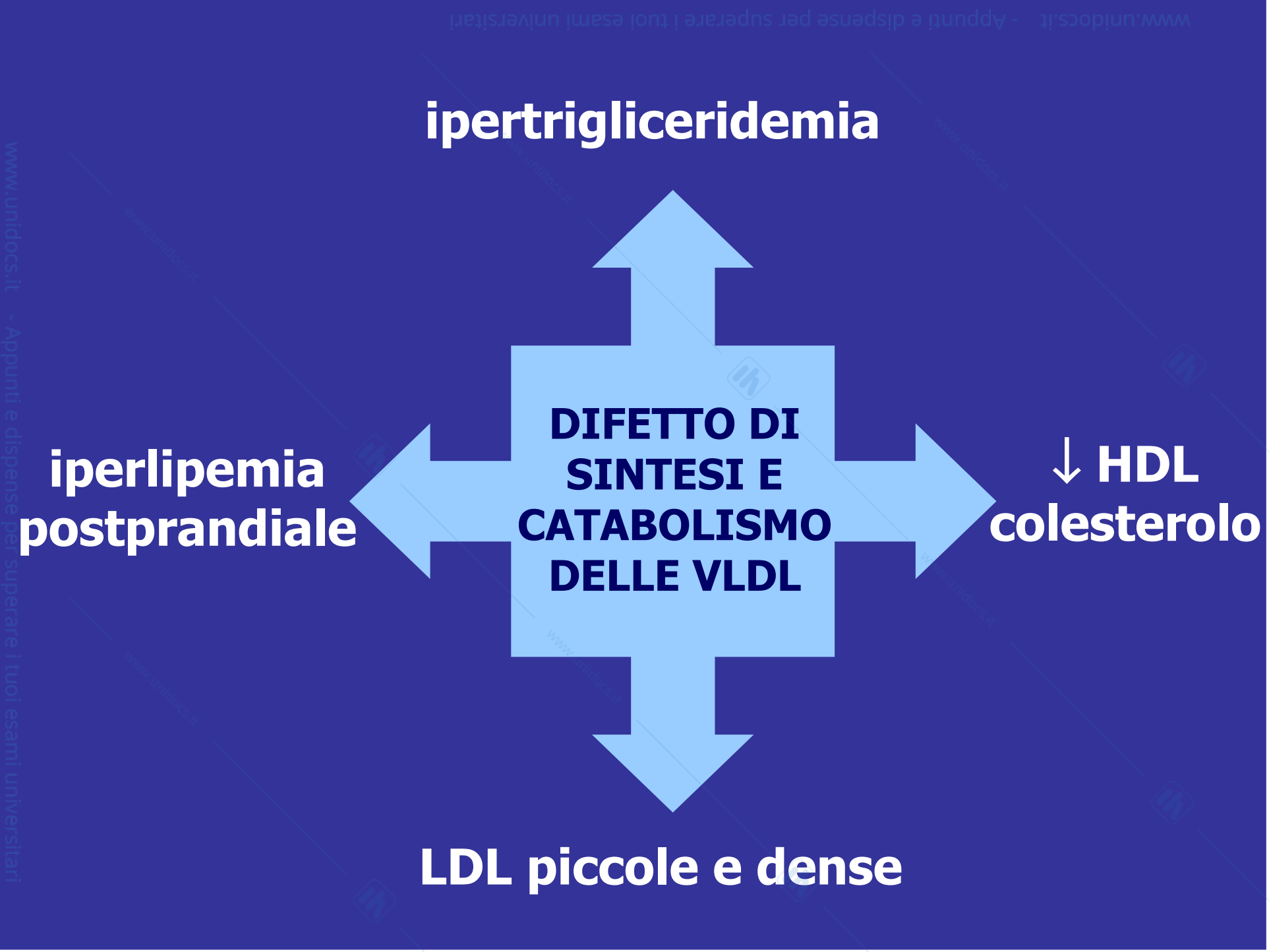


Ridotta attivazione della LPL da parte dell'insulina

Variazioni quantitative della composizione in apo C delle VLDL



Aumento delle VLDL



CV Risk Factors and Insulin Resistance: San Antonio Heart Study

Subjects free of CVD and DM at Baseline

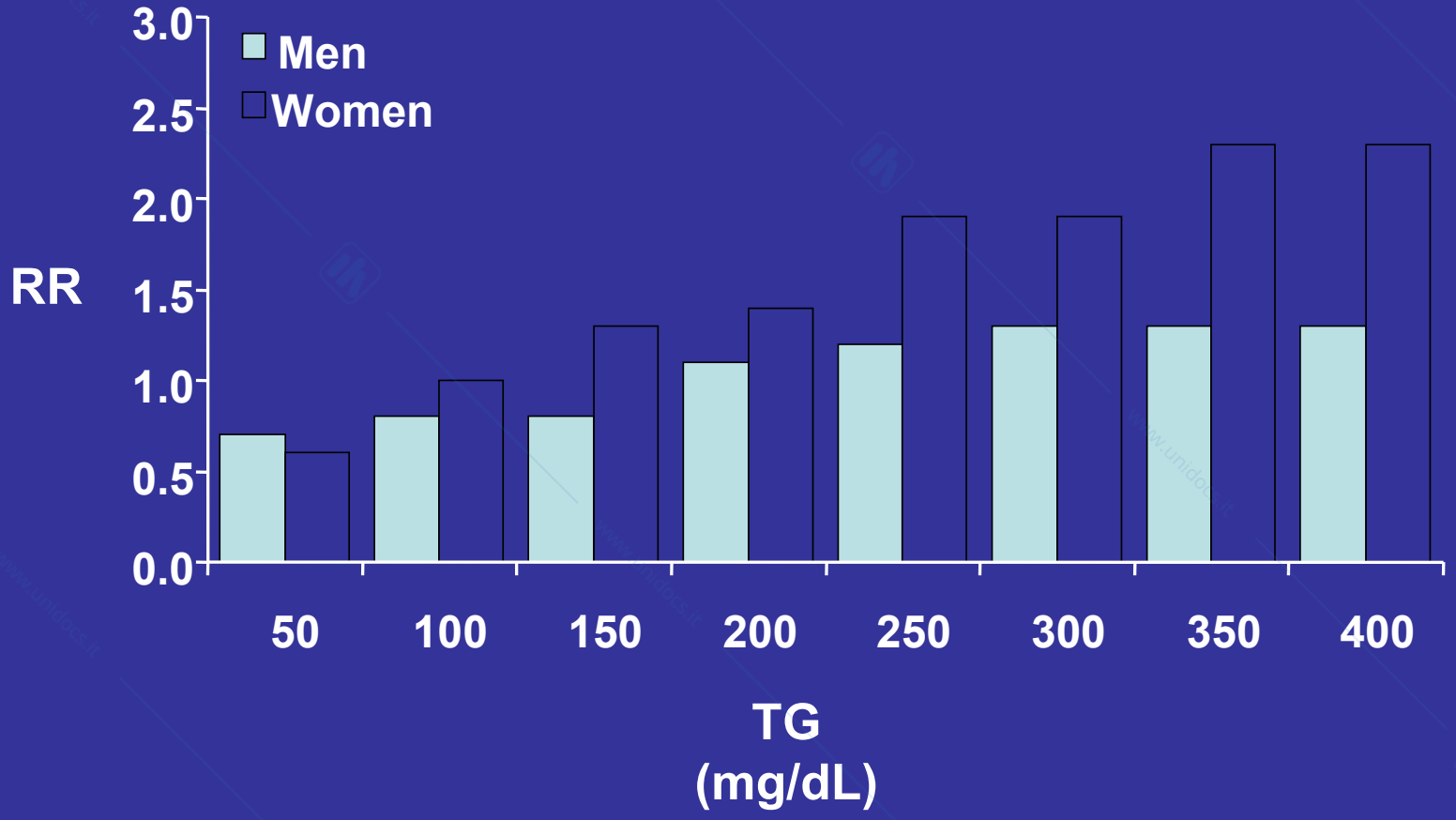
HOMA-Insulin Resistance Quintiles

	Q1	Q2	Q3	Q4	Q5
HDL-C (mg/dL)	51.7	49.3	47.8	45.0	41.2
LDL-C (mg/dL)	115.7	119.3	125.0	128.1	124.8
Total cholesterol (mg/dL)	188.0	191.6	197.9	200.8	199.0
Triglyceride (mg/dL)	105.7	116.6	129.7	145.4	187.2
Systolic BP (mm Hg)	114.9	116.5	118.3	119.3	123.0
Diastolic BP (mm Hg)	69.0	70.4	71.9	73.1	75.4

Adjusted for age, sex, ethnicity
All *P* (trend) <0.0001

Hanley A et al. *Diabetes Care*. 2002;25:1177-1184.

Impact of TG Levels on Relative Risk of CHD: Framingham Heart Study



Castelli WP. *Can J Cardiol*. 1988;4:5A-10A.

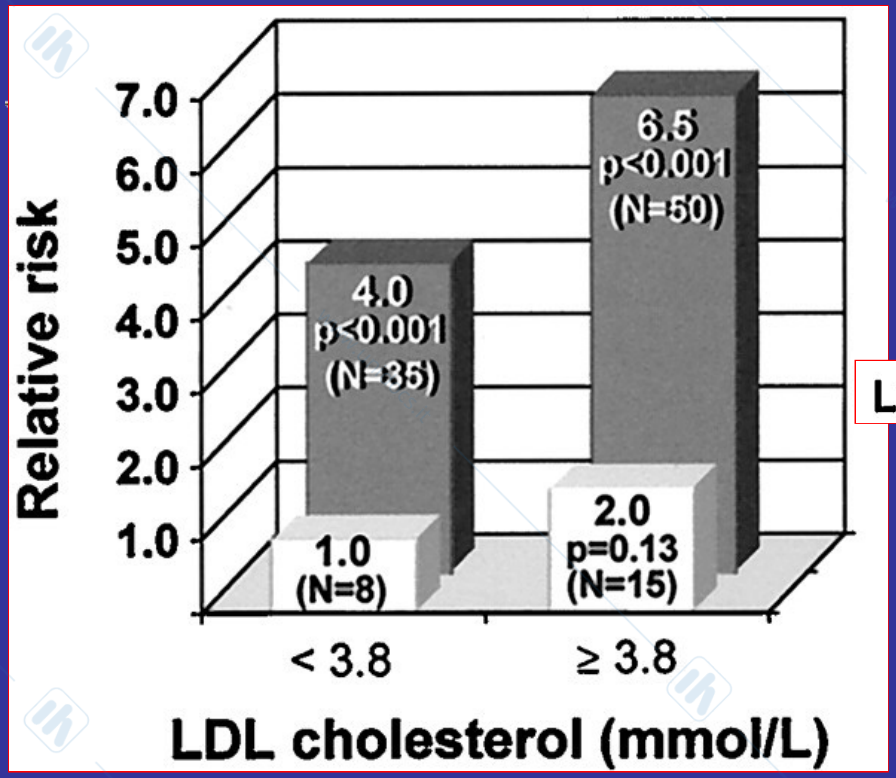
Circulation

Small, Dense Low-Density Lipoprotein Particles as a Predictor of the Risk of Ischemic Heart Disease in Men

Prospective Results From the Quebec Cardiovascular Study

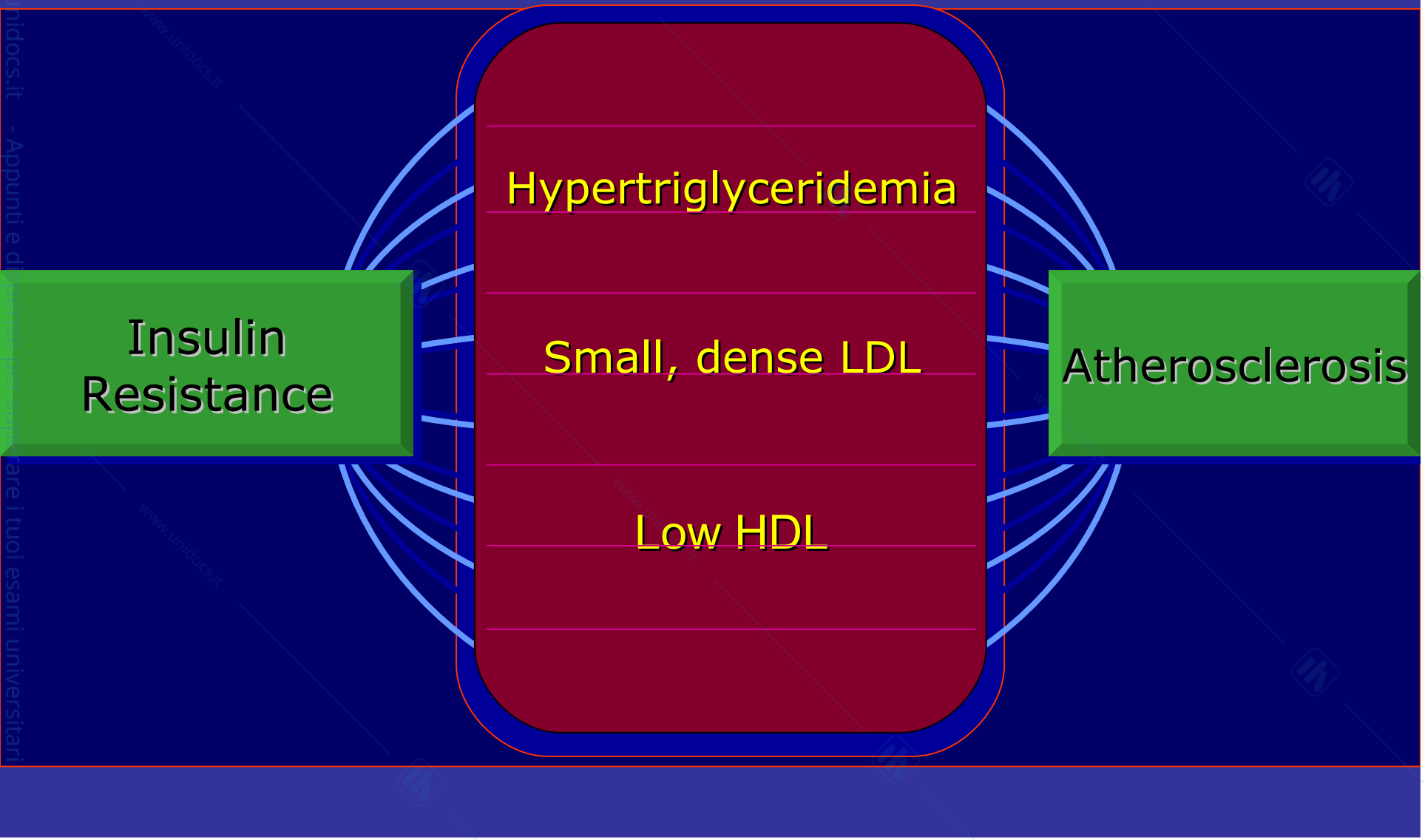
Benoit Lamarche, PhD; Andre Tchernof, PhD; Sital Moorjani, PhD; Bernard Cantin, MD;

Gilles R. Dagenais, MD; Paul J. Lupien, MD; Jean-Pierre Despres, PhD

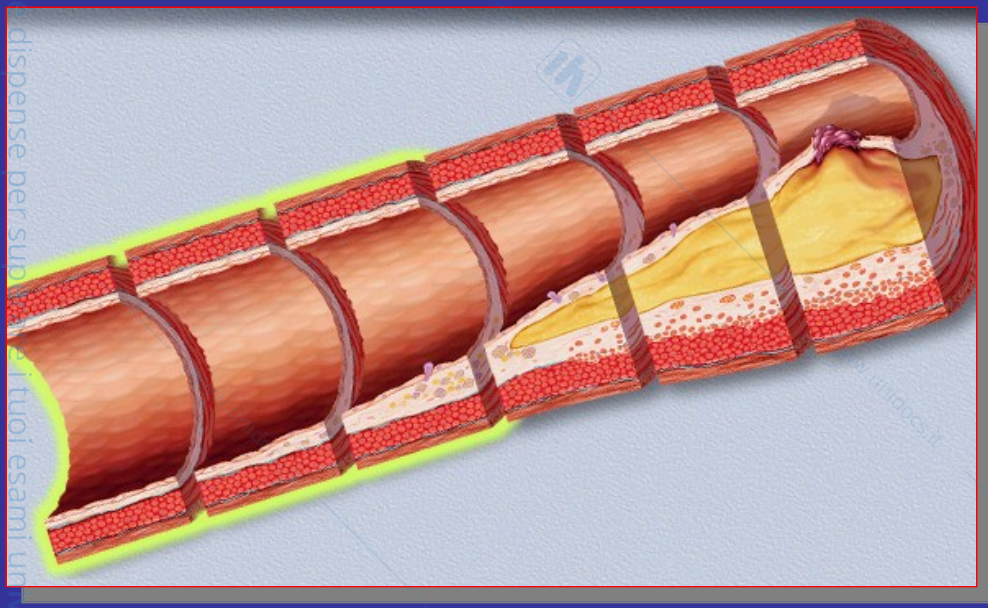


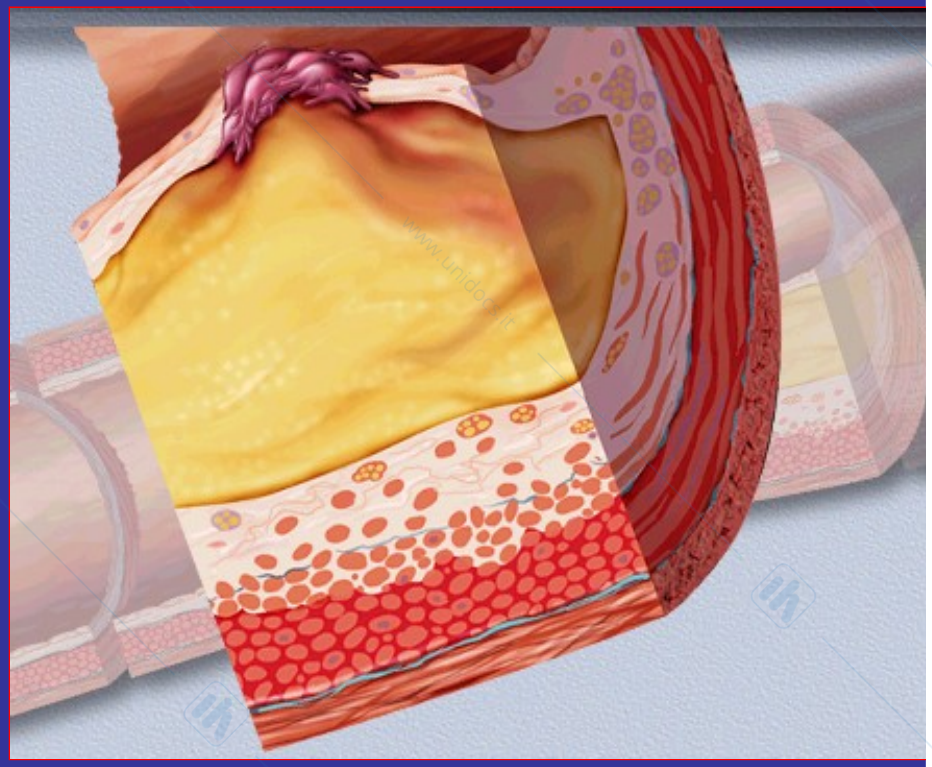
(*Circulation.* 1997;95:69-75.)

Interrelation Between Atherosclerosis and Insulin Resistance



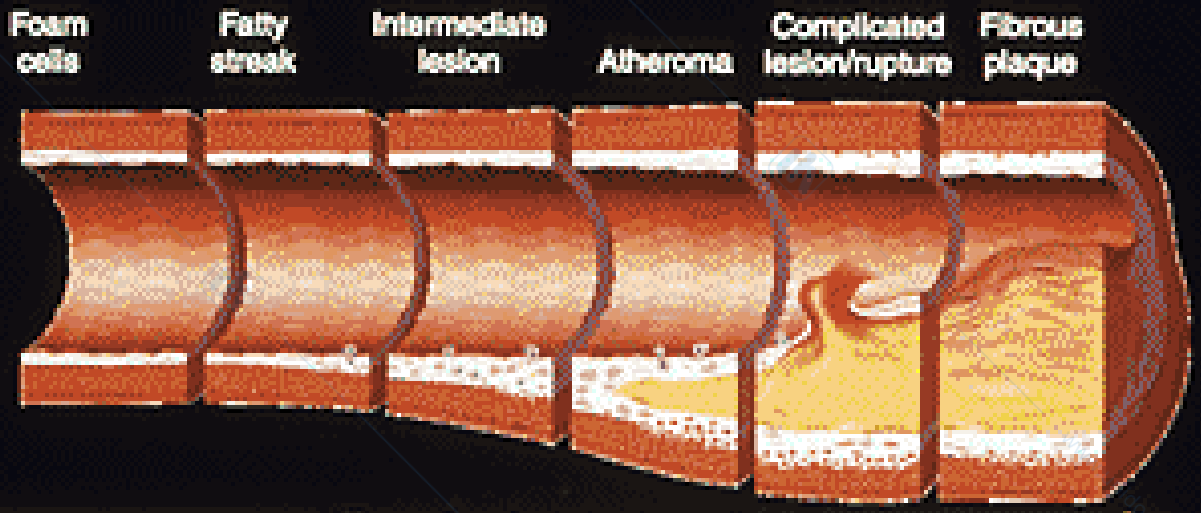
In che modo la dislipidemia diabetica può condizionare l'inizio e la progressione dell'aterosclerosi?





Atherosclerosis timeline

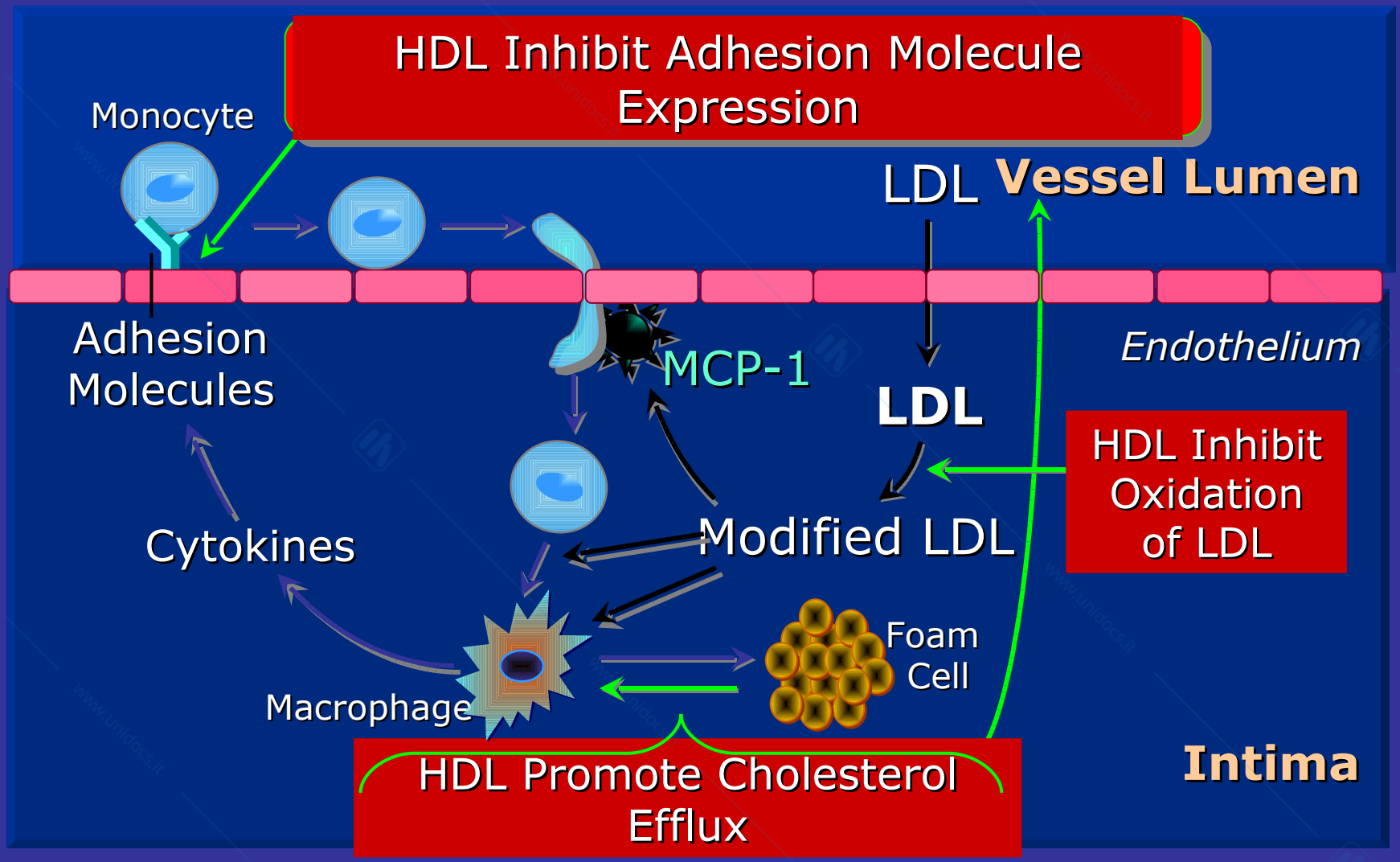
VBWG



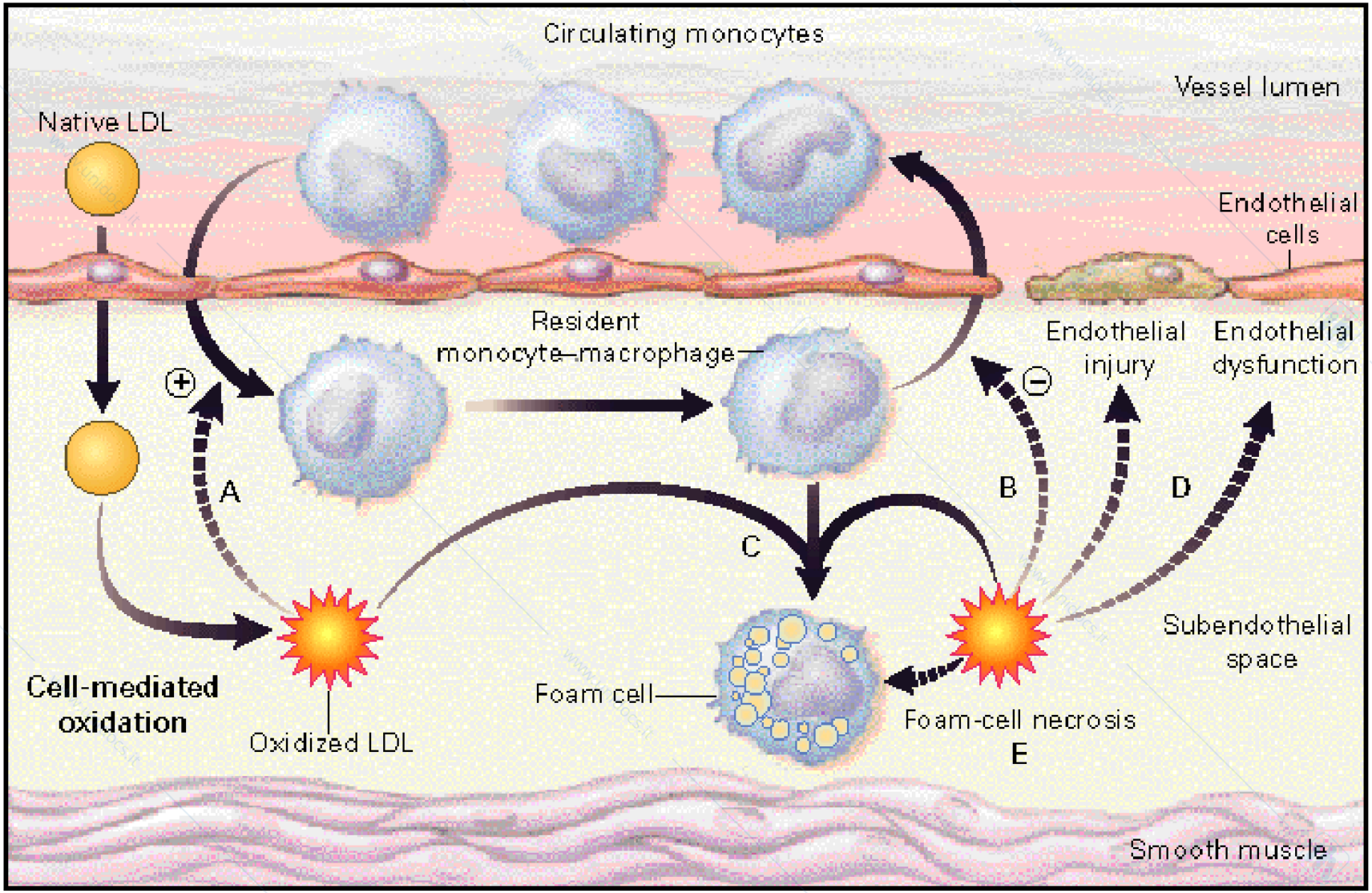
Endothelial dysfunction

From first decade	From third decade	From fourth decade	
Growth mainly by lipid accumulation		Thrombosis, hematoma	Smooth muscle and collagen

Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 10A:23S-27S).



Cockerill GW et al. *Arterioscler Thromb Vasc Biol* 1995;15:1987-1994.



Ross R. *N Engl J Med* 1999;340:115-126.

Sources of endothelial insult: Diabetes

VBWG

Diabetes

↓

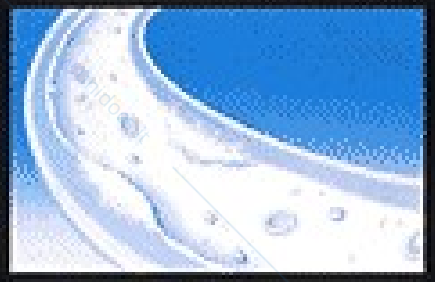
Hyperglycemia

↓

Insulin resistance

↓

Dyslipidemia



Screening delle complicanze croniche del diabete mellito

- Microalbuminuria notturna
- Creatininemia, Clearance creatinina
- Visita oculistica con esame del fundus
- Tests neurologici
- Elettromiografia arti inferiori
- Doppler arterioso arti inferiori
- Elettrocardiogramma

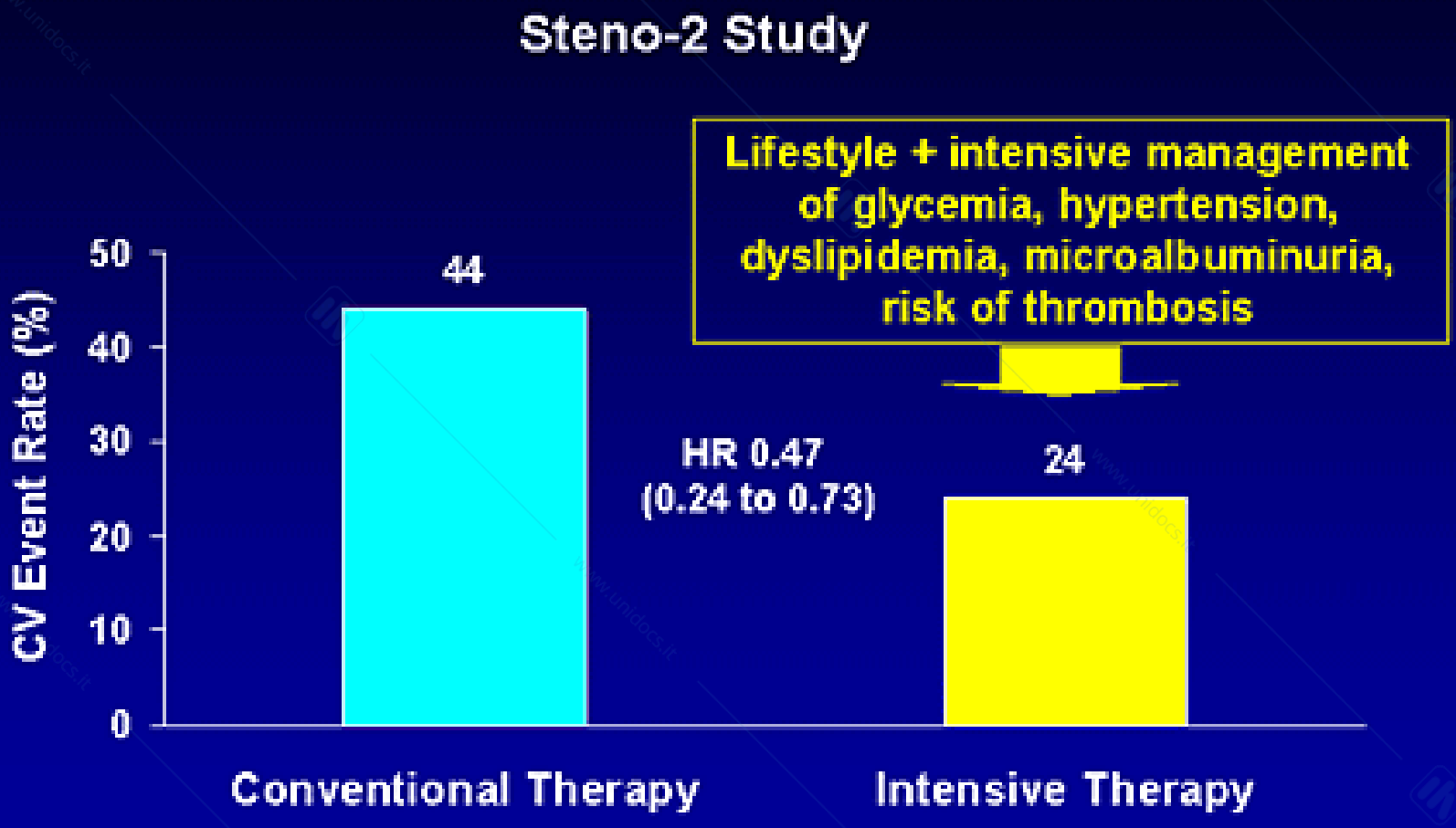
Una diagnosi precoce consente di evitare molti degli effetti delle complicanze

AHA Prevention V: Office Assessment

"Global Risk should be part of every patient's medical record"

AHA Prevention V: Beyond Secondary Prevention - Identifying the High Risk Patient for Primary Prevention. Smith,Greenland & Grundy.Circulation 2000 101: 111-116

Residual CV Risk After Intensive Therapy: The Therapeutic Gap in Type 2 Diabetes



Gaede P, et al. *N Engl J Med.* 2003;348:383-393.