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Insulino-resistenza: si può misurare nella pratica clinica?

Enzo Bonora

Endocrinologia, Diabetologia e Metabolismo
Università e Azienda Ospedaliera Universitaria
di Verona

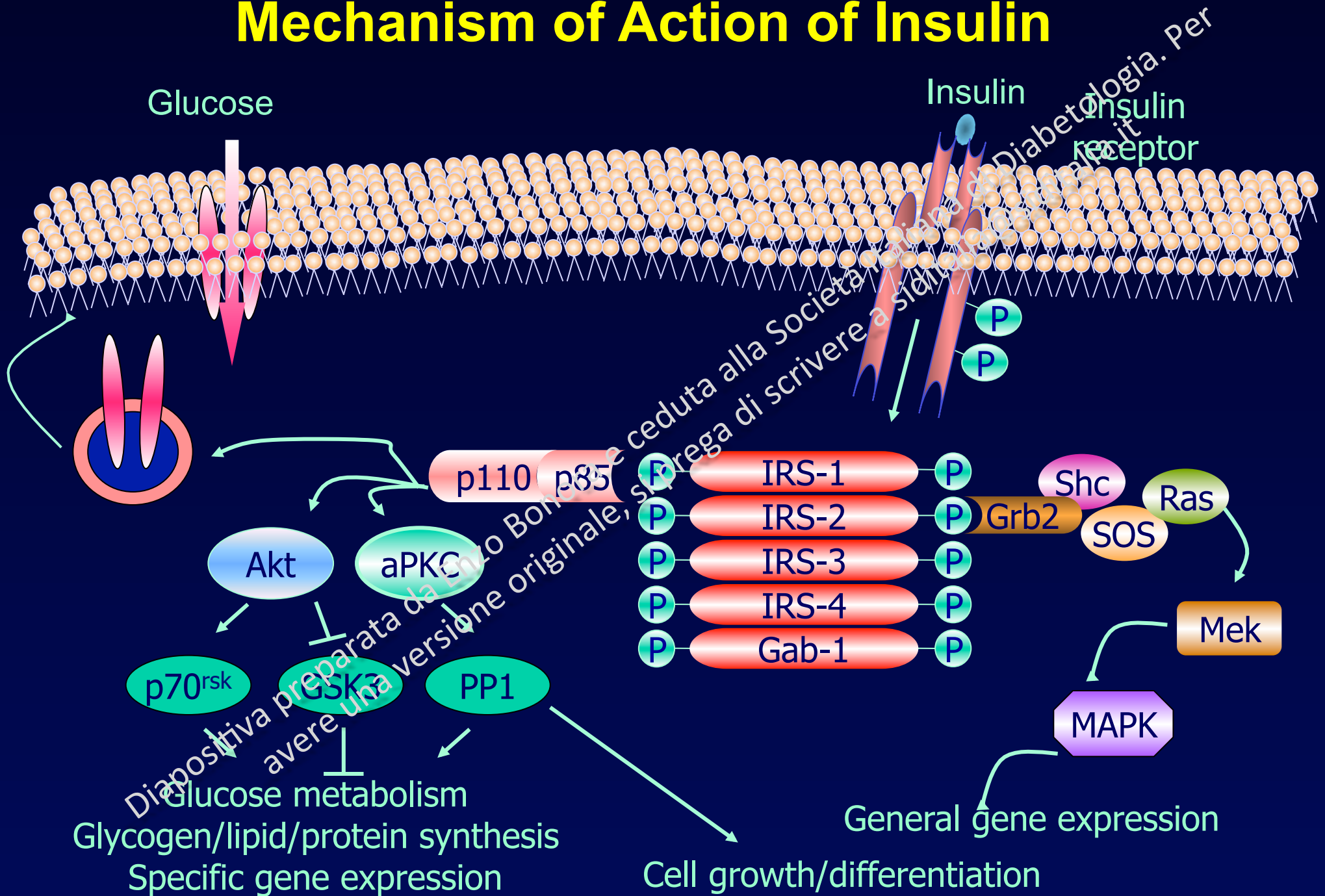


Insulino-resistenza

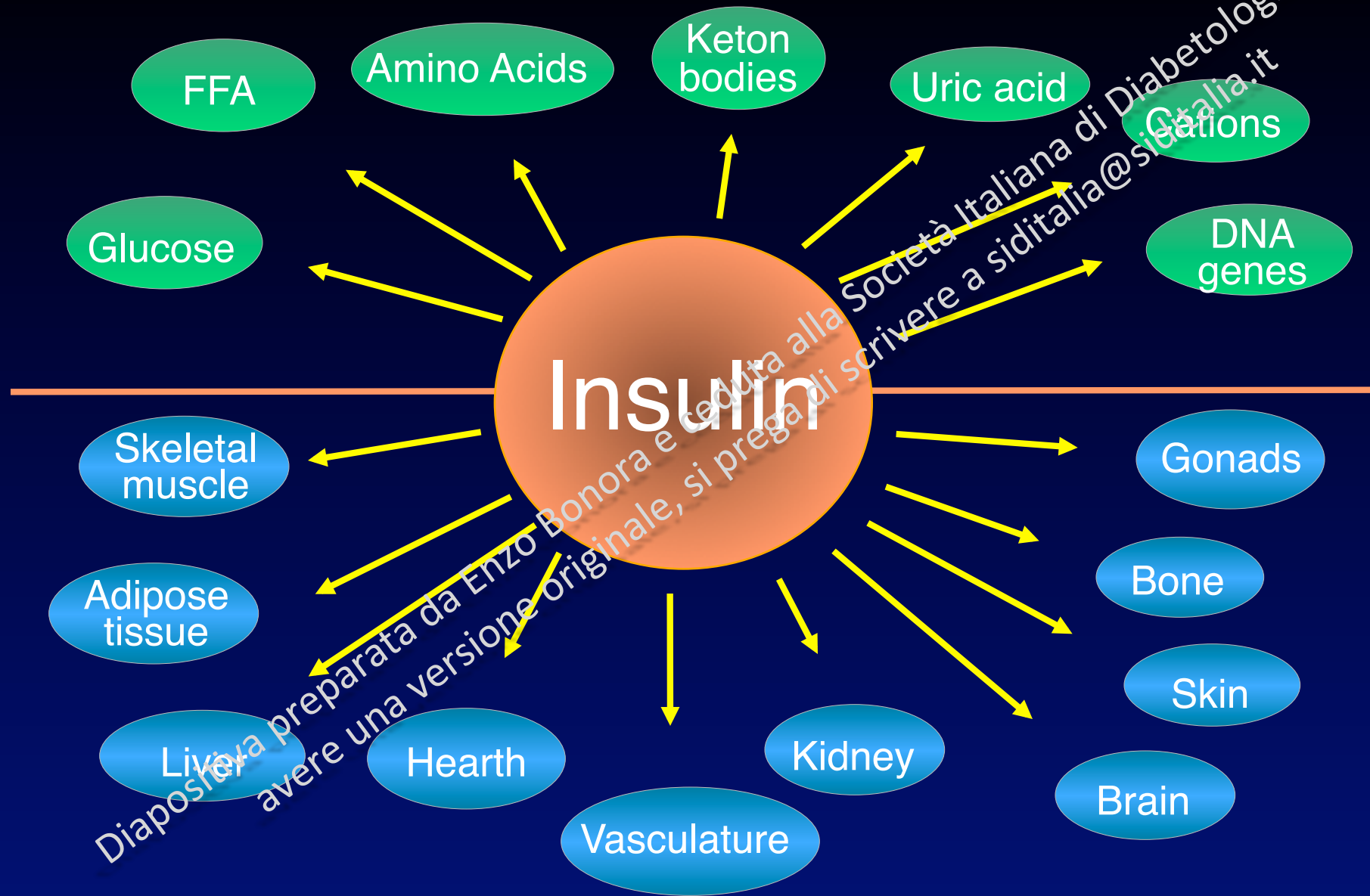
Condizione clinica in cui l'insulina esercita un effetto biologico inferiore al normale

- Organismo intero
- Singolo organo
- Singolo tipo cellulare
- Singolo processo biologico

Mechanism of Action of Insulin



The wide spectrum of insulin biological effects



Diabetes

Dyslipidemia

Hyperuricemia

Hypertension

Infertility

Insulin Resistance

Thrombophilia

Endothelial
dysfunction

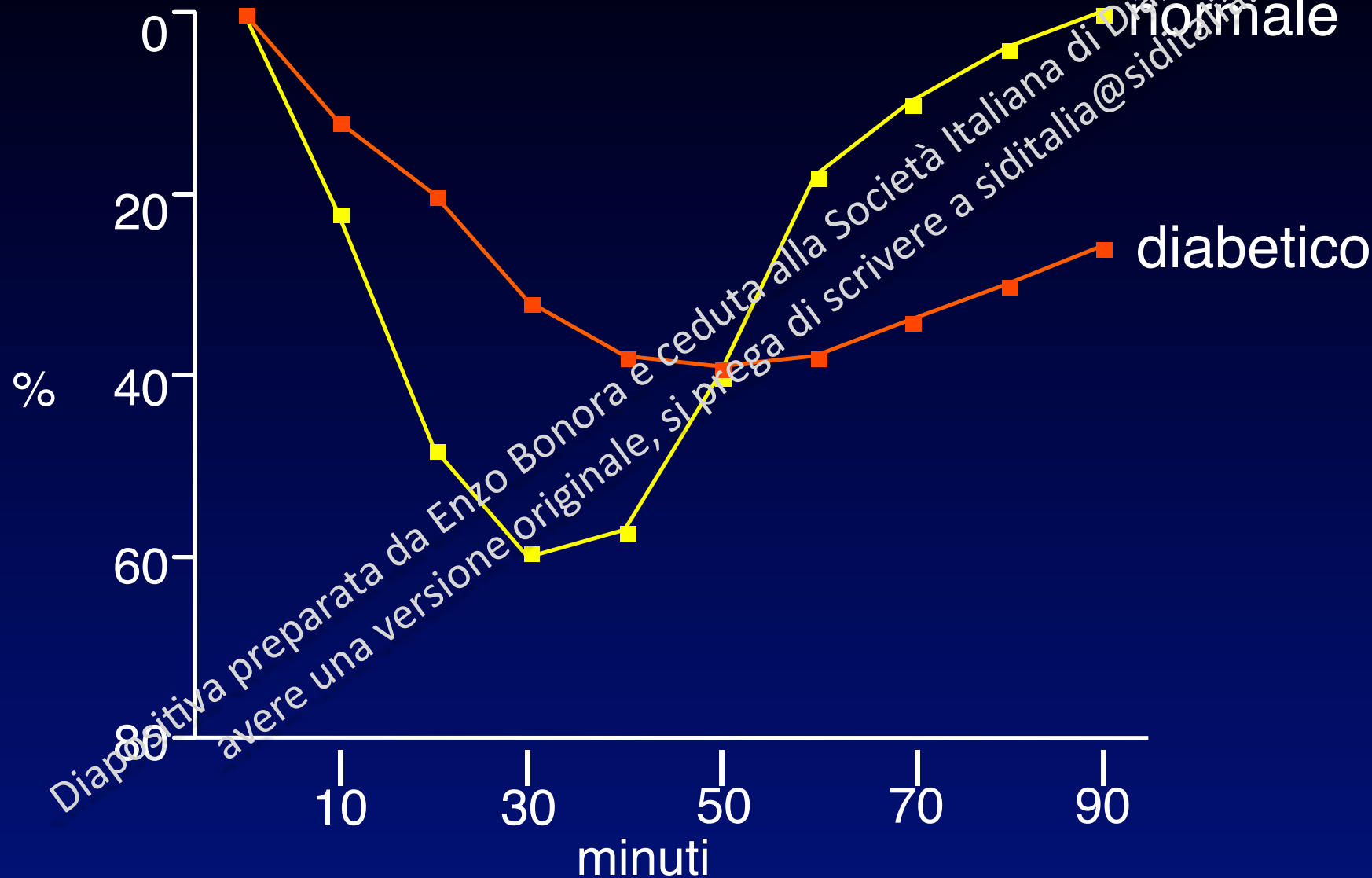
Oxidative
stress

NAFLD/NASH

Chronic mild
inflammation

Diapositiva preparata da Enzo Bonora e ceduta alla Società Italiana di Diabetologia. Per avere una versione originale, si prega di scrivere a siditalia@siditalia.it.

Decremento glicemico dopo insulina e.v. (0.1 U/Kg BW)



Insulino-resistenza del metabolismo glucidico

NELLA FISILOGIA

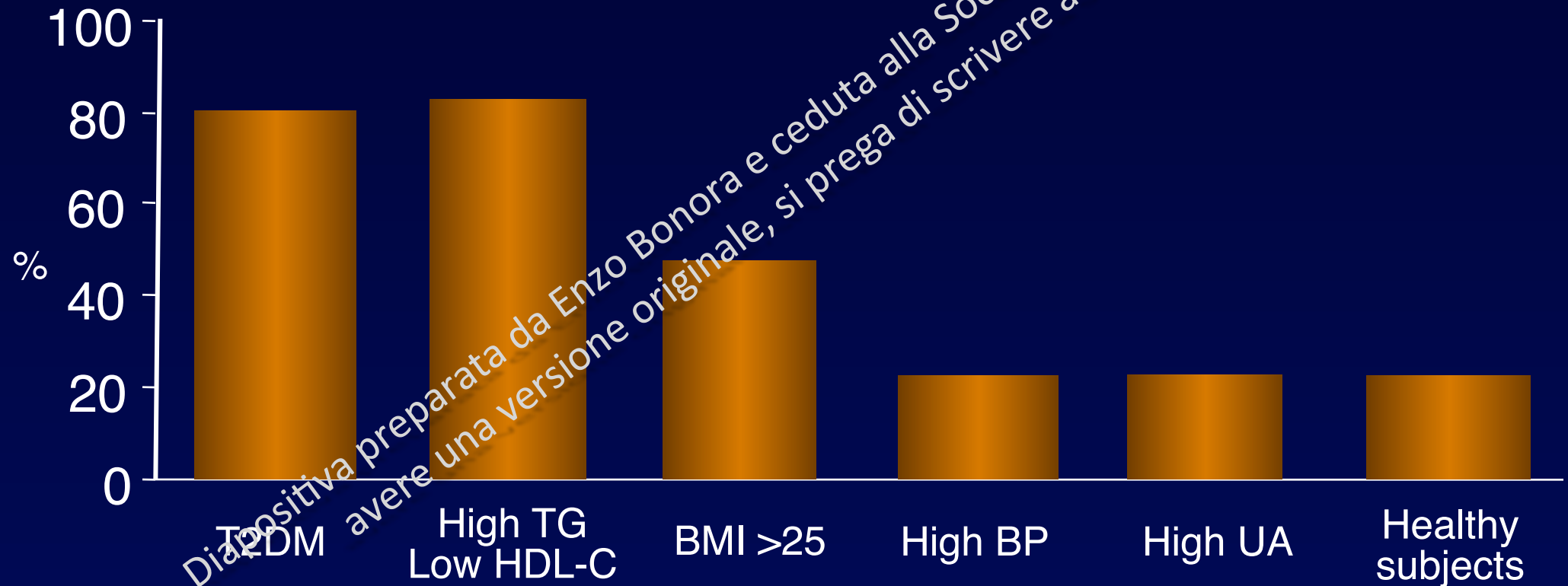
- Pubertà
- Gravidanza
- Invecchiamento

NELLA PATOLOGIA

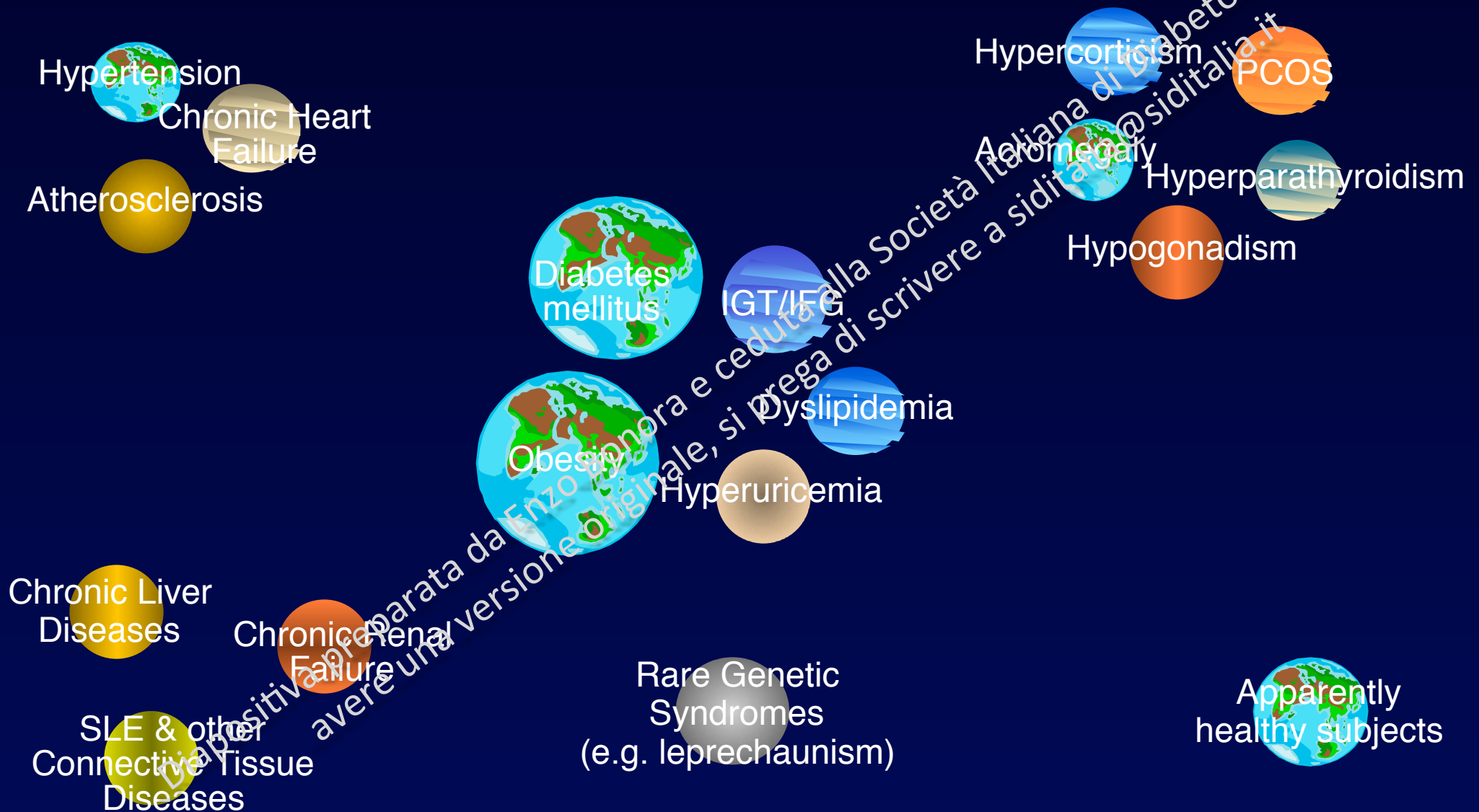
- Diabete mellito tipo 2 e disglucemia (IFG/IGT)
- Obesità
- Dislipidemie (fenotipi IIb e IV), iperuricemia
- Ipertensione arteriosa essenziale
- Epatopatie croniche (NAFLD, NASH, ecc.)
- Uremia, scompenso cardiaco, malattie infiammatorie
- Policistosi ovarica e iperandrogenismi
- Acromegalia, ipercorticismi, altre endocrinopatie
- Sindromi genetiche complesse (es. leprecaunismo)

Prevalence of Insulin Resistance in Different Clinical Conditions (Isolated Conditions)

(Bruneck Study; Bonora et al, Diabetes 47:1643, 1998)



The Galaxy of Insulin Resistance



Epidemiology of Insulin Resistance of Glucose Metabolism

Not only diabetes but...
...a mass phenomenon

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Subjects with Insulin Resistance in the World

Type 2 Diabetes - IFG/IGT - Overweight & Obesity - Dyslipidemia
Hypertension - Hyperuricemia - Endocrine Diseases (e.g., PCOS)
Non-Metabolic Diseases (e.g., NASH) - Healthy subjects



Prevalence up to 50% and more

Hundreds of millions people

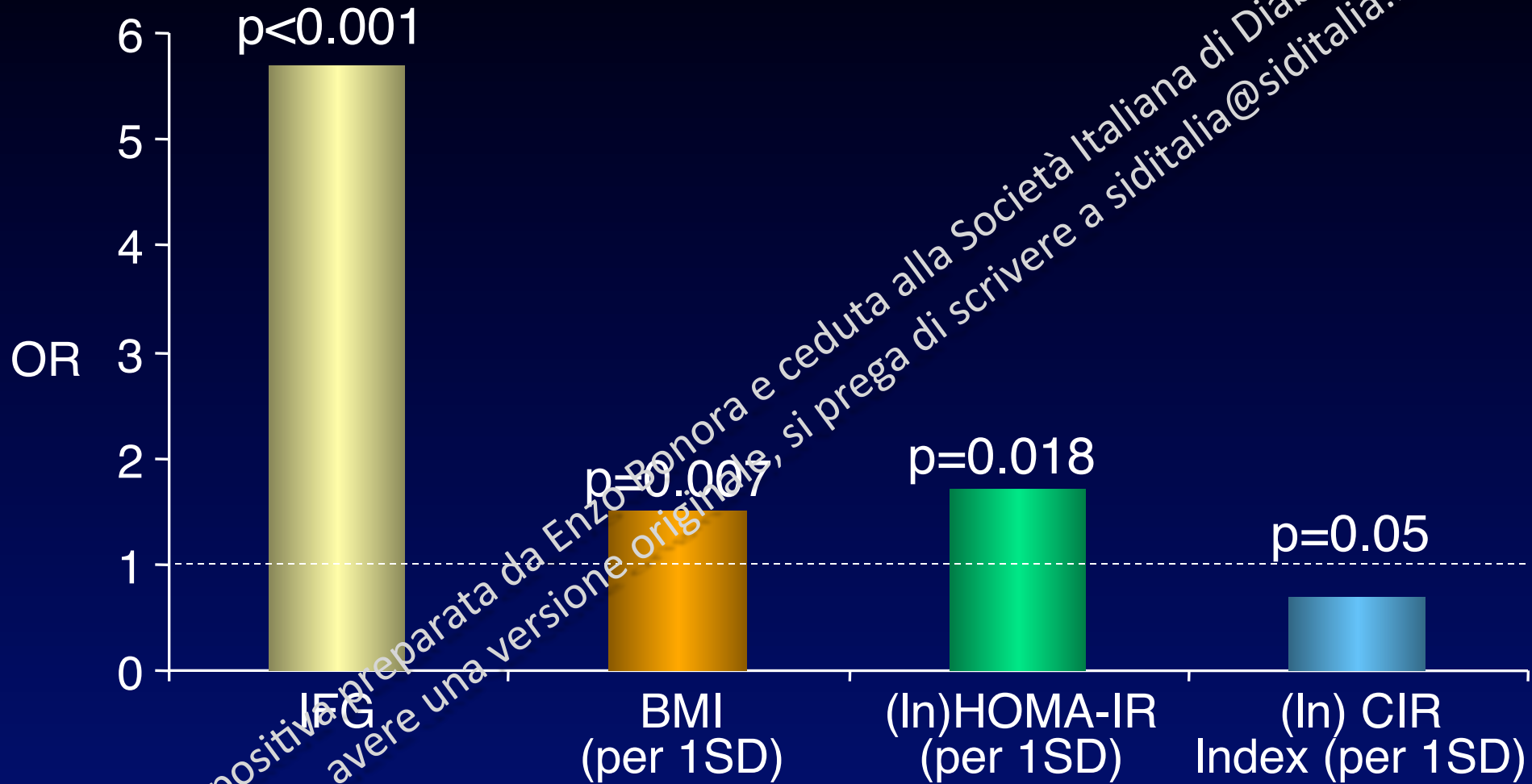
Major risks associated to Insulin Resistance

- Type 2 diabetes mellitus
- Cardiovascular disease

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Factors Independently Related to 10-yr Incidence of T2DM in the General Population Aged 40-79 yrs

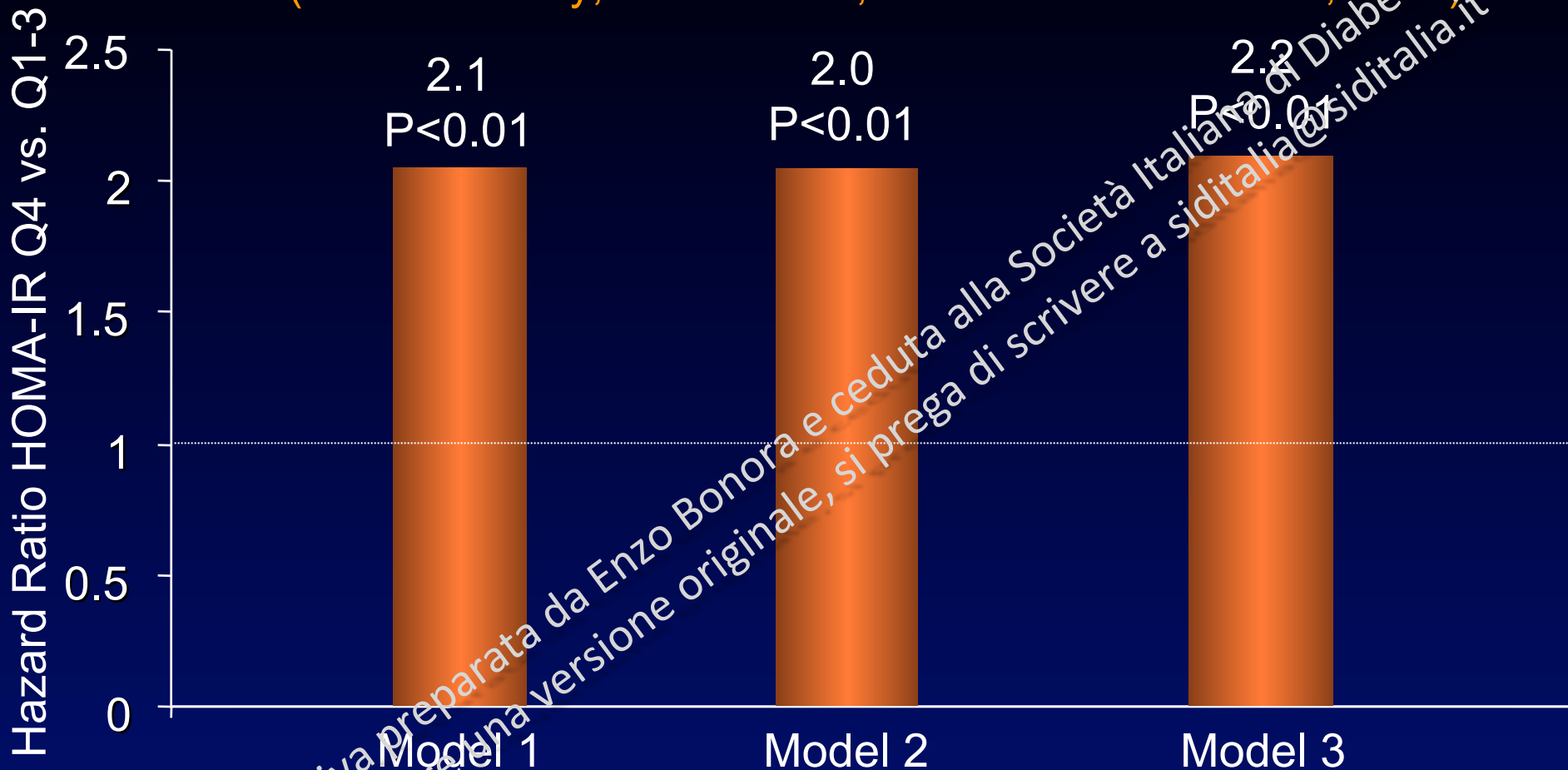
(Bruneck Study; Bonora et al, Diabetes 53:1582, 2004)



Model including sex, age, family history of DM, life style factors, hypertension, dyslipidemia, BMI, IFG, IGT, HOMA-IR, CIR (insulin secretion), ICAM-1, CRP.

Insulin Resistance is an Independent Predictor of Incident CVD in Caucasian Subjects from the General Population

(Bruneck Study; Bonora et al, Diabetes Care 30: 318, 2007)



N=850, age 40-79, follow-up 10 years; subjects with symptomatic CVD at baseline excluded)

CVD=MI, stroke, TIA, symptomatic PVD, any revascularization. Cases n=97.

Model 1: sex, age, HOMA-IR - **Model 2:** sex, age, HOMA-IR, smoking, LDL-C, hypertension, HbA1c

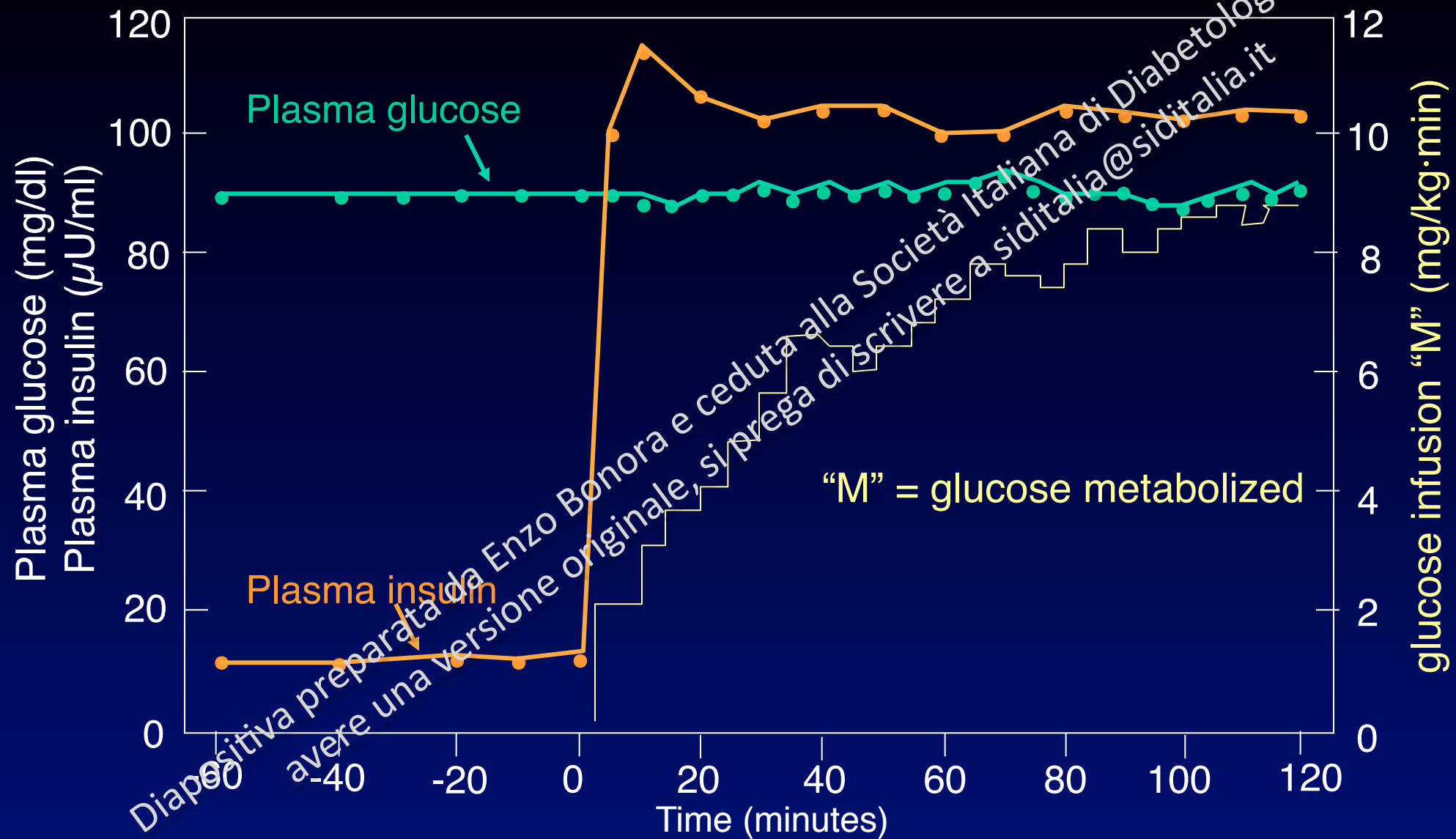
Model 3: sex, age, HOMA-IR, smoking, LDL-C, hypertension, HbA1c, HDL-C, triglycerides, BMI

Insulino-resistenza

Come si può misurare?

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La tecnica del clamp del glucosio (“glucose clamp”)



Il clamp euglicemico iperinsulinemico

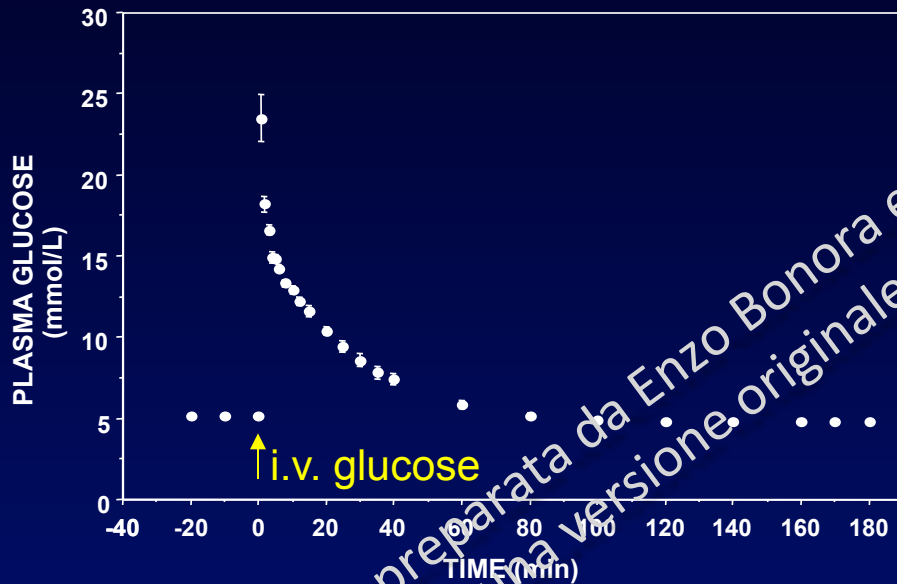


Cosa serve: 2 pompe da infusione, un analizzatore di glucosio al letto del paziente, una minicentrifuga, due operatori addestrati

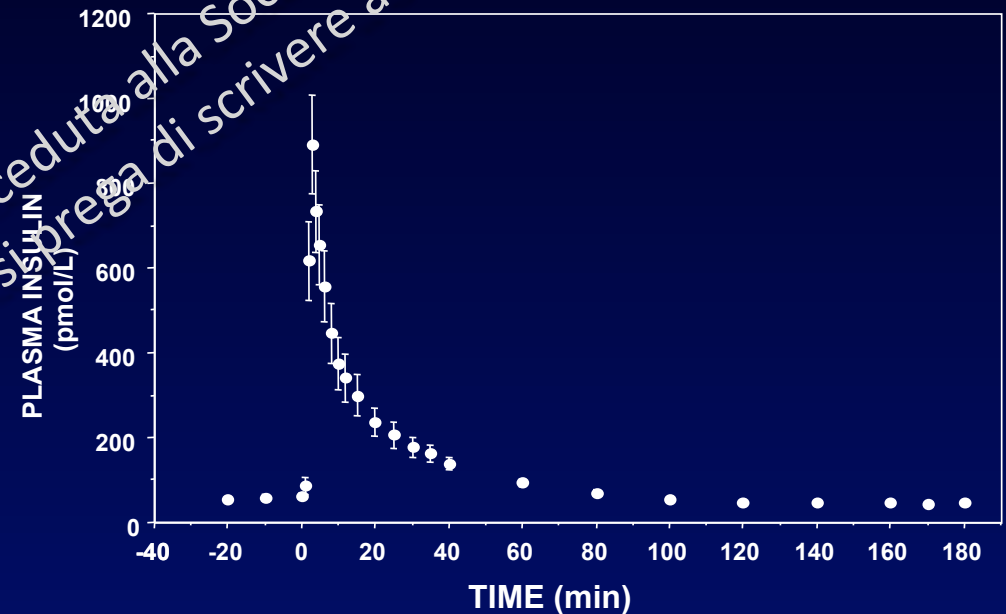
Durata: Almeno 3 ore

Frequently sampled IVGTT & Minimal Model

PLASMA GLUCOSE

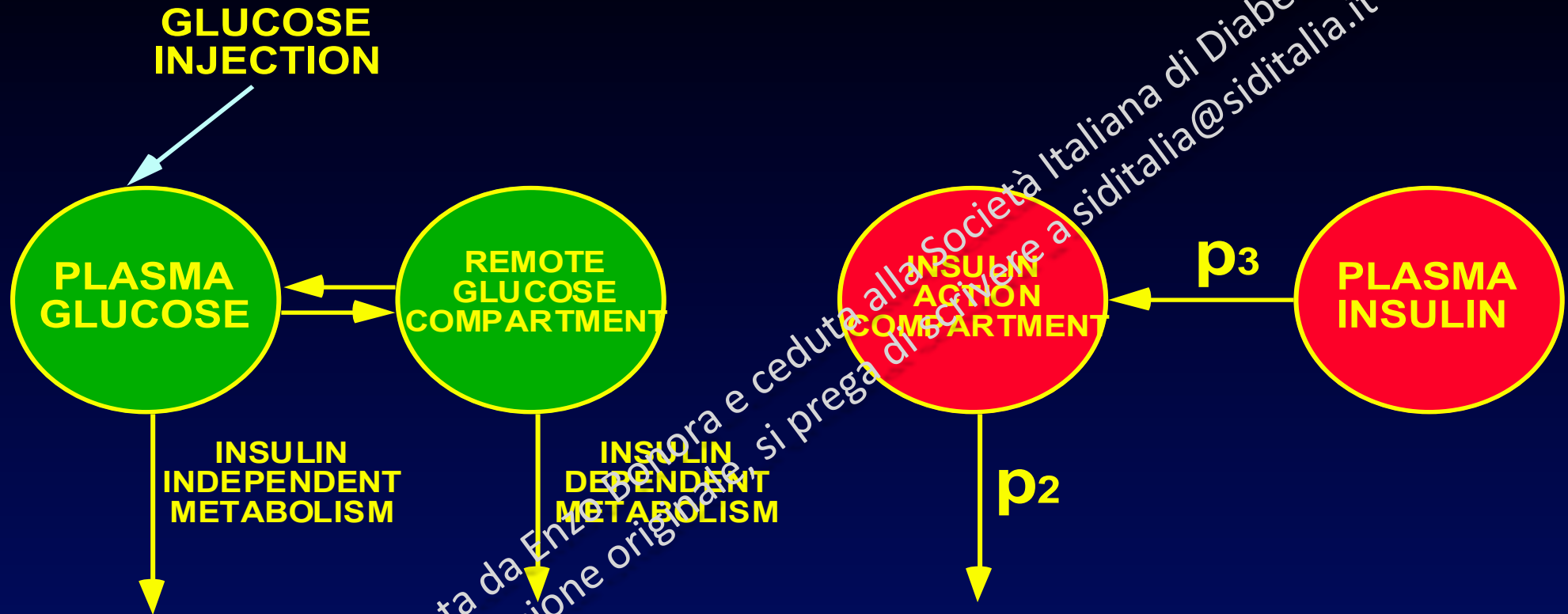


PLASMA INSULIN



Insulin Sensitivity derived from IVGTT (SI-IVGTT) = increment in plasma glucose clearance per one pmol/L of increase in plasma insulin concentration

THE TWO-COMPARTMENT MINIMAL MODEL OF GLUCOSE METABOLISM



Insulin Sensitivity derived from IVGTT (SI-IVGTT) = increment in plasma glucose clearance per one pmol/L of increase in plasma insulin concentration

Cosa serve: un software ad hoc, un esperto di modellistica

Durata: almeno 3 ore

Insulin suppression test (IST)

Constant i.v. infusion of glucose (240 mg/min/m^2), insulin (40 mU/min/m^2) and somatostatin ($300 \text{ }\mu\text{g/hr}$) for 180 minutes

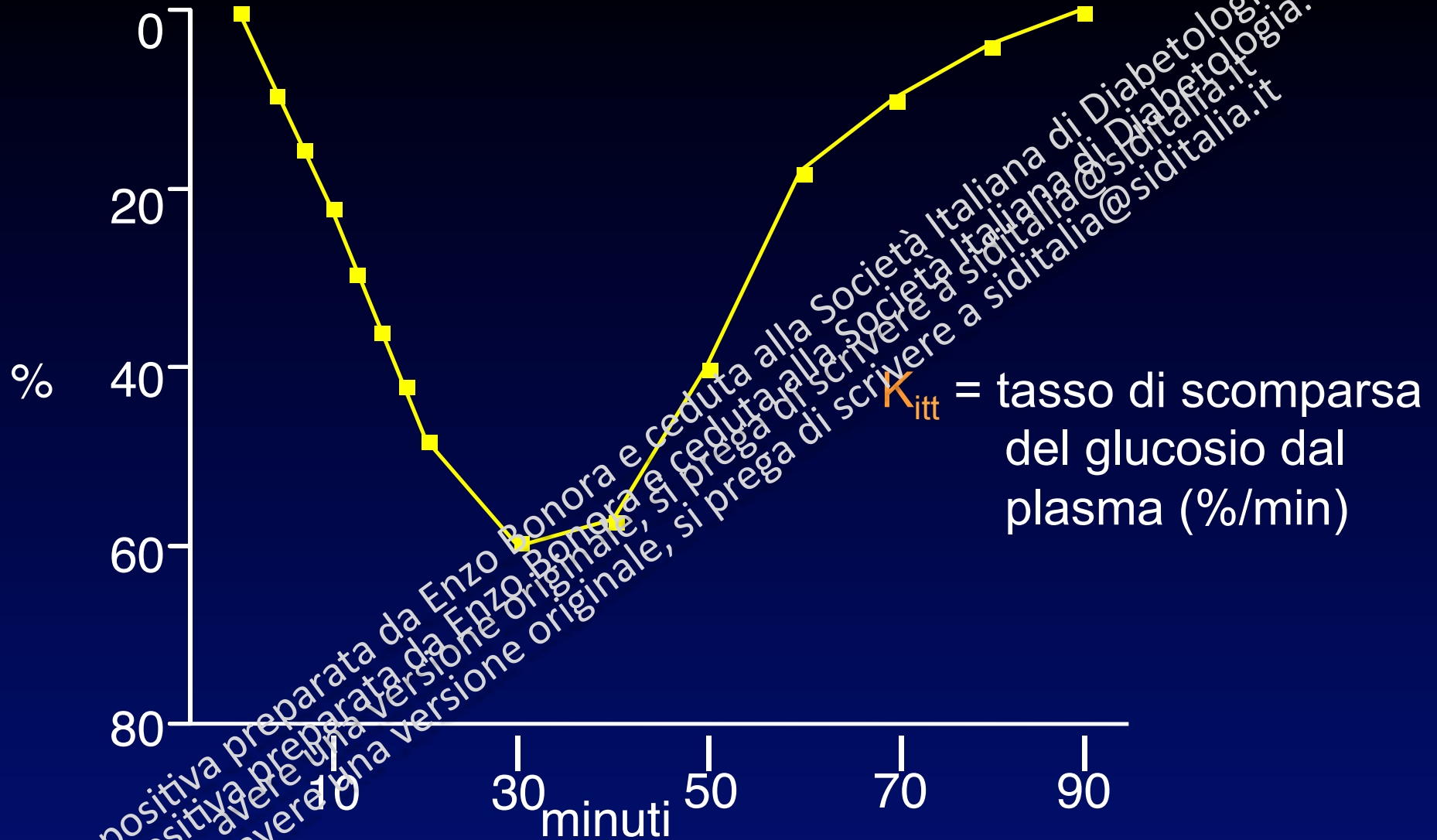
Repeated measures of plasma glucose in the last 30 minutes when a near steady state (SSPG) is achieved

SSPG measures insulin resistance (IR); the higher it is, the more severe is IR

Cosa serve: 3 pompe

Durata: almeno 3 ore

Insulin Tolerance Test (ITT)

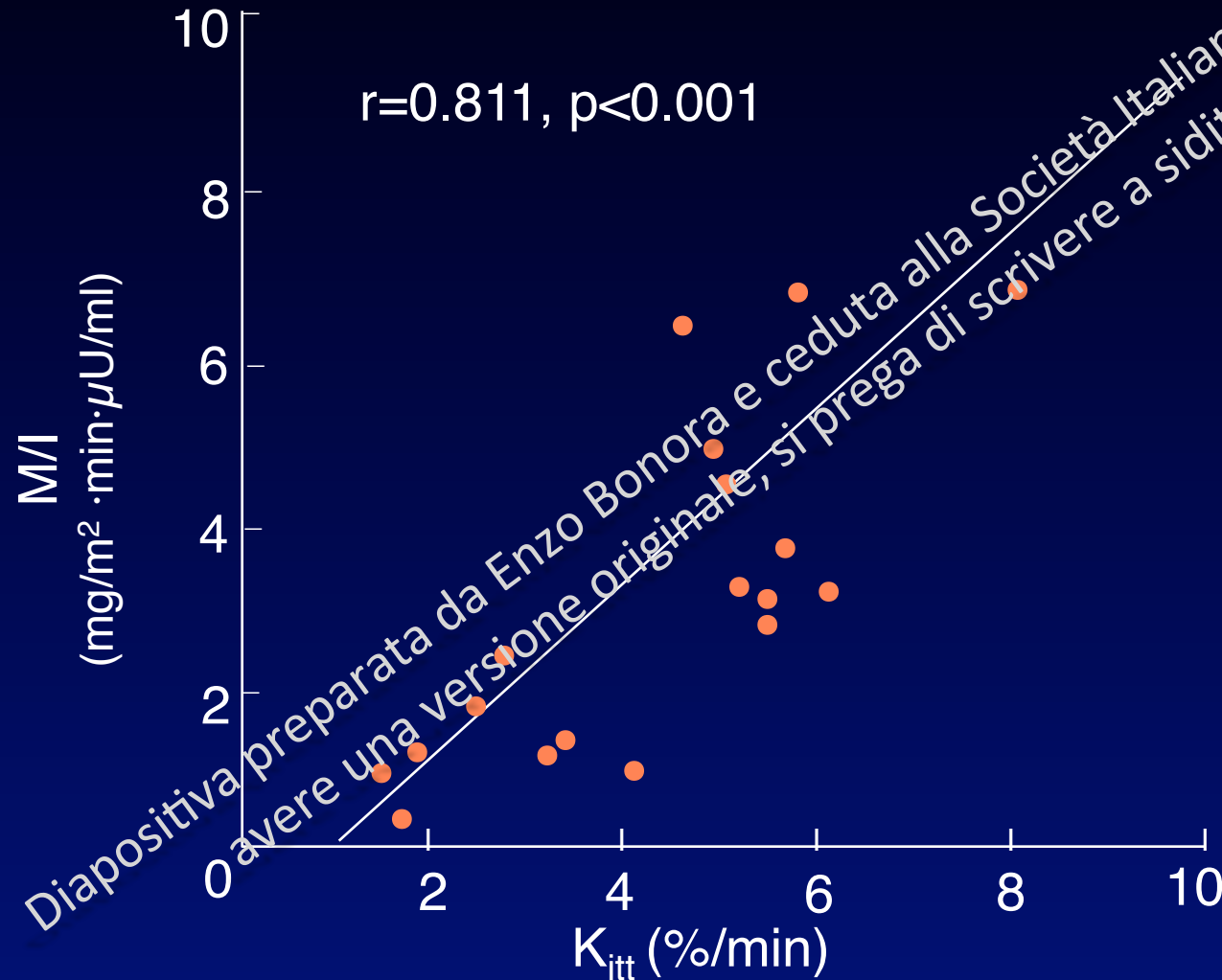


Cosa serve: un calcolatore da taschino con funzioni matematiche

Durata: circa un'ora

Correlation of clamp-measured and ITT-estimated insulin sensitivity subjects with variuos degree of glucose tolerance

(Bonora et al, JCEM 68: 374, 1989)



Assessment of insulin resistance

Comparison of different methods vs. euglycemic clamp

Correlation
(r-value)

ITT vs. clamp

- | | |
|--------------------------------------|------|
| • Bonora et al, JCEM 1989 | 0.81 |
| • Akinmokun et al, Diabetic Med 1992 | 0.86 |

IST vs. clamp

- | | |
|-----------------------------------|-------|
| • Greenfield et al, Diabetes 1981 | -0.93 |
|-----------------------------------|-------|

IVGTT + Min Mod vs. clamp

- | | |
|------------------------------|------|
| • Beard et al, Diabetes 1986 | 0.84 |
| • Saad et al, Diabetes 1994 | 0.62 |
| • Saad et al, Diabetes 1997 | 0.71 |

Assessment of Insulin Resistance

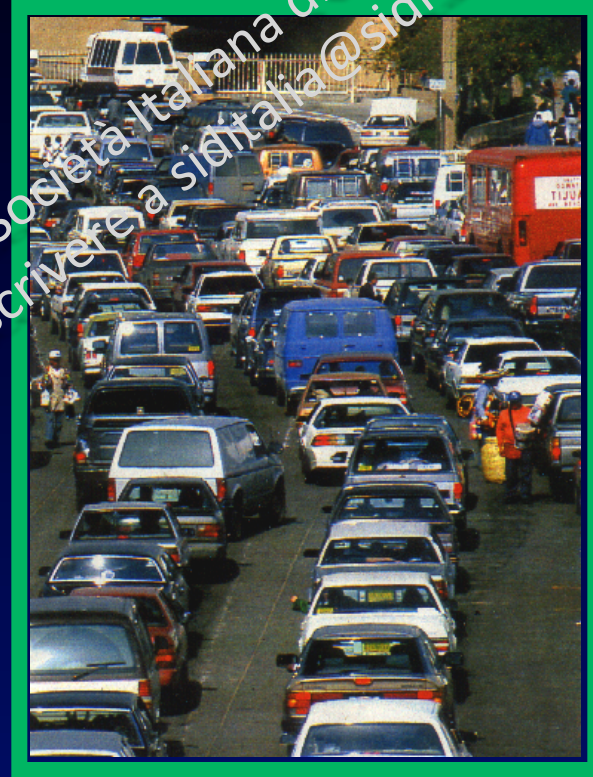
Clinical Investigation



Ideal world

Glucose clamp

Epidemiology
Clinical Practice



Real world

~~Glucose clamp~~
Simpler test

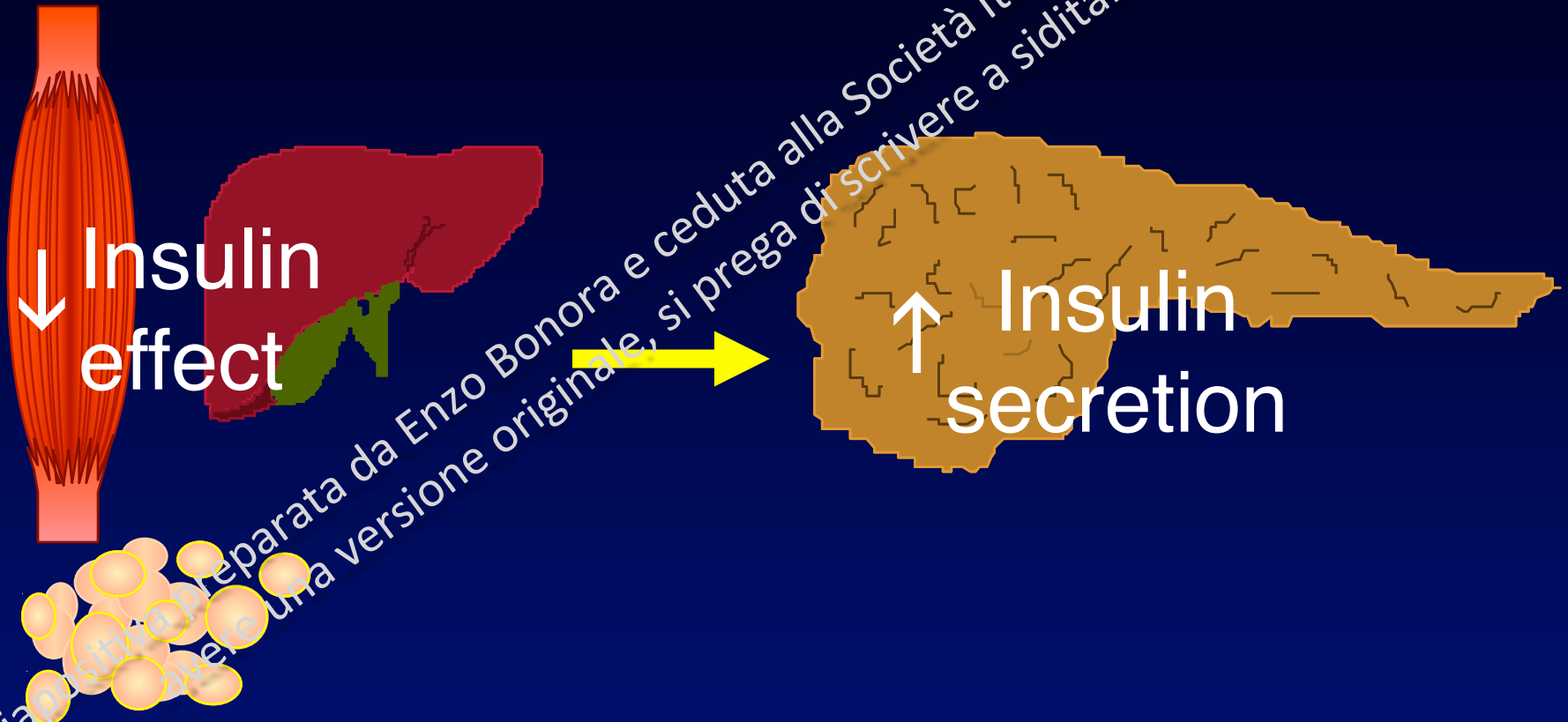
Assessment of insulin resistance in epidemiology and clinical practice

The requirements of the test

- Short duration
- Few samples (better if just one)
- Minimal invasivity
- No pumps, no arterialization
- No infusions (better if no injections)
- No real time glucose monitoring
- Simplicity of calculation (no special software)
- Low cost

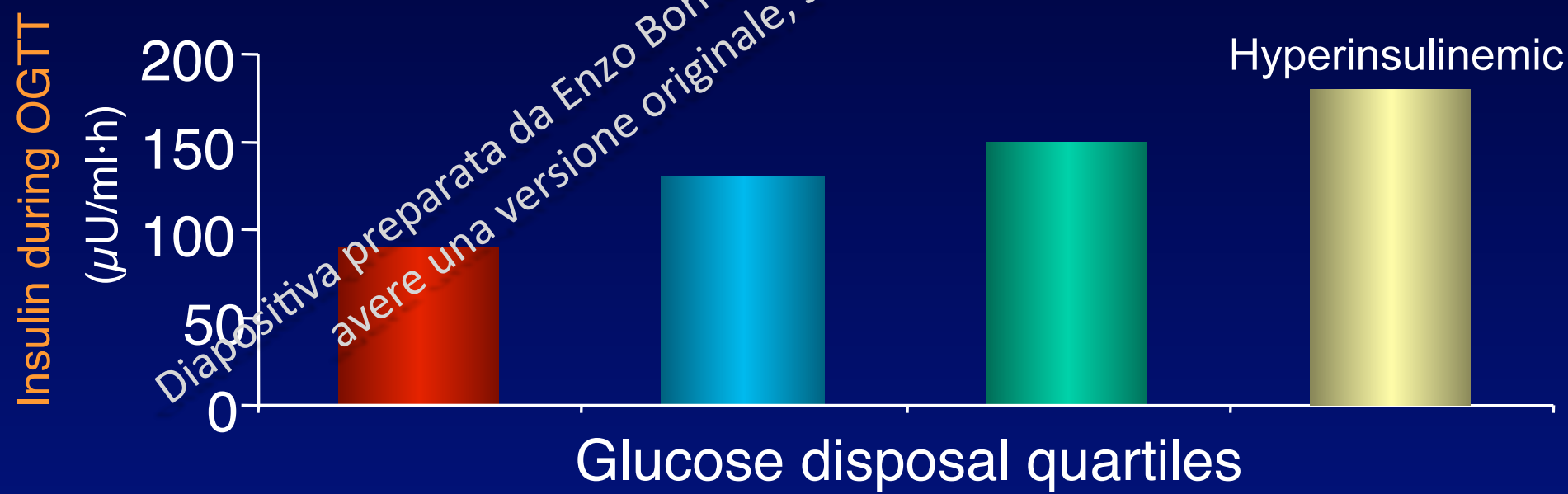
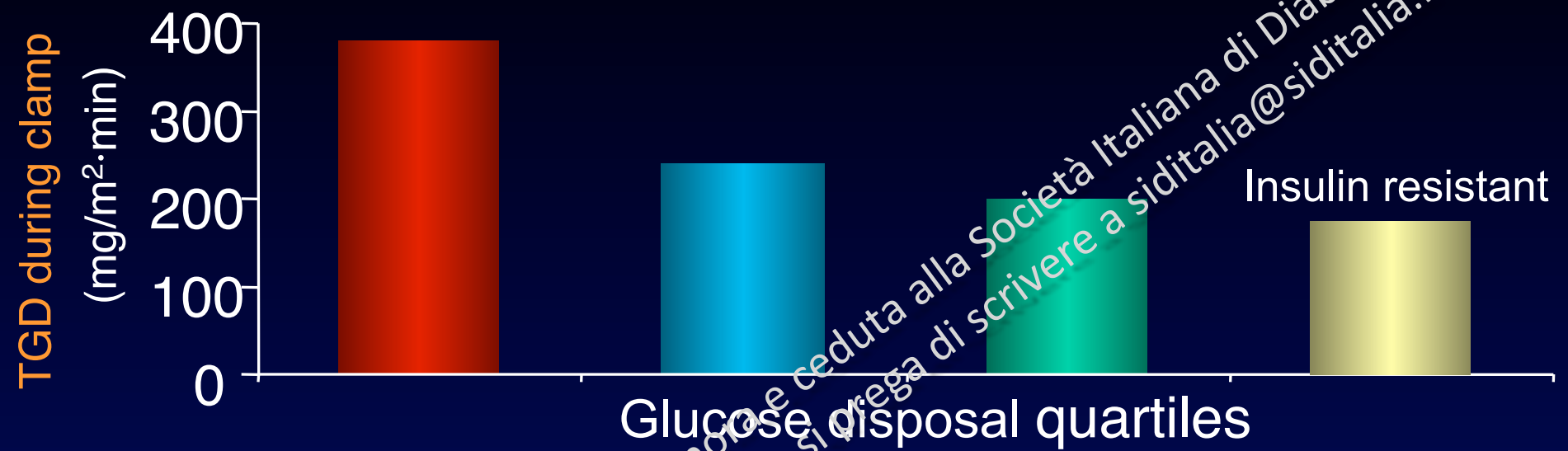
Insulin resistance

The homeostatic compensation



Diapostitmo preparata da Enzo Bonora e ceduta alla Società Italiana di Diabetologia. Per una versione originale, si prega di scrivere a siditalia@siditalia.it

Insulin resistance and hyperinsulinemia after OGTT are generally associated in nondiabetic people



Indexes of Insulin Resistance from OGTT

- Insulin Glucose Ratio
$$I_{120}/G_{120}$$
- Insulin Sensitivity Index
$$10000/(I_{2h} \times G_{2h})$$
- Stumvoll Index
complex formula
- Gutt Index
complex formula
- Cederlhom Index
complex formula
- Belfiore Index
complex formula
- Matsuda Index
complex formula

Formulas for estimating insulin resistance from OGTT

- Cederholm et al. (Diab Res Clin Pract 10: 167, 1990)

$$ISI = \frac{75.000 + (Gluc_0 - Gluc_{120}) \cdot 1.15 \cdot 100 \cdot 0.19 \cdot BW}{[120 \cdot Ln Ins_{mean} \cdot Gluc_{mean}]}$$

- Matsuda et al. (Diabetes Care 22: 1462, 1999)

$$ISI = 10.000 \sqrt{\frac{Gluc_0 \cdot Ins_0 \cdot Gluc_{mean} \cdot Ins_{mean}}{Ln}}$$

- Stumvoll et al. (Diabetes Care 23: 295, 2000)

$$ISI = 0.226 - 0.0032 \cdot BMI - 0.0000645 \cdot Ins_{120} - 0.0037 \cdot Gluc_{90}$$

Gutt index

(Gutt et al - Diabetes Res Clin Pract 2000 47:177, 2000)

$$\text{Gutt index} = (m/\text{MPG})/\log \text{MSI}$$

$$m = \frac{[75000 + (G_0 - G_{120}) \times 0.19 \times \text{BW}]}{120 \text{ min}}$$

$$\text{MPG} = \frac{(G_0 + G_{120})}{2}$$

$$\text{MSI} = \frac{(I_0 + I_{120})}{2}$$

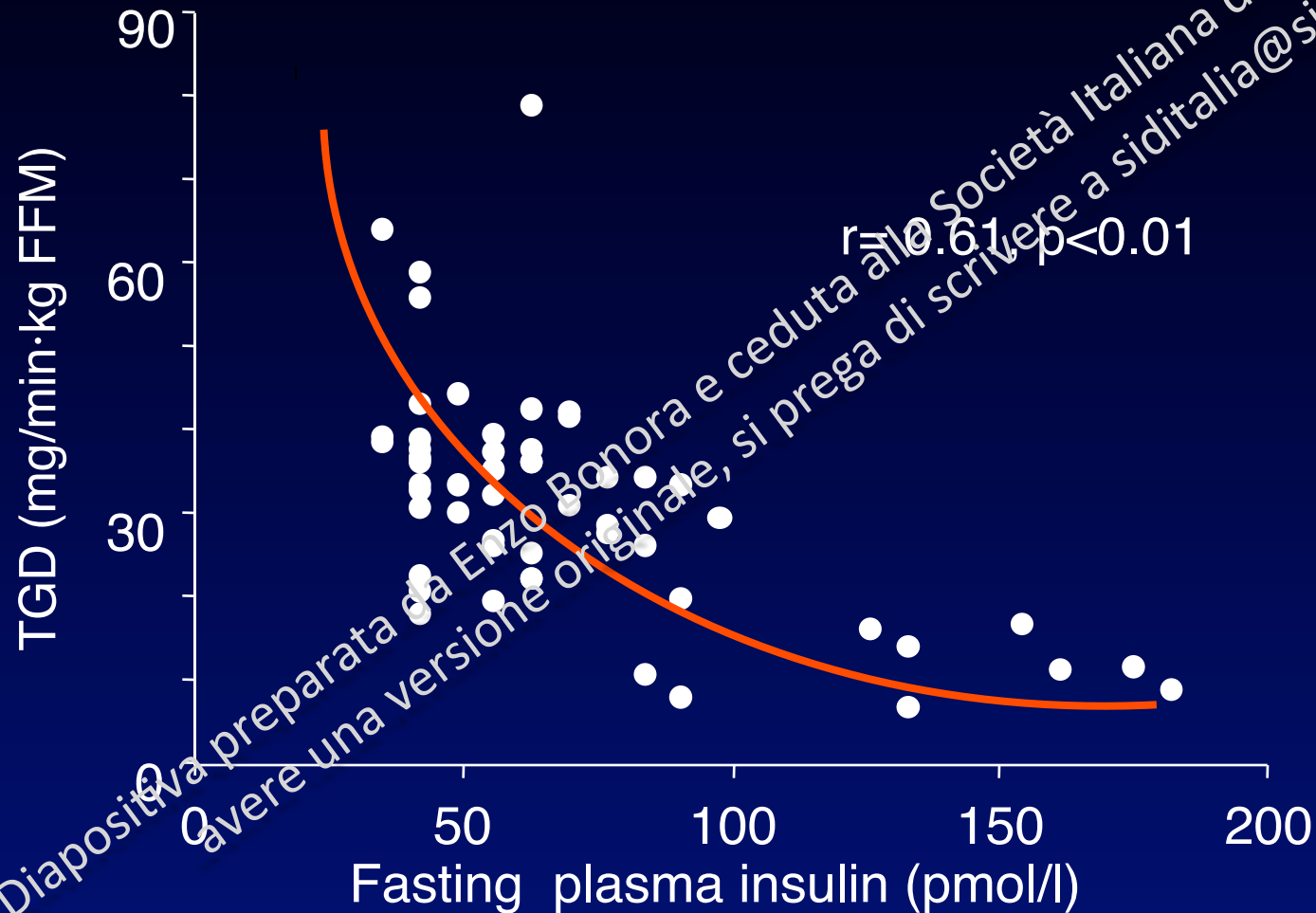
G = glucose, mg/dl

I = insulin, $\mu\text{U}/\text{ml}$

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Relationship between Fasting Insulin and Total Glucose Disposal during Insulin Clamp in Non-Diabetic Subjects

(Bonora et al, unpublished data)



Indexes of insulin resistance from fasting sample

- Fasting insulin (I_o)
- Insulin sensitivity index $(I_o \times G_o)$
- Insulin glucose ratio (I_o/G_o)
- HOMA-IR $(I_o \times G_o)/22.5$
- FIRI $(I_o \times G_o)/25$
- Raynaud Index $40/I_o$
- QUICKI $1/(\log I_o + \log G_o)$
- Bennett index $1/(\log I_o \times \log G_o)$
- Belfiore index $2[(I_o/G_o) + 1]$
- Mc Anley index complex formula

Assessment of Insulin Resistance by HOMA (Homeostasis Model Assessment)

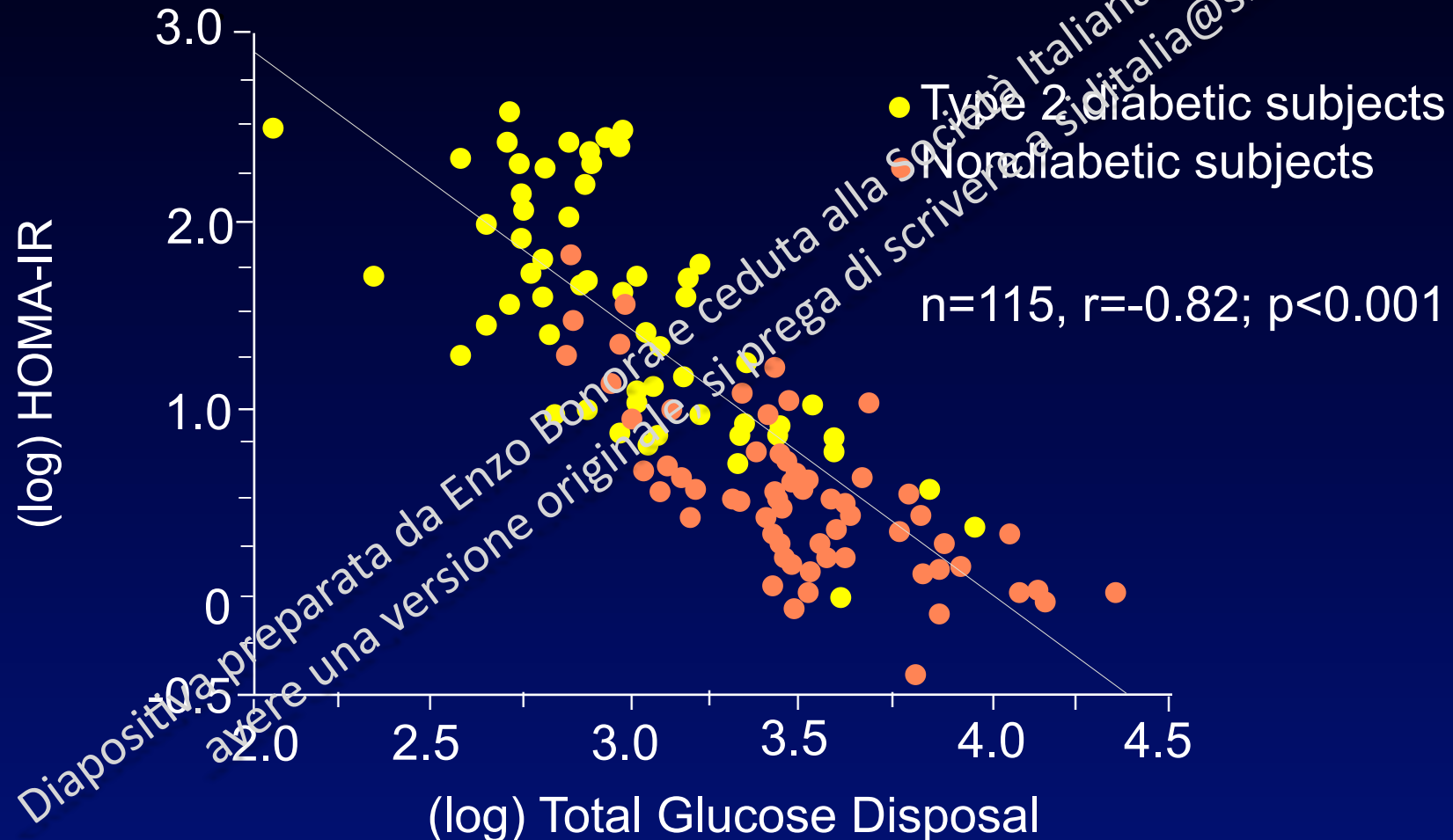
(Matthews et al; Diabetologia 28: 412, 1985)

$$\text{HOMA-IR} = \frac{\text{Fasting glucose (mmol/l)} \cdot \text{Fasting insulin (}\mu\text{U/ml)}}{22.5}$$

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Correlation between Total Glucose Disposal during Euglycemic Hyperinsulinemic Clamp and HOMA-estimated Insulin Resistance

(Bonora et al, Diabetes Care 23: 57, 2000)



Reproducibility of methods to assess insulin resistance

	CV (%)
• Insulin clamp	10-25
• IVGTT + Minimal Model	14-30
• IST	23
• ITT	6-13
• HOMA	11-30

HOMA-IR reproducibility

Within laboratory
reproducibility

quite
good

Between laboratories
reproducibility

probably
poor

Lack of standardization of insulin assay

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Fasting plasma insulin in large epidemiological studies

	Mean (μ U/ml)	Mean+2SD (μ U/ml)
ARIC Study	10	25
Bruneck Study	11	25
Eastern Finland	15	35
EGIR	9	20
Framingham Offspring Study	6	11
Helsinki Policemen Study	8	17
Honolulu Heart Program	9	20
IRAS	18	50
Paris Prospective Study	10	38
Quebec Heart Study	11	20

Which cut off point for insulin resistance?

Hyperinsulinemia to identify insulin resistance (European Group of Insulin Resistance)

Insulin resistance= higher limit of lowest decile of M value distribution of nonobese subjects in each center
(range 15-39 $\mu\text{mol}/\text{min}\cdot\text{kg BW}$)

Hyperinsulinemia= lowest limit of top decile of fasting insulin distribution of nonobese subjects in each center
(range 50-187 pmol/l)

	Normo-insulinemic	Hyper-insulinemic	Total
Insulin sensitive	856	135	991
Insulin resistant	165	182	347

False negative
(47.6%)

False positive
(13.7%)

Hyperinsulinemia specificity: 86.3%

Hyperinsulinemia sensibility: 52.4%

Soglia diagnostica dell'insulinoresistenza (criteri da EBM)

- Insulinemia a digiuno $> 20 \mu\text{U/ml}$
- HOMA-IR > 3

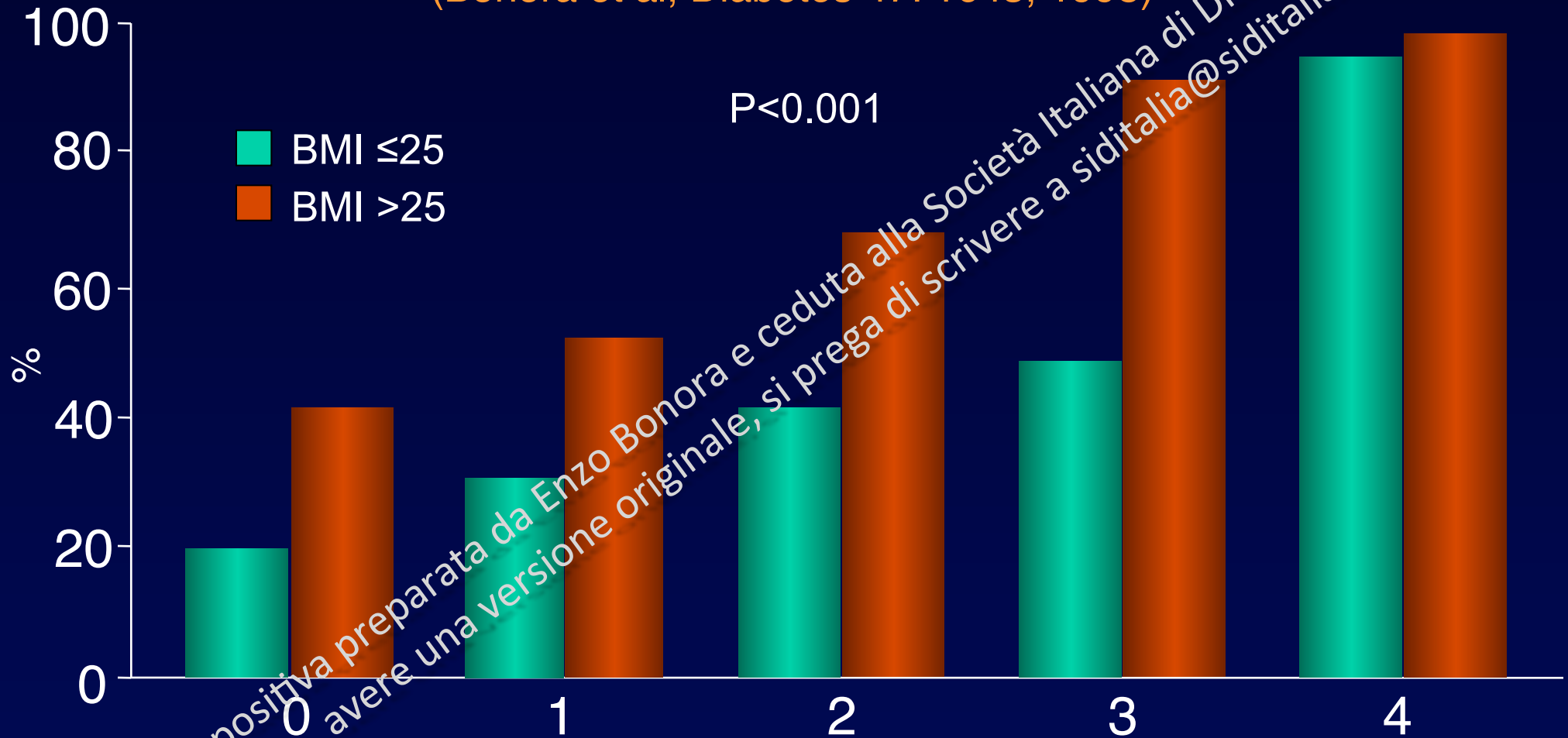
Buona specificità (pochi falsi positivi)

Bassa sensibilità (molti falsi negativi)

EBM = Enzo Bonora Medicine

Prevalence of Insulin Resistance according to the Number of Abnormalities clustering in the Single Individual

(Bonora et al, Diabetes 47: 1643, 1998)



N=888; age 40-79 yr; abnormalities: impaired glucose regulation (IGT,DM), hypertension, dyslipidemia, hyperuricemia.
Insulin resistance estimated by HOMA-IR in the upper quintile of lean controls

Conclusioni

- L'insulino-resistenza è molto comune e interessa fino ad una persona adulta su due nei paesi industrializzati
- L'insulino-resistenza è un predittore e fattore patogenetico di T2DM
- L'insulino-resistenza è un predittore ed un probabile fattore patogenetico (diretto e/o indiretto) di CVD
- L'insulino-resistenza può essere misurata solo con tecniche complesse e costose, inapplicabili nella comune pratica clinica
- Esistono vari metodi surrogati per stimare l'insulino-resistenza che si basano sulla misura dell'insulinemia a digiuno e/o dopo OGTT
- L'insulino-resistenza può essere considerata presente se nello stesso individuo, in particolare se in eccesso ponderale, coesistono multiple alterazioni metaboliche (sindrome metabolica)

Fine

Grazie!

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