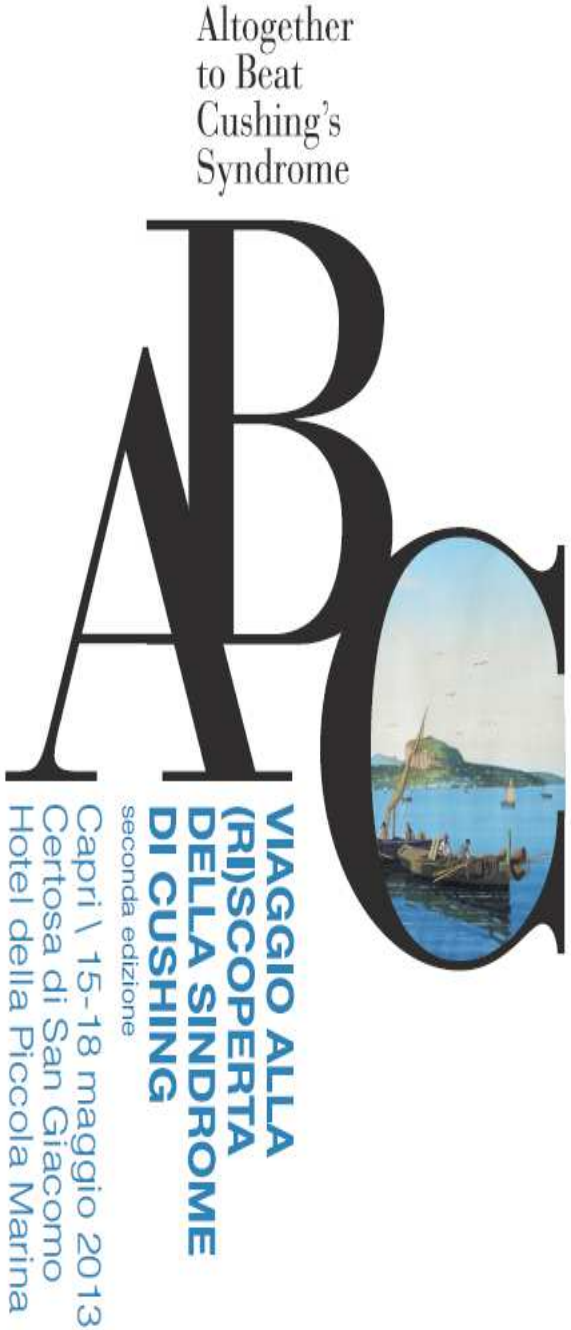

Il Diabete da Glucocorticoidi: Che Tipo di diabete è?

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Università degli Studi di Palermo

Classificazione eziologica del diabete

I. **Diabete**
A. Immu
B. Idiopa

II. **Diabete**

III. **Diabete**
A. Difett
B. Difett ipoatrofico,altri)
C. Malat cistica, altri)
D. **Endo** onn,
Ipertiroi
E. Malat li, ormoni tiroidei,
tiazidici,
F. Infezi
G. Rare nticorpi
antirece
H. Altre , Klinefelter,
Turner,

IV. **Diabete mellito gestazionale**

Diabetes Metab. 1997 Nov;23(5):454-5.

Tabella II. Criteri per la diagnosi di diabete.

	Glicemia a digiuno		Glicemia 2ª ora OGTT (OGTT = curva da carico 75 g di glucosio per os)
Normale	< 110*	e	< 140
IFG	110*-125	e	< 140
IGT	< 126	e	140-199
Diabete	≥ 126	o	≥ 200

**L'ADA (American Diabetes Association) ha proposto come valore normale glicemie inferiori a 100 mg/dl, quindi secondo l'ADA sono da considerarsi soggetti con alterata glicemia a digiuno (IFG) se la glicemia a digiuno è compresa tra 100 e 125 mg/dl. Questa classificazione al momento non è stata accettata dall'IDF (International Diabetes Federation) e dall'OMS che considerano validi i valori riportati in tabella.*

Sindrome metabolica

NCEP ATP III

≥3 dei seguenti criteri

Obesità viscerale	Maschi: circonferenza vita ≥102 cm Femmine: circonferenza alla vita ≥88 cm
Trigliceridi	≥150 mg/dl
Colesterolo HDL	Maschi: <40 mg/dl Femmine: <50 mg/dl
Pressione arteriosa	≥130/85 mmHg
Glicemia a digiuno	≥110 mg/dl

Grundy SM et al., Circulation 109: 433-438, 2004

Prevalenza di sindrome di Cushing "subclinico" in pazienti affetti da DM2

Autore-Anno	Numero (N)	Criteri di inclusione	Modalità di screening	Prevalenza di CS (%)
Chiodini, 2005	294	Età 30 aa alla diagnosi, BMI 19–49 kg/m2, ospedalizzati	1 mg overnight DST	9,4
Reimondo, 2007	100	Età>18, BMI >25 kg/m2	1 mg overnight DST	1
Newsome, 2008	171	Età 18–80 anni, BMI 25 kg/m2, T2DM 1 anno	1 mg overnight DST	0
Taniguchi, 2008	77	T2DM, ospedalizzati	Cortisolo salivare notturno	2,6
Murakami, 2010	90	Età>20 anni alla diagnosi, BMI 16–45 kg/m2, ospedalizzati, T2DM	1 mg overnight DST	8,9

DST, Test di soppressione al desametasone;
DM2, Diabete mellito di tipo 2; CS, sindrome di Cushing

J Clin Endocrinol Metab, May 2010, 95(5):2262–2265

Prevalenza di sindrome di Cushing “subclinico” in pazienti affetti da DM2

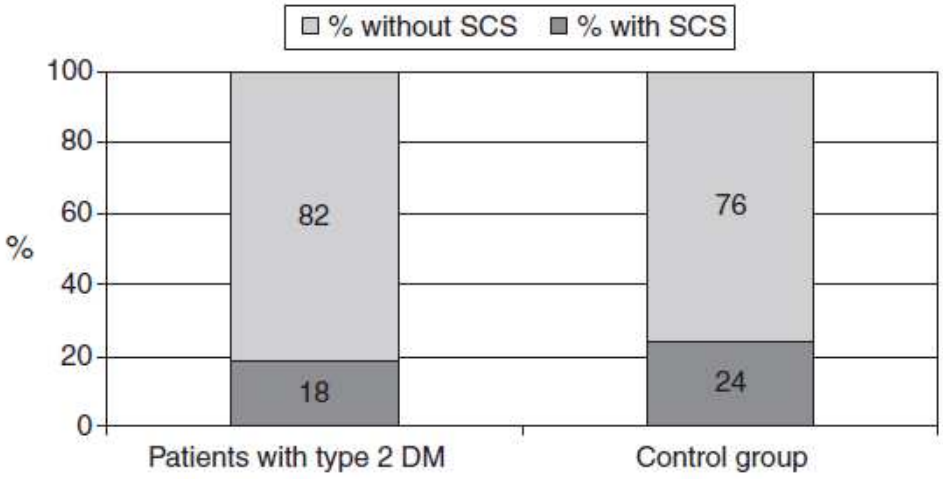


Fig. 1. Subclinical Cushing’s syndrome occurrence according to NIH criteria (serum cortisol after 1 mg DST > 138 nmol/l) in patients with type 2 DM and in control group ($p = 0.54$)

N. 50 vs 25

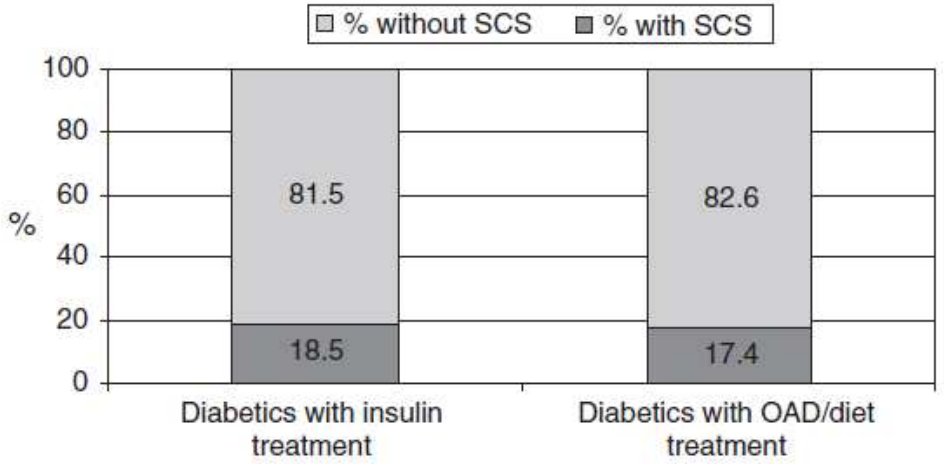


Fig. 2. Subclinical Cushing’s syndrome occurrence according to NIH criteria (serum cortisol after 1 mg DST > 138 nmol/l) in patients with type 2 DM divided according to diabetes treatment (insulin *vs.* OAD/diet)

Felsöci et al. Wien Klin Wochenschr. 2011 Jan;123 (1-2):28-33

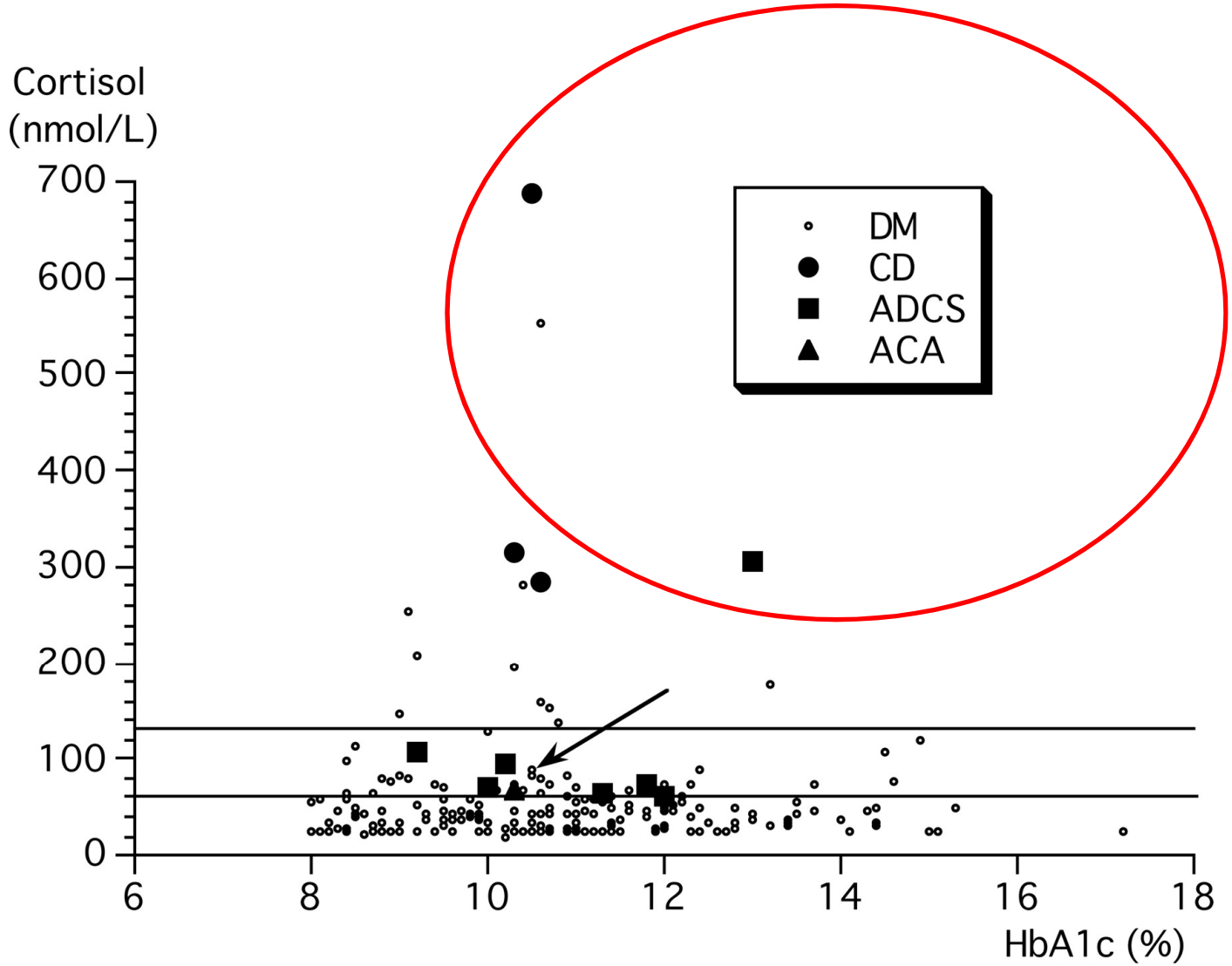
Prevalenza di sindrome di Cushing “clinico” in pazienti affetti da DM2

Autore-Anno	Numero (N)	Criteri di inclusione	Modalità di screening	Prevalenza di CS (%)
Leibowitz, 1996	90	BMI 25 kg/m2, HbA1c 9%	1 mg overnight DST	3
Catargi, 2003	200	BMI 25 kg/m2, HbA1c 8%	1 mg overnight DST	2
Liu, 2005	141	DMT2-BMI>30 kg/m2	Cortisolo salivare notturno	0
Mullan, 2010	201	BMI 25 kg/m2, HbA1c 7%, Ipertensione, Età 60 anni	Cortisolo salivare notturno	0

DST, Test di soppressione con desametasone;
T2DM, diabete mellito di tipo 2; CS, Sindrome di Cushing

J Clin Endocrinol Metab, May 2010, 95(5):2262–2265

Sindrome di Cushing nei pazienti affetti da Diabete mellito di tipo 2.



Catargi B et al. JCEM 2003;88:5808-5813

Screening CS nei pazienti con DM2

L'analisi di tutti i dati presenti in letteratura dal 1970 al 2010 relativi alla prevalenza di sindrome di Cushing (subclinico e clinicamente manifesto) nei pazienti affetti da diabete mellito di tipo 2 ha mostrato **risultati variabili dallo 0 a 9,4%.**

LIMITI:

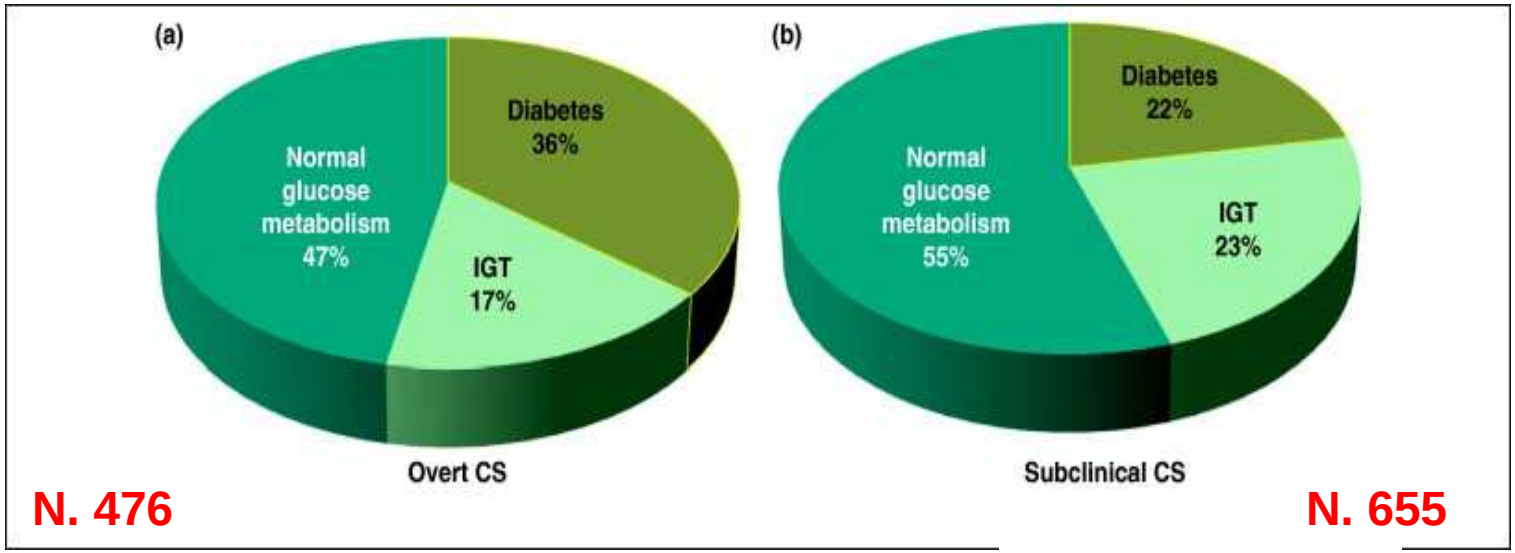
- selezione del tipo di paziente
- test utilizzato per lo screening
- cut-off di riferimento
- metodi di dosaggio del cortisolo.

Uno screening di routine per sindrome di Cushing nei pazienti diabetici non è utile né proficuo

Prevalenza di diabete mellito e IGT in pazienti con SC clinicamente manifesta e subclinica

		n	%DM	%IGT
Friedman et al.	1996	16	37.5	12.5
Biering et al.	2000	131	40.5	28
Pecori Giraldi et al.	2003	280	44	
Manicini et al.	2004	49	47	21
			(64% FBG <6.1 mmol/l)	

FBG = Fasting blood glucose.



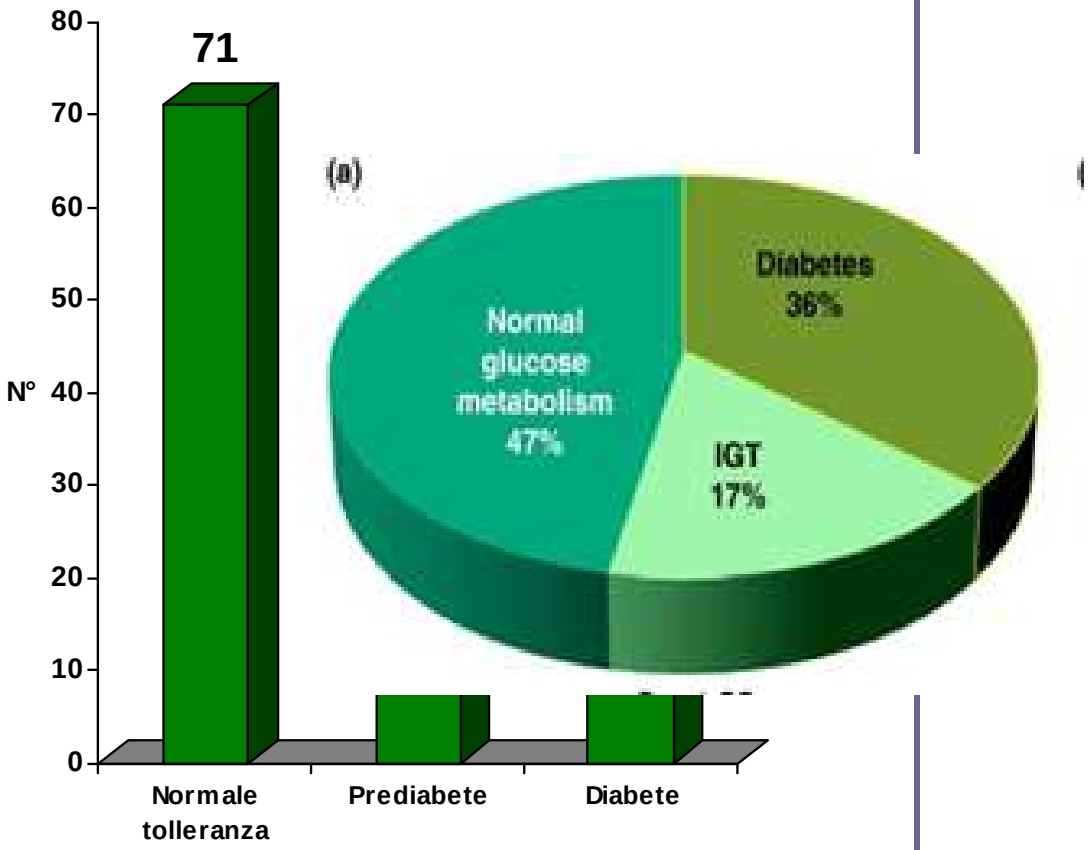
N. 476

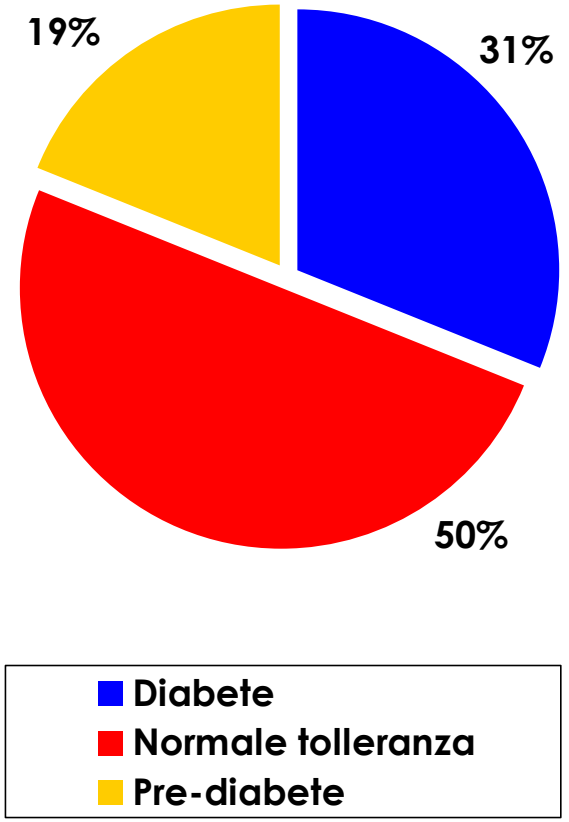
N. 655

Mazziotti et al., Trends Endocrinol Metab. 2011

DATI IN CORSO DI PUBBLICAZIONE

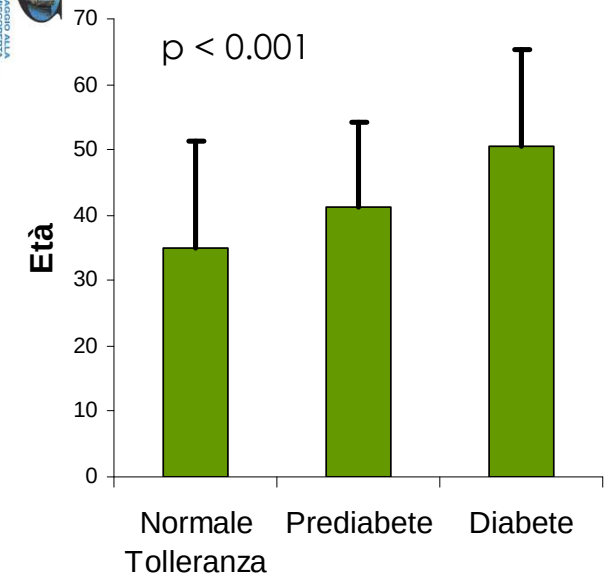
Prevalenza dei difetti di tolleranza glucidica nella casistica PA+NA

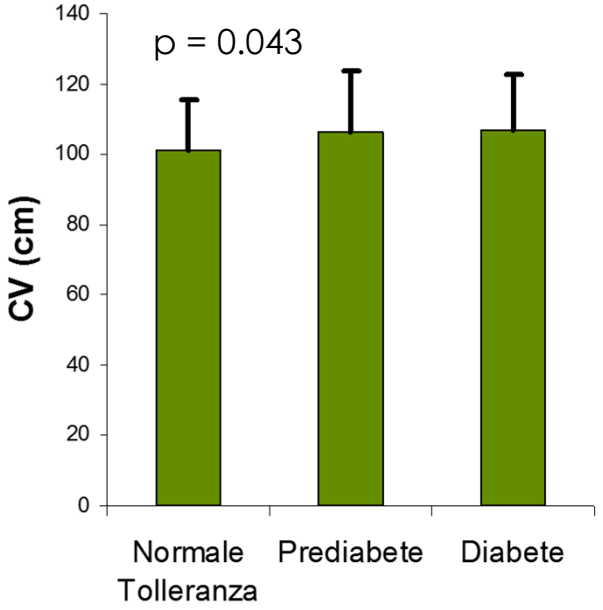




DATI IN CORSO DI PUBBLICAZIONE

Trend analysis

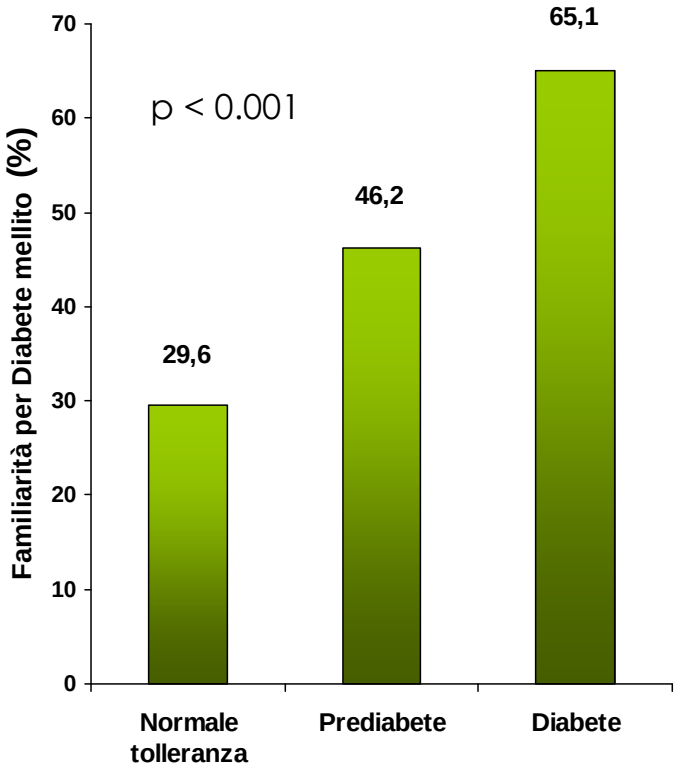




	Normal glucose tolerance No 71	Prediabetes No 26	Diabetes No 43	
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*p*
Age (yr)	35.05 ± 16.34	41.27 ± 12.97	50.58 ± 14.64	<0.001
BMI (Kg/m²)	30.00 ± 5.07	31.18 ± 6.08	32.07 ± 7.19	0.072
WC	100.85 ± 14.77	106.28 ± 17.49	106.76 ± 16.00	0.043
WHR	1.01 ± 0.09	1.02 ± 0.09	1.01 ± 0.08	0.900
	Subjects (%)	***Subjects (%)***	***Subjects (%)***	
Male	14 (19.7)	6 (23.1)	7 (16.3)	0.696
Female	57 (80.3)	20 (76.9)	36 (83.7)	0.696

DATI IN CORSO DI PUBBLICAZIONE

Trend analysis

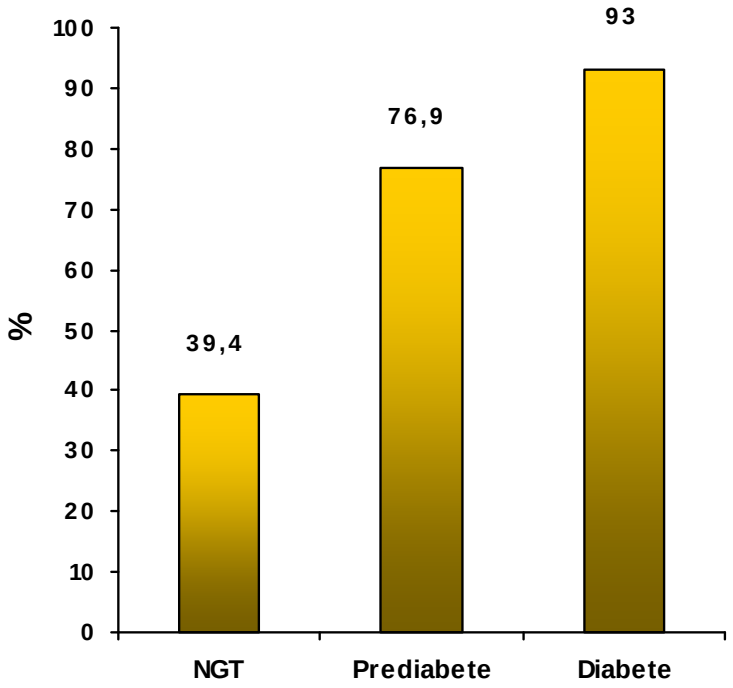


	NGT N 71	Prediabetes N 26	Diabetes N 43	
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*p*
Family history of Diabetes	21 (29.6)	12 (46.2)	28 (65.1)	<0.001
Pituitary disease	48 (67.6)	21 (80.8)	30 (69.8)	0.704
Adrenal disease	23 (32.4)	5 (19.2)	13 (30.2)	0.704
Multinodular goiter	3 (4.2)	2 (7.7)	11 (25.6)	<0.001
Visceral obesity	54 (76.1)	23 (88.5)	37 (86)	0.152
Moon face	34 (47.9)	16 (61.5)	20 (46.5)	1
Buffalo hump	23 (32.4)	11 (42.3)	16 (37.2)	0.547
Purple strie	31 (43.7)	14 (53.8)	13 (30.2)	0.212
Ecchymoses	12 (16.9)	7 (26.9)	13 (30.2)	0.090
Arterial hypertension	48 (67.6)	20 (76.9)	37 (86)	0.026
Coronary heart disease	8 (11.3)	2 (7.7)	13 (30.2)	0.012
Coagulopathy	2 (2.8)	1 (3.8)	7 (16.3)	0.009
Peripheral vascular disease	2 (2.8)	0	7 (13.9)	0.049
Cerebral vascular disease	4 (5.6)	1 (3.8)	7 (16.3)	0.007
Depression	13 (18.3)	5 (19.2)	14 (32.6)	0.090
Osteoporosis	13 (18.3)	6 (23.1)	13 (30.2)	0.143
Metabolic syndrome	28 (39.4)	20 (76.9)	40 (93)	<0.001

DATI IN CORSO DI PUBBLICAZIONE

Sindrome metabolica

P< 0.001

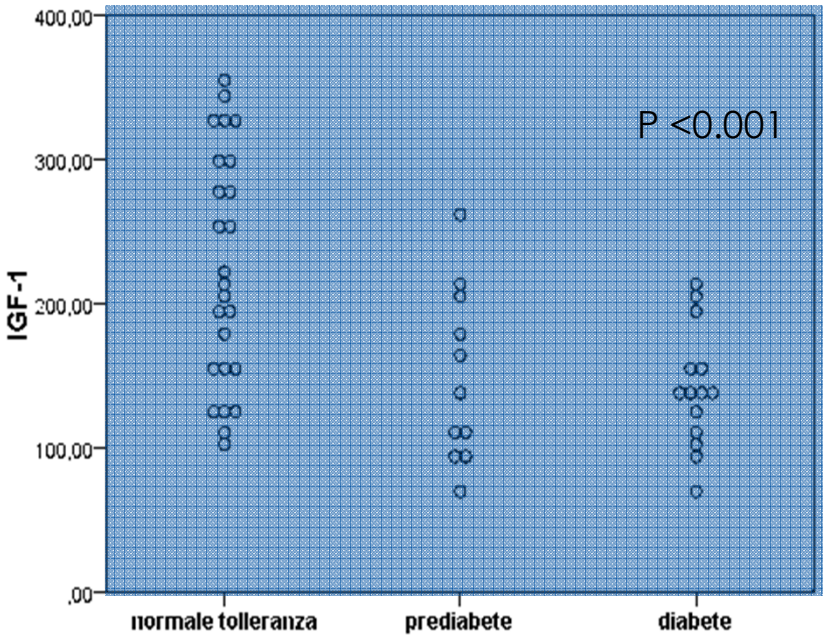


I dati della letteratura indicano, che nei pazienti con Cushing vi sia una prevalenza di SM pari al 60-65% dei pazienti. Nella nostra casistica è stato riscontrato che il 63% dei pazienti presentava una SM. Tale quadro patologico è stato riscontrato con maggiore prevalenza nei pazienti con DM.

DATI IN CORSO DI PUBBLICAZIONE

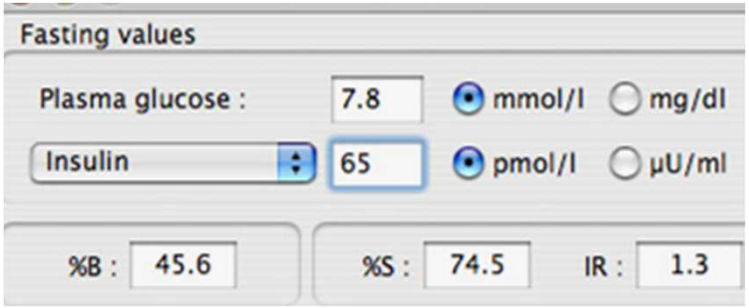
Trend analysis

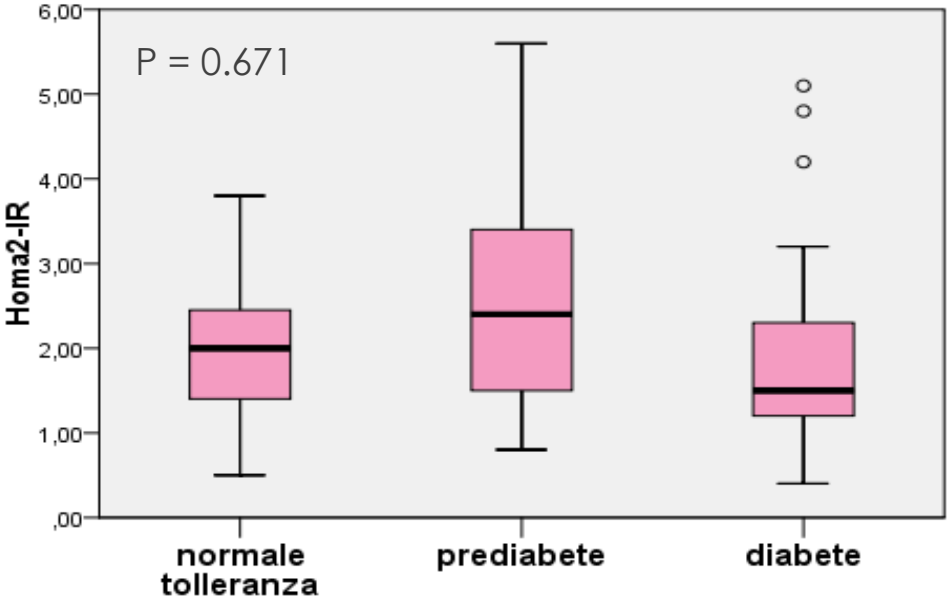
	NGT No 71	Prediabetes No 26	Diabetes No 43	
	Mean ± SD			P
GH (µg/l)	0.80 ± 1.53	0.33 ± 0.32	0.58 ± 0.88	0.425
PRL (ng/ml)	14.66 ± 8.86	14.04 ± 7.66	17.69 ± 25.54	0.478
TSH (µU/ml)	1.58 ± 1.53	1.69 ± 1.48	1.23 ± 0.97	0.231
FT4 (ng/dl)	2.68 ± 3.67	2.01 ± 2.72	1.6[illegible] ± 1.95	0.082
IGF-1 (ng/ml)	223.00 ± 82.24	174.69 ± 61.65	14[illegible].00 ± 42.07	<0.001
FT3 (pg/ml)	2. 86 ± 0.89	2.64 ± 0.75	2.61 ± 0.84	0.141
ACTH h 8 (pg/ml)	51.11 ± 42.87	65.85 ± 34.47	57.86 ± 52.00	0.365
ACTH h 16 (pg/ml)	40.90 ± 36.18	55.58 ± 35.24	45.58 ± 35.47	0.530
ACTH h 24 (pg/ml)	41.27 ± 31.00	52.66 ± 20.32	51.00 ± 31.50	0.209
Cortisol h 8 (ng/ml)	246.83 ± 66.73	257.52 ± 74.38	270.72 ± 85.53	0.102
Cortisol h 16 (ng/ml)	231.90 ± 60.15	227.00 ± 72.81	226.98 ± 107.81	0.815
Cortisol h 24 (ng/ml)	175.05 ± 75.17	191.92 ± 93.49	203.32 ± 115.23	0.249
Urinary free cortisol (mcg/24h)	436.25 ± 334.20	376.82 ± 322.03	409.54 ± 457.89	0.668
Cortisol after DMZ (ng/ml)	95.83 ± 86.75	105.51 ± 83.93	101.17 ± 92.63	0.783

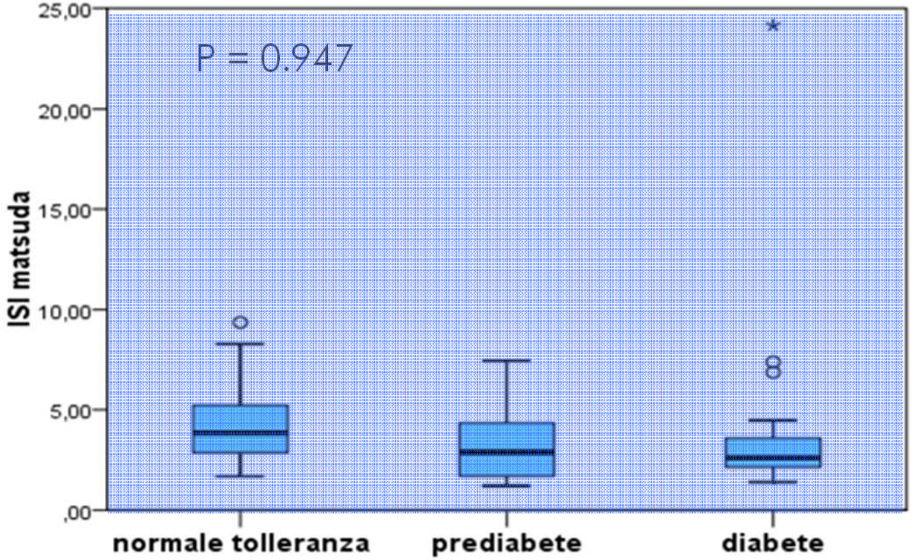


DATI IN CORSO DI PUBBLICAZIONE

Trend analysis – indici di sensibilità insulinica



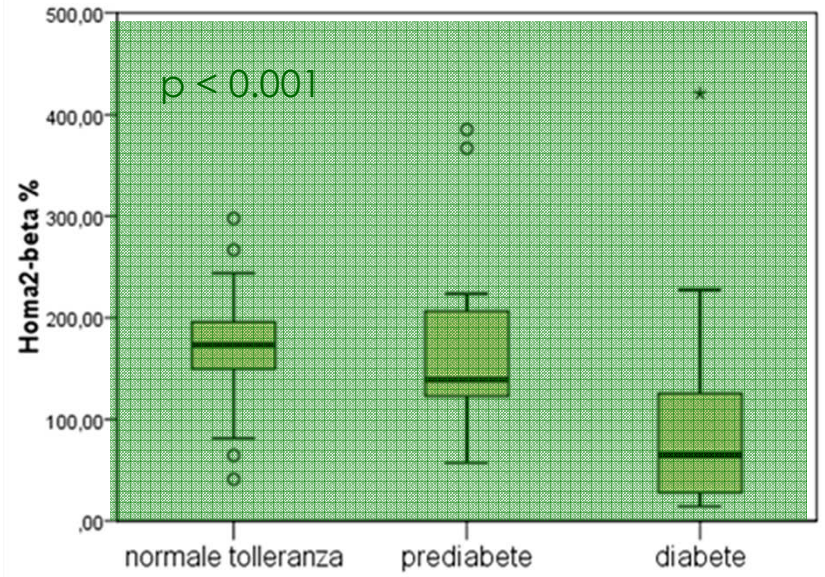


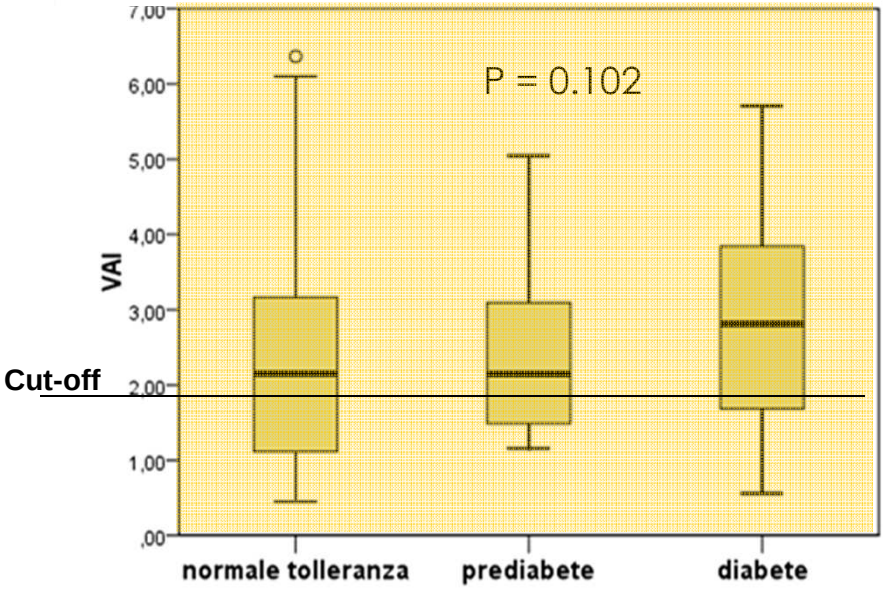


$$ISI_{(Matsuda)} = \frac{10000}{\sqrt{G_0 \times I_0 \times G_{mean} \times I_{mean}}}$$

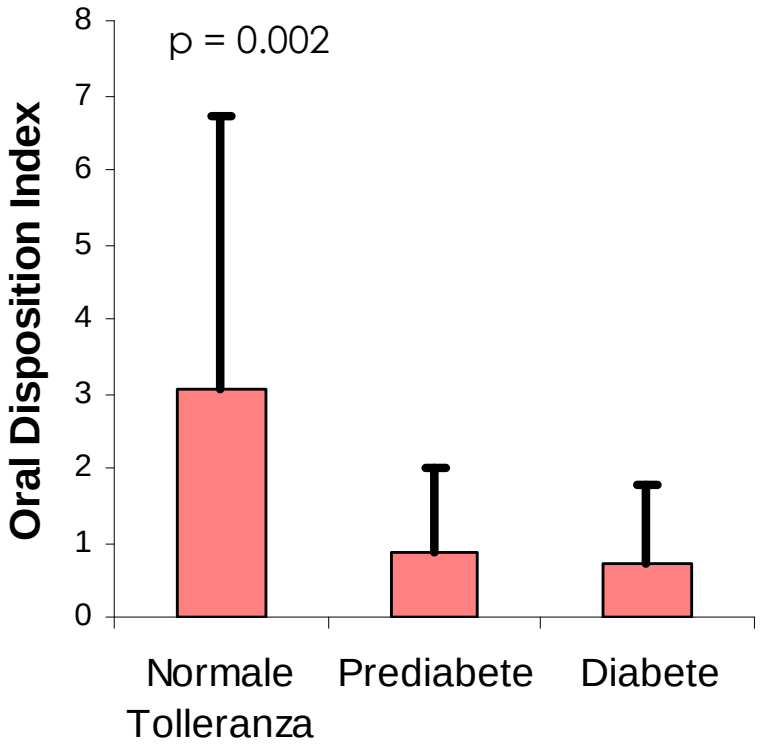
DATI IN CORSO DI PUBBLICAZIONE

Trend analysis – indici di sensibilità insulinica

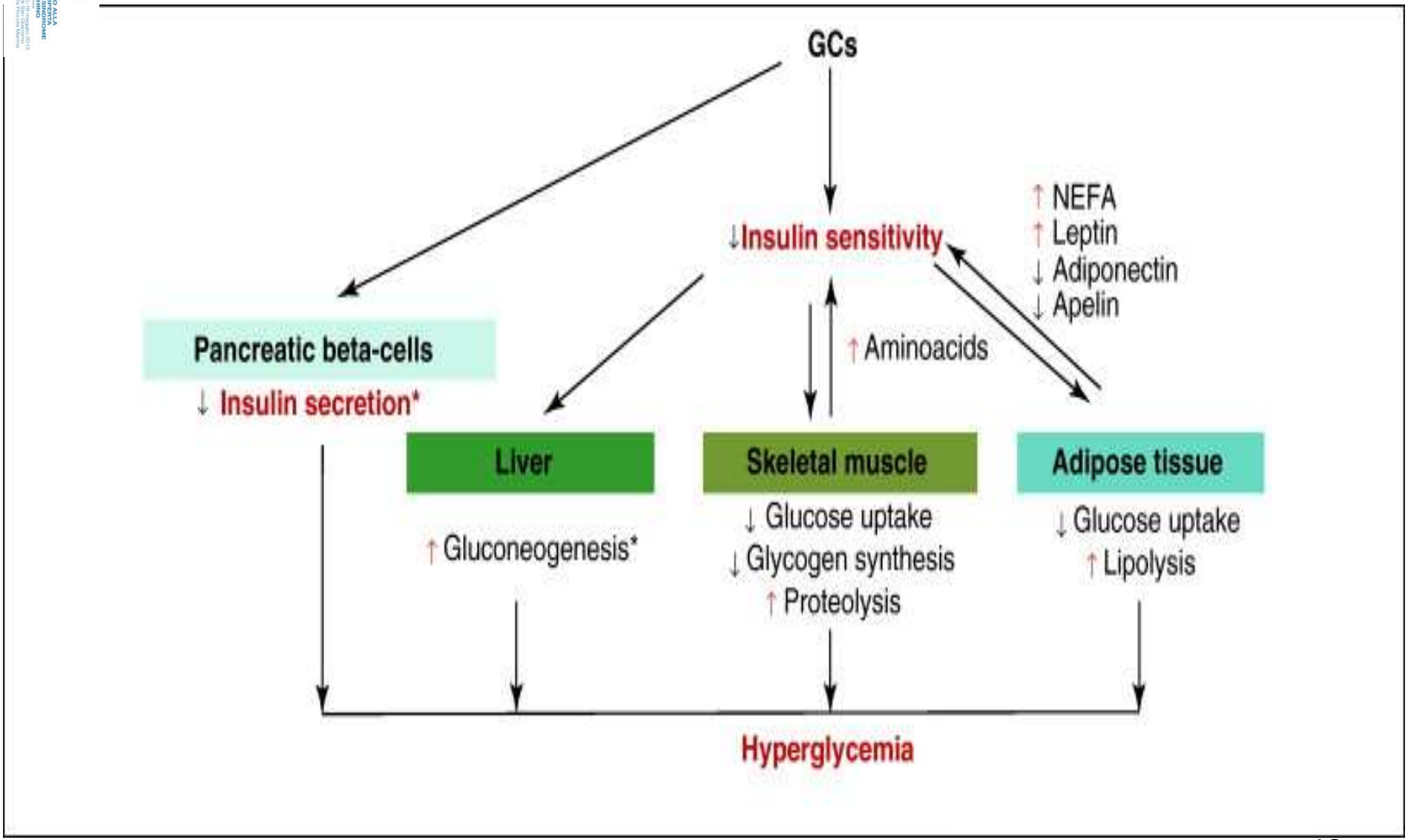




Cut-off

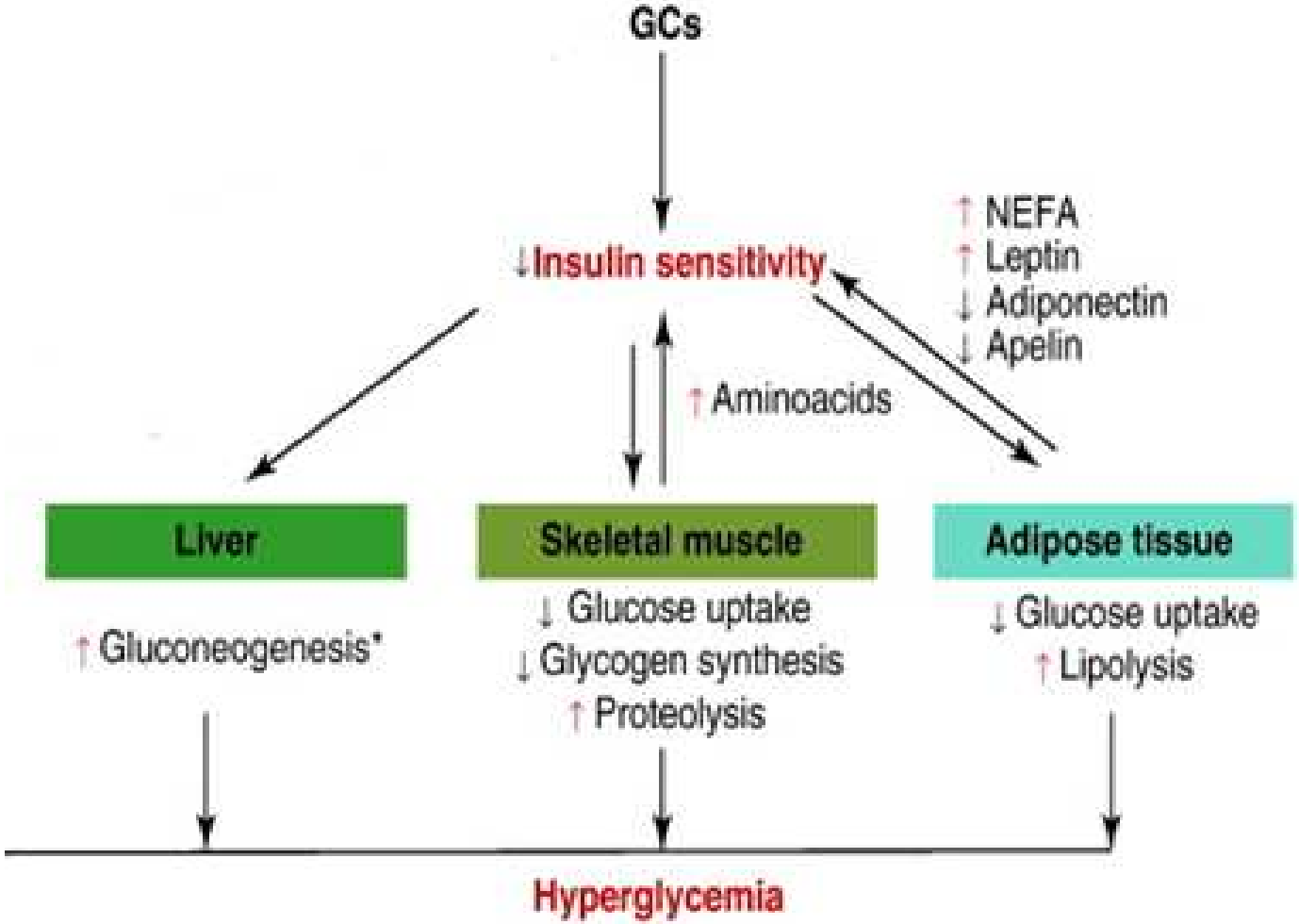


Metabolismo glucidico & Cushing



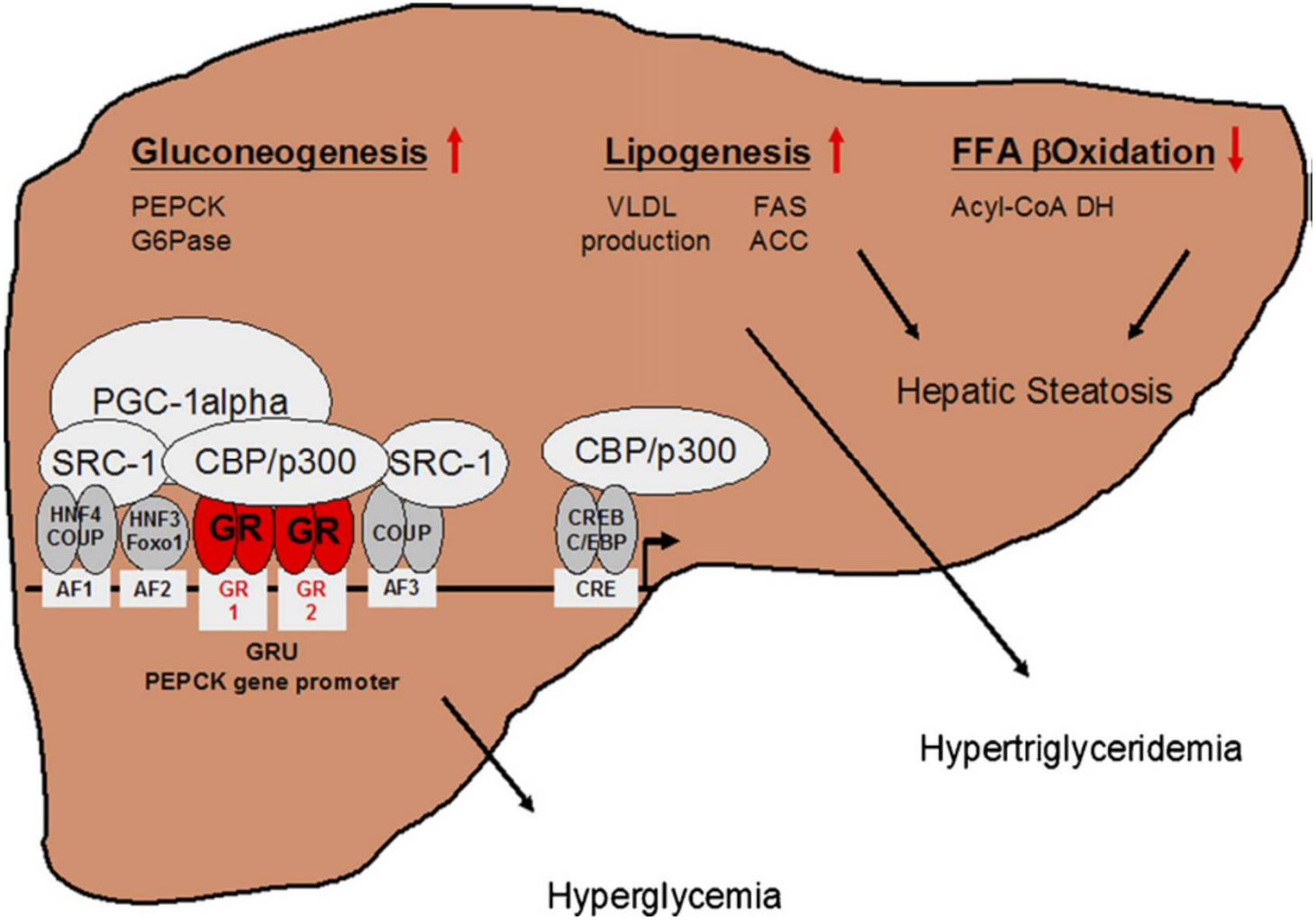
Mazziotti et al., Trends Endocrinol Metab. 2011

Cushing & insulino-resistenza



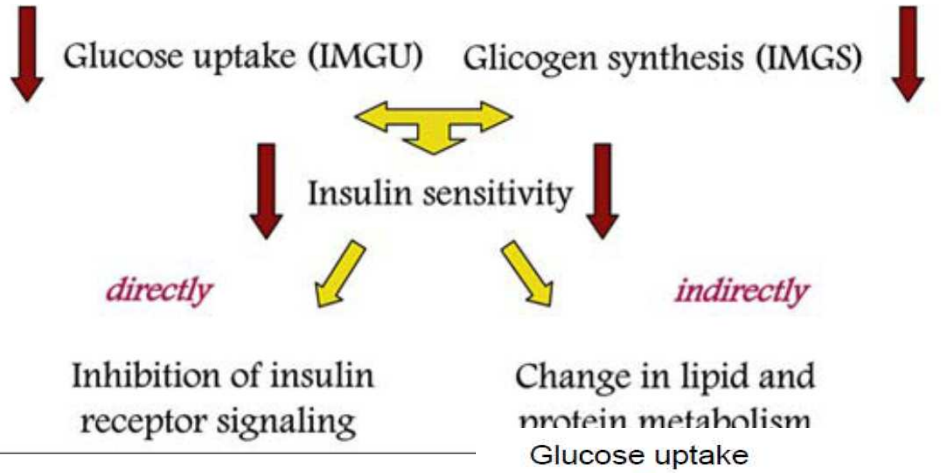
Mazziotti et al., Trends Endocrinol Metab. 2011

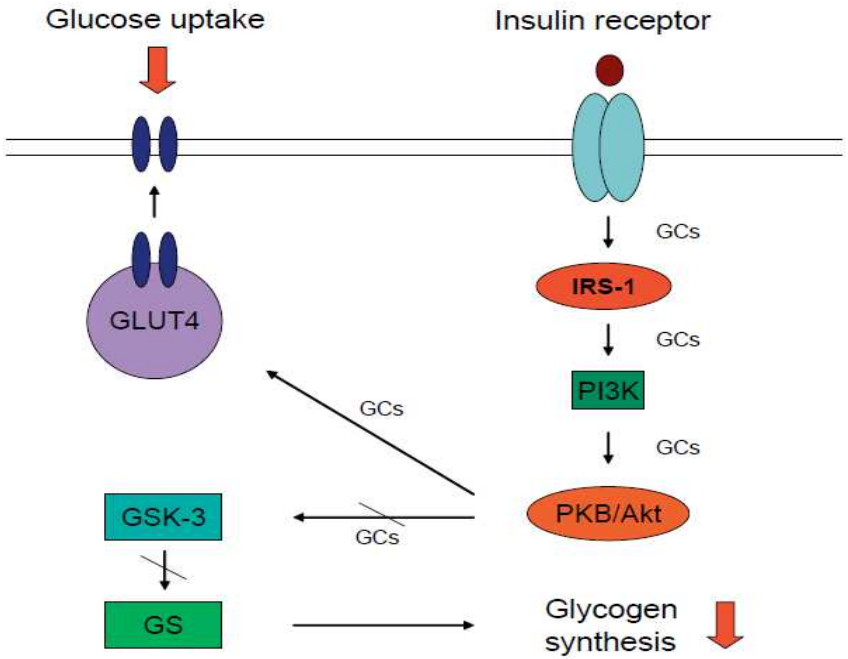
GC/GR-regulated metabolic pathways in the liver



Vegiopoulos & Herzig, Molecular and Cellular Endocrinology 275 (2007) 43–61

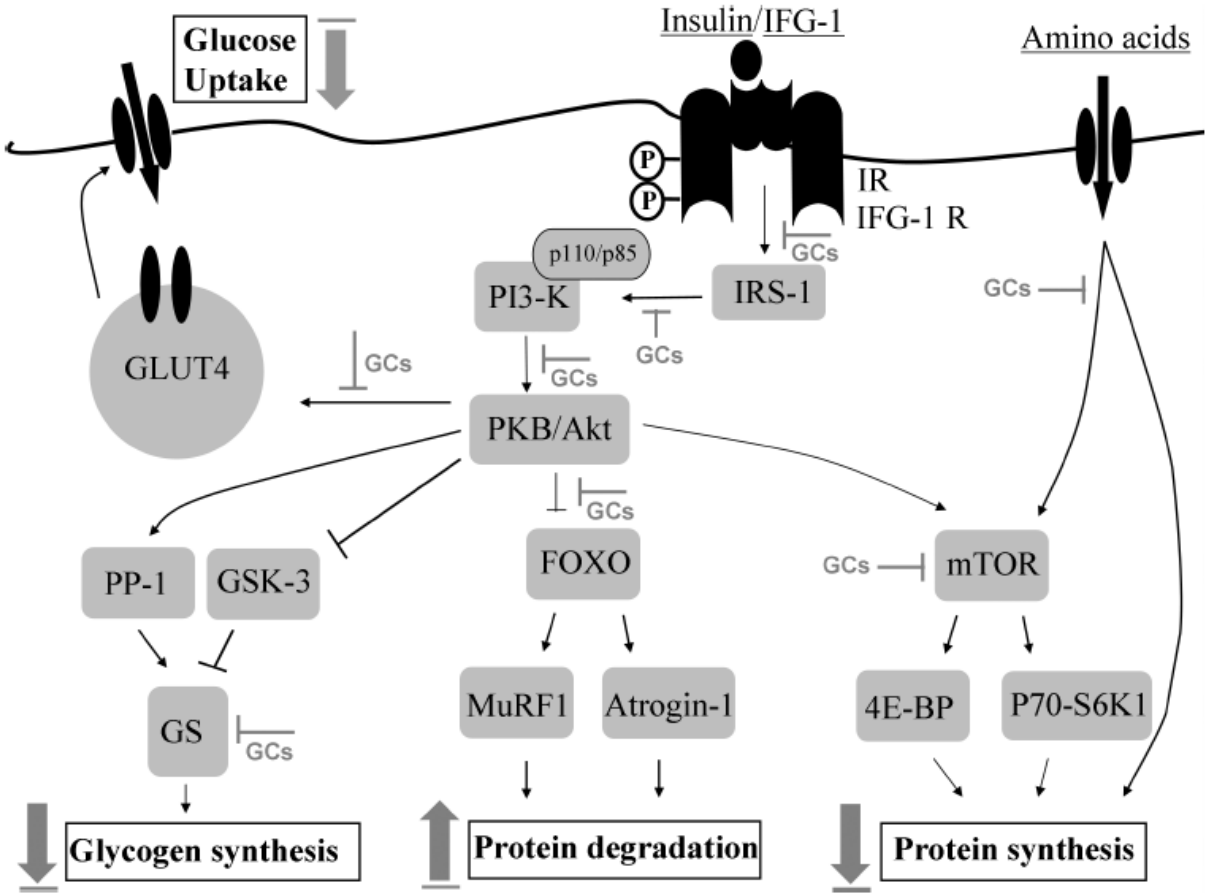
Muscolo





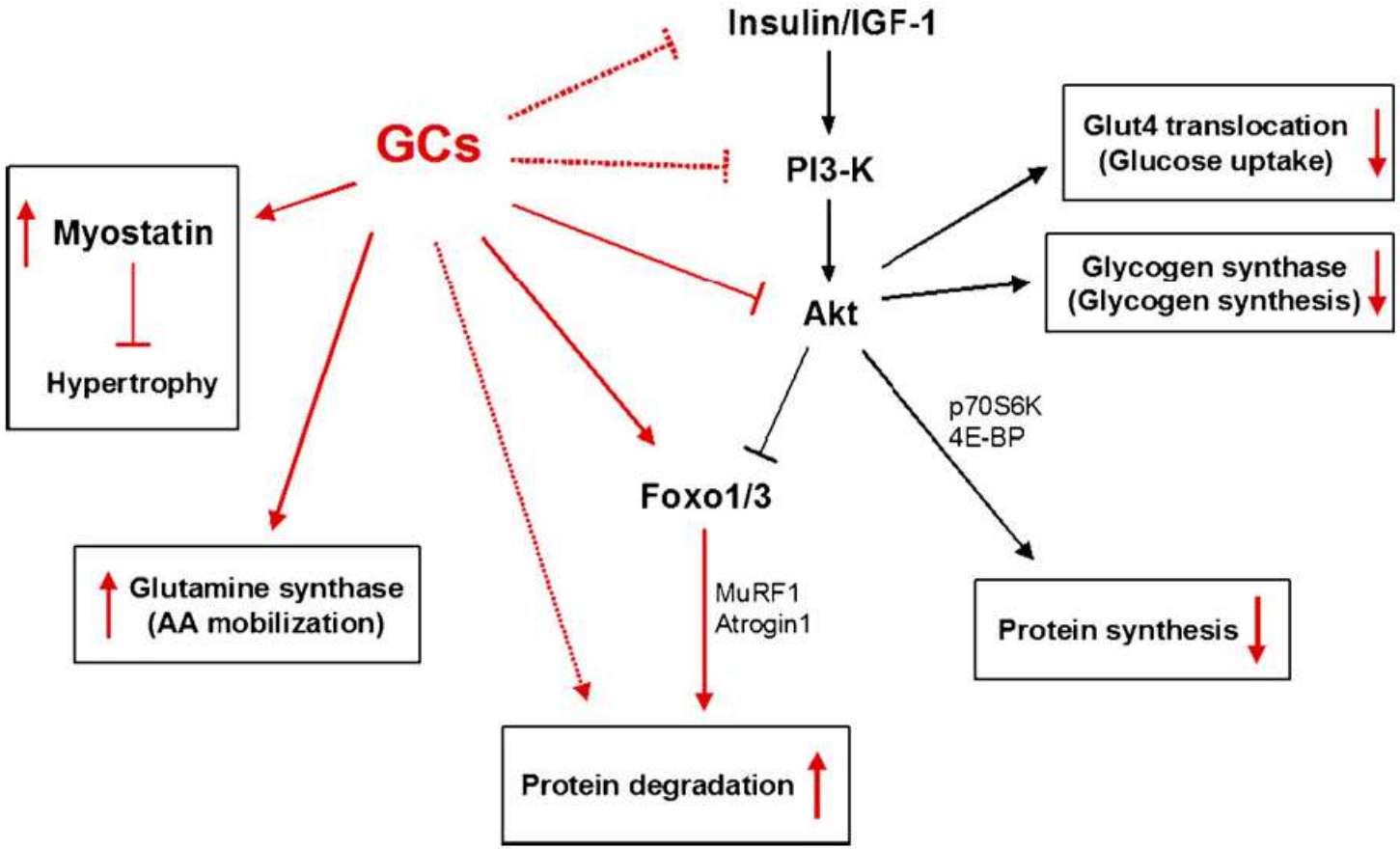
Pivonello et al., Neuroendocrinology 2010

Glucocorticoid-induced effects on glucose and protein metabolism in skeletal muscle tissue.

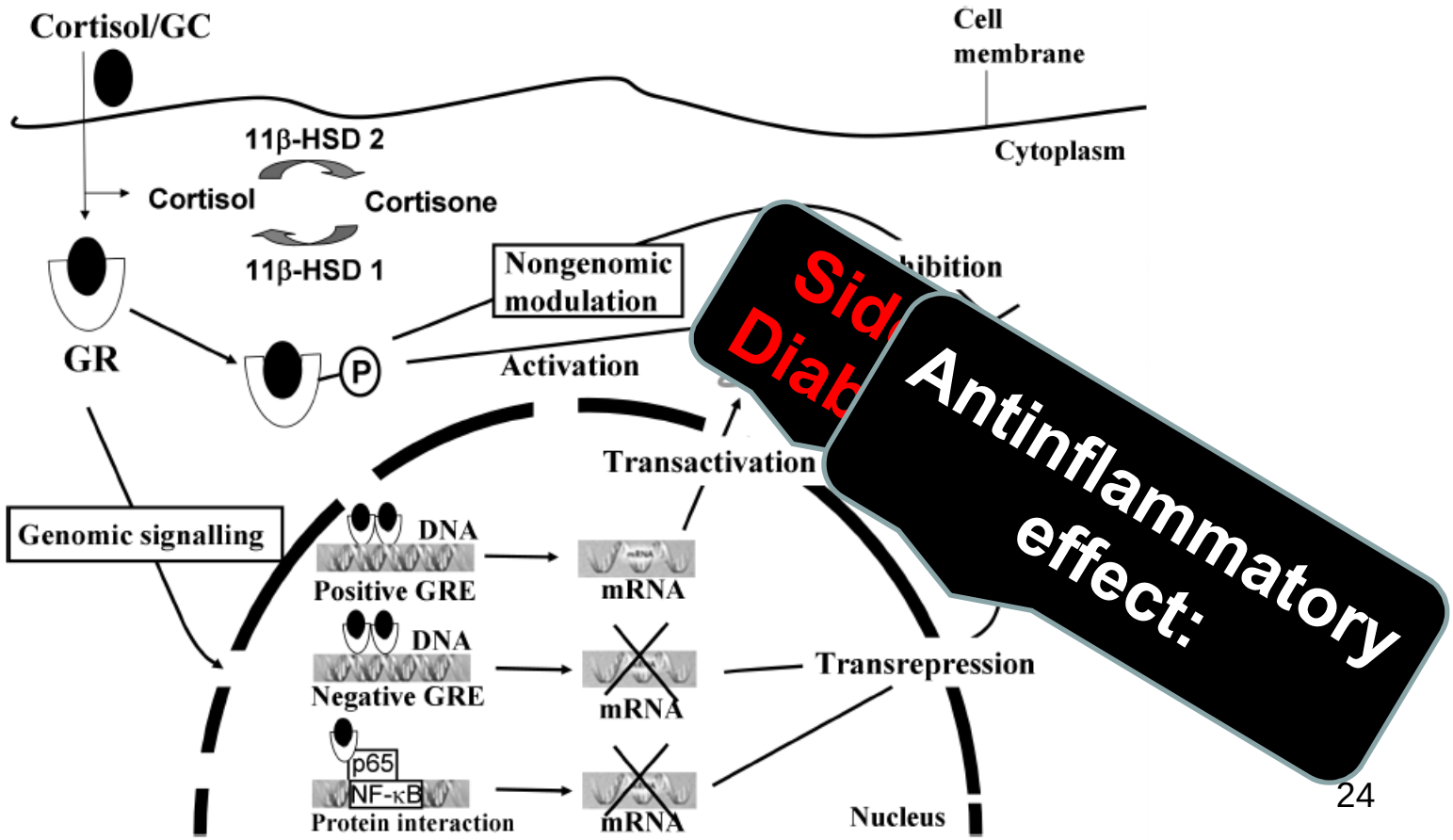


Van Raalte DH, European Journal of Clinical Investigation, 2009

GC action on skeletal muscle

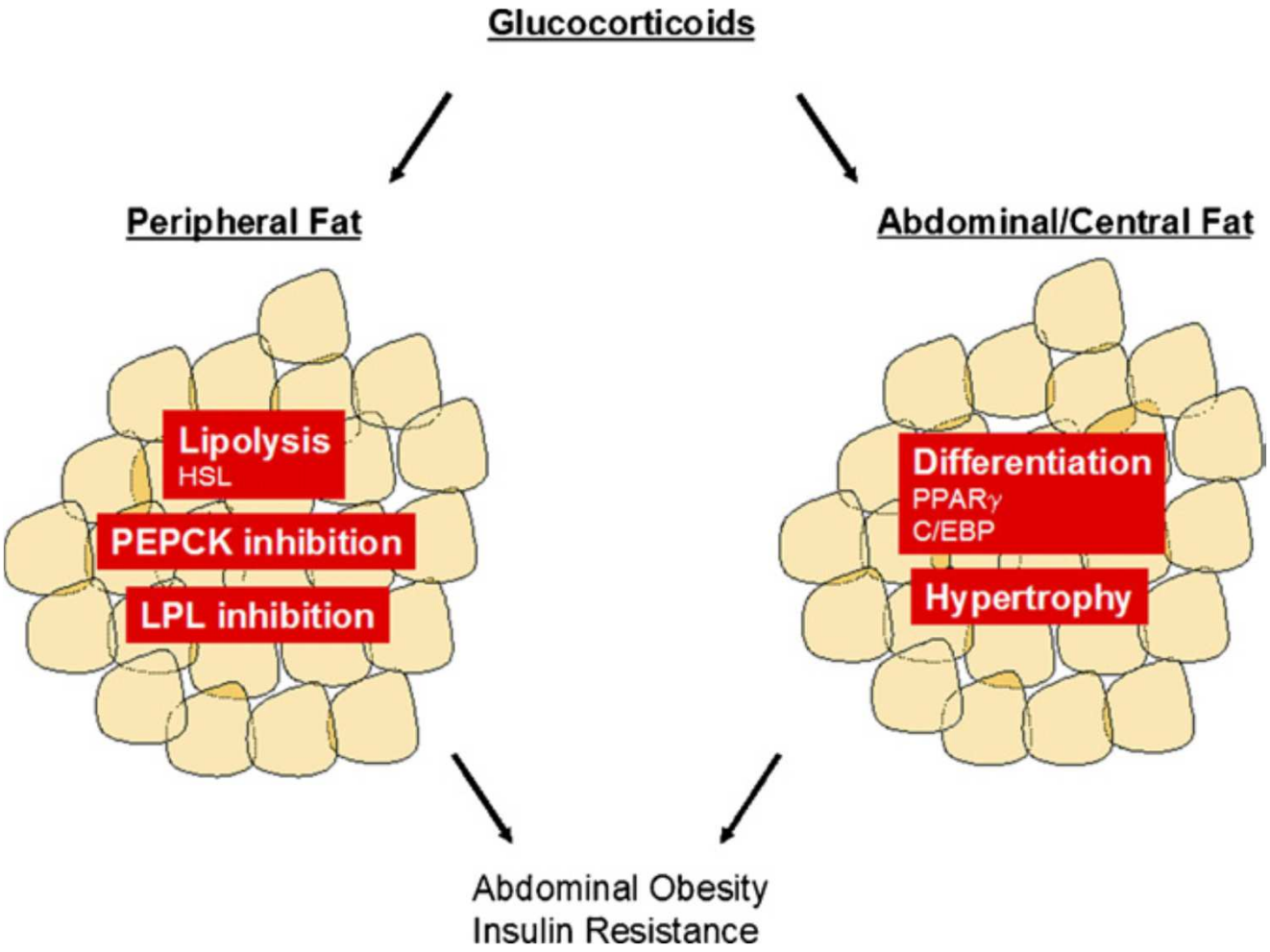


Molecular mechanisms of GR action
GCs regulate protein activity both by genomic and non-genomic pathways



Van Raalte DH, European Journal of Clinical Investigation, 2009

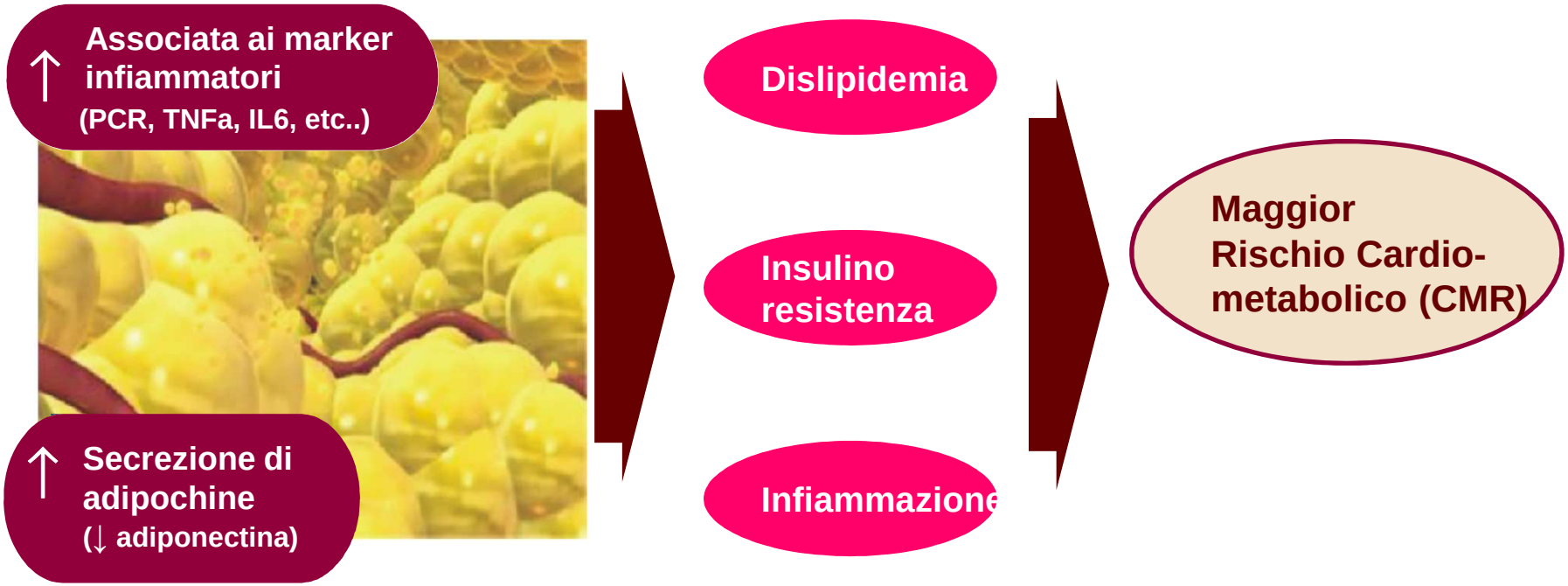
Tessuto adiposo



Molecular and Cellular Endocrinology 275 (2007) 43–61

Rischio Cardiometabolico globale
Ruolo del tessuto adiposo
nella genesi del Diabete Mellito tipo 2

L'adiposità intra-addominale è uno degli elementi che contribuisce maggiormente all'aumento del rischio cardiometabolico



Gelfand EV et al, 2006; Vasudevan AR et al, 2005

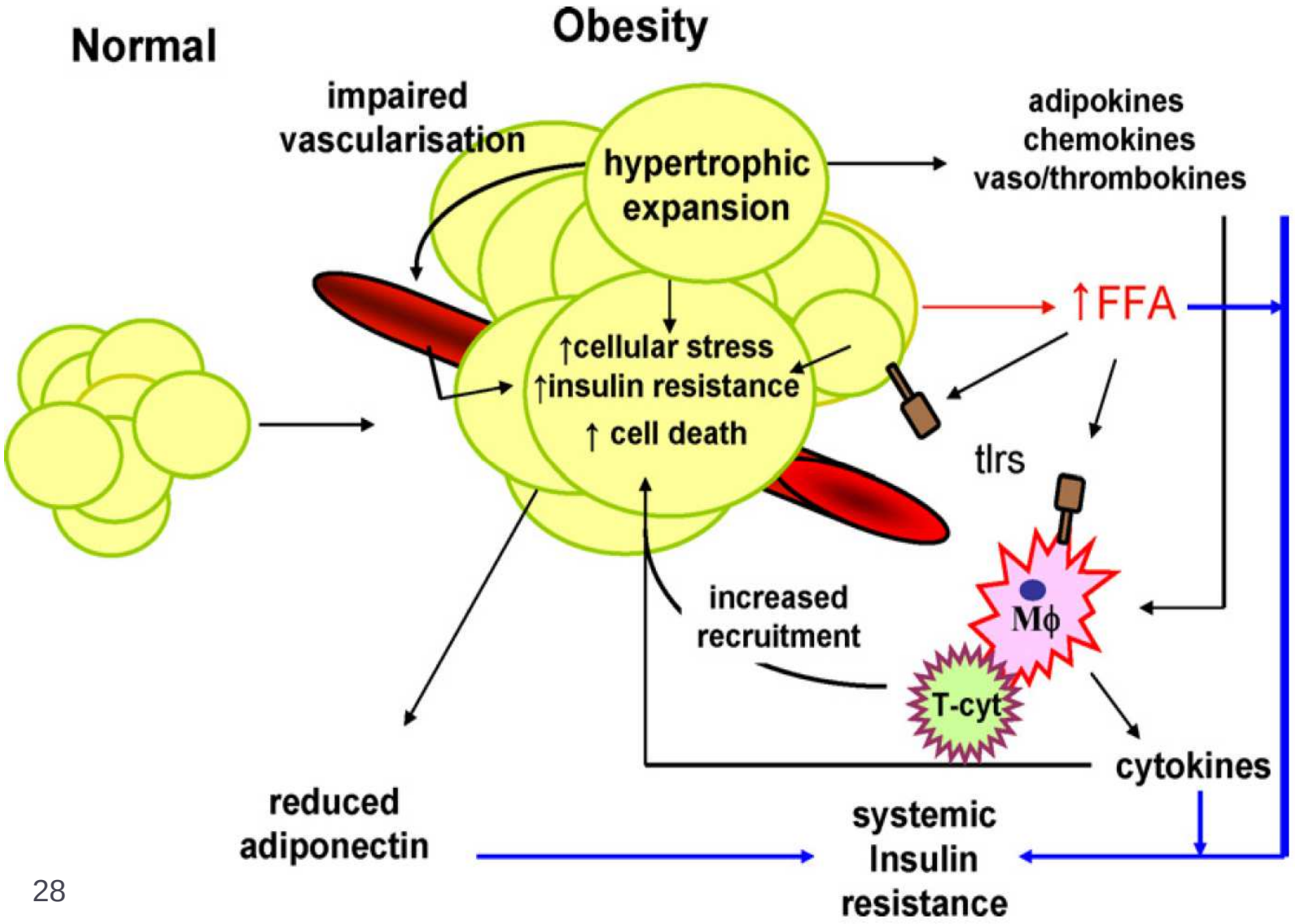
Adipokine patterns in CD

Adipokines	Pattern in active CS patients vs. BMI-matched controls	Pattern in CS after correction of hypercortisolism	
		change of levels vs. baseline	postsurgery time
Leptin	Increased [56–58, 62] Increased only in men [60] Unchanged [63]	Unchanged [58] Decreased [60, 63, 68]	10 days 9–36 months
Adiponectin	Decreased in non-obese; no difference in obese CD vs. non-obese [87] Unchanged [63, 89, 90]	Unchanged [63, 89, 90]	9–132 months
Resistin	Increased in females [63]	Unchanged [63]	9 months
TNF-α	Unchanged [68, 129, 130] Increased sTNF-R1 [90]	Increased in hypoadrenal patients [129] Increased sTNF-R1 vs. BMI-matched controls [90]	10 days 132 ± 72 months
IL-6	Unchanged [129, 130]	Increased in hypoadrenal patients [129] Increased vs. BMI-matched controls [90]	10 days 132 ± 72 months
Angiotensinogen	Increased expression of Ang II receptor 1A [166]	Not known	
PAI-1	Increased [172] Increased although not significantly [173]	Decreased vs. controls [173]	9 months
Ghrelin	Decreased [89] Increased; similar to controls with lower BMI [192]	Increased [89, 191]	3–24 months

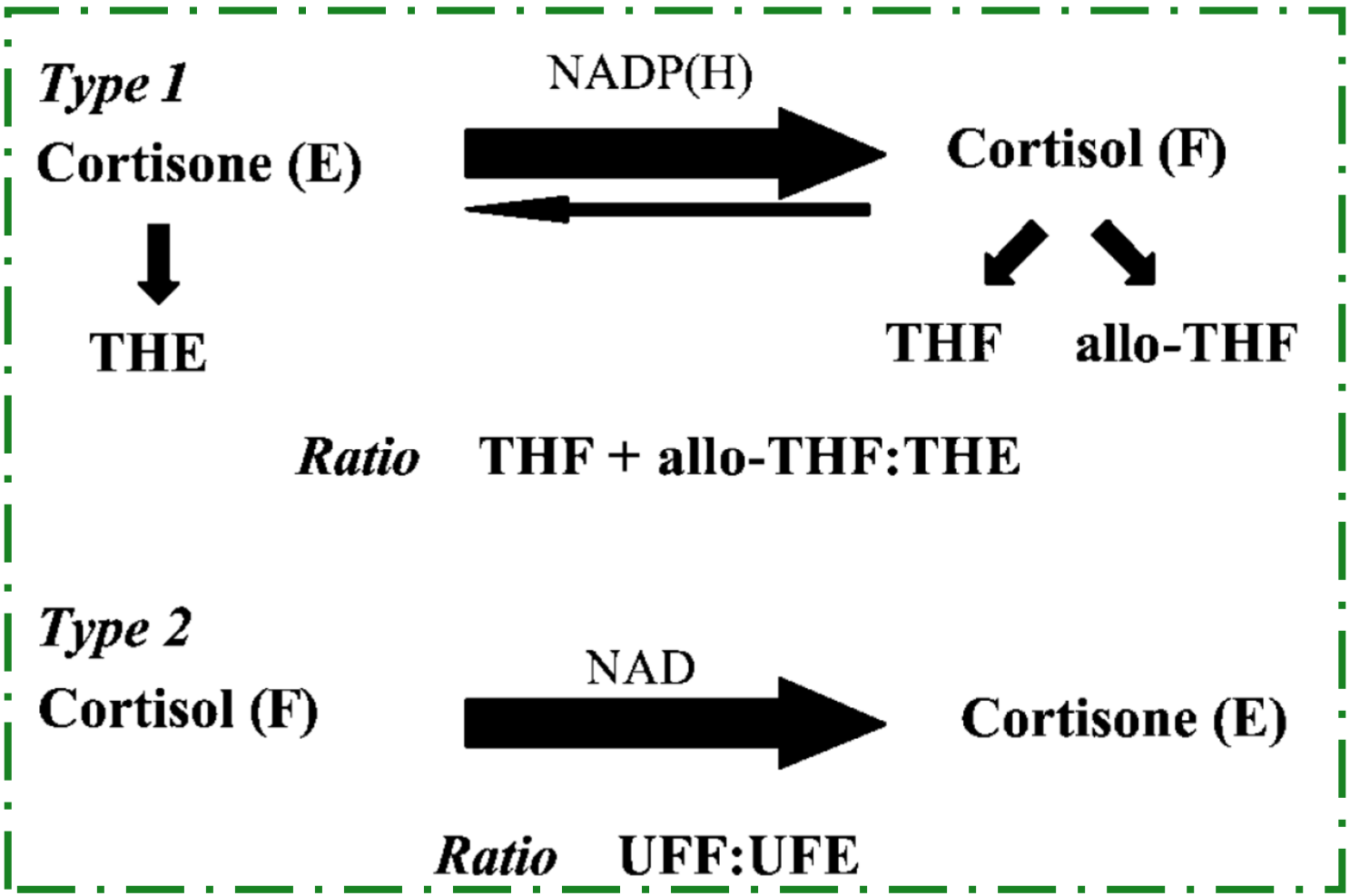
sTNF-R1 = Soluble TNF-α receptor.

Valassi et al.,Neuroendocrinology 2012;95:187–206

Metabolic consequences of adipose tissue hypertrophy in obesity



Two isoforms of 11b-hydroxysteroid dehydrogenase catalyse the interconversion of cortisol (F) to cortisone (E)



THE LANCET

Does central obesity reflect “Cushing’s disease of the omentum”?

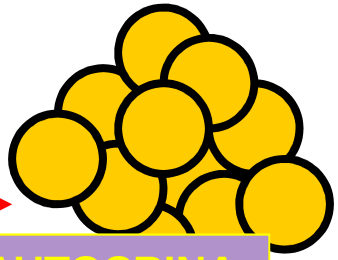
Iwona J Bujalska, Sudhesh Kumar, Paul M Stewart

Lancet 1997; 349: 1210–13

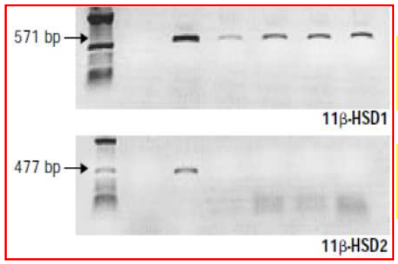
omental adipose stromal cells

subcutaneous adipose stromal cells

INSULINA
CORTISOLO



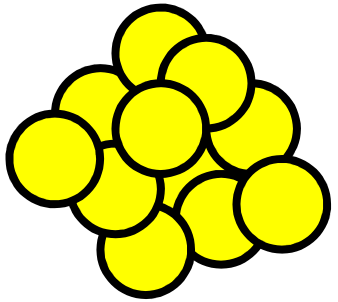
ESPRESSIONE AUTOCRINA



11βHSD- 1 **+**

11βHSD- 2 **-**

CORTISONE → **CORTISOLO**



11βHSD- 1 **+**

11βHSD- 2 **-**

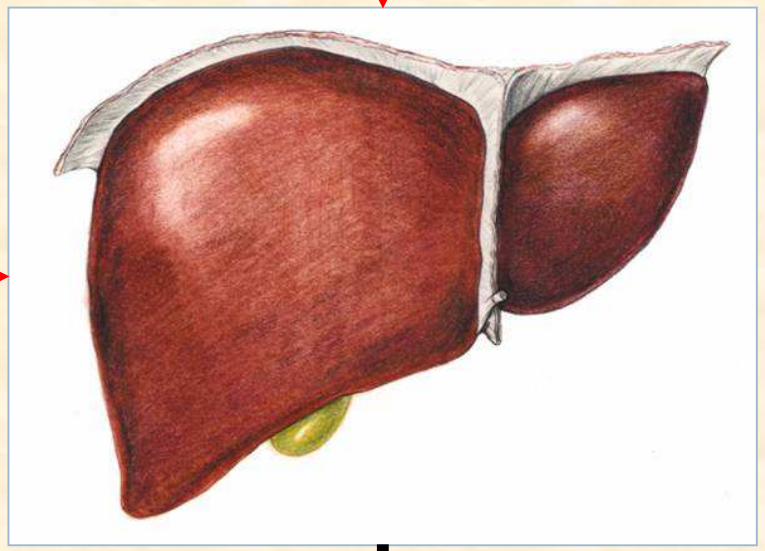
CORTISONE ← **CORTISOLO**

The "intracellular" Cushing state

Visceral obesity

TNF-alfa

IL-1 beta

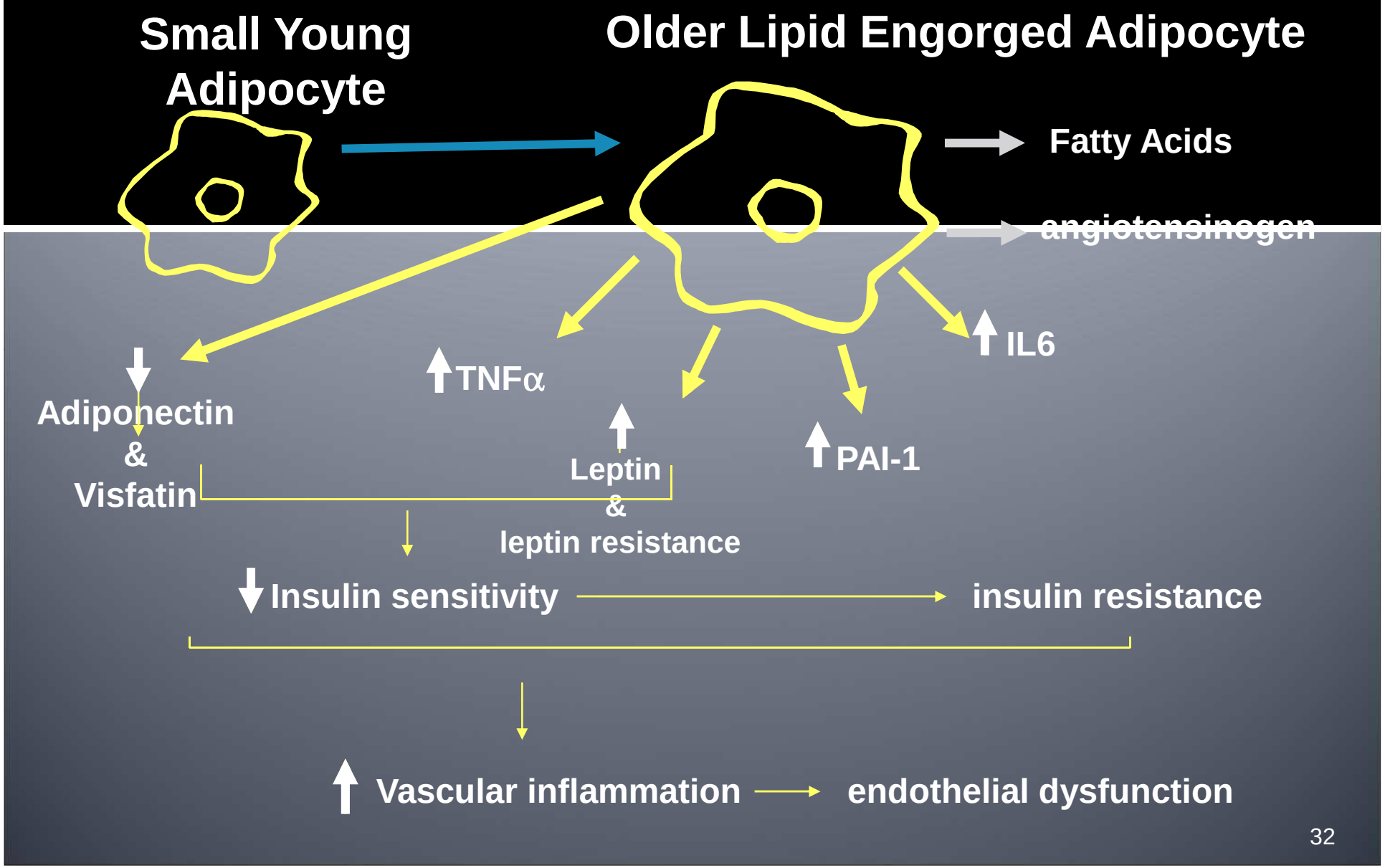


Insulin-resistance

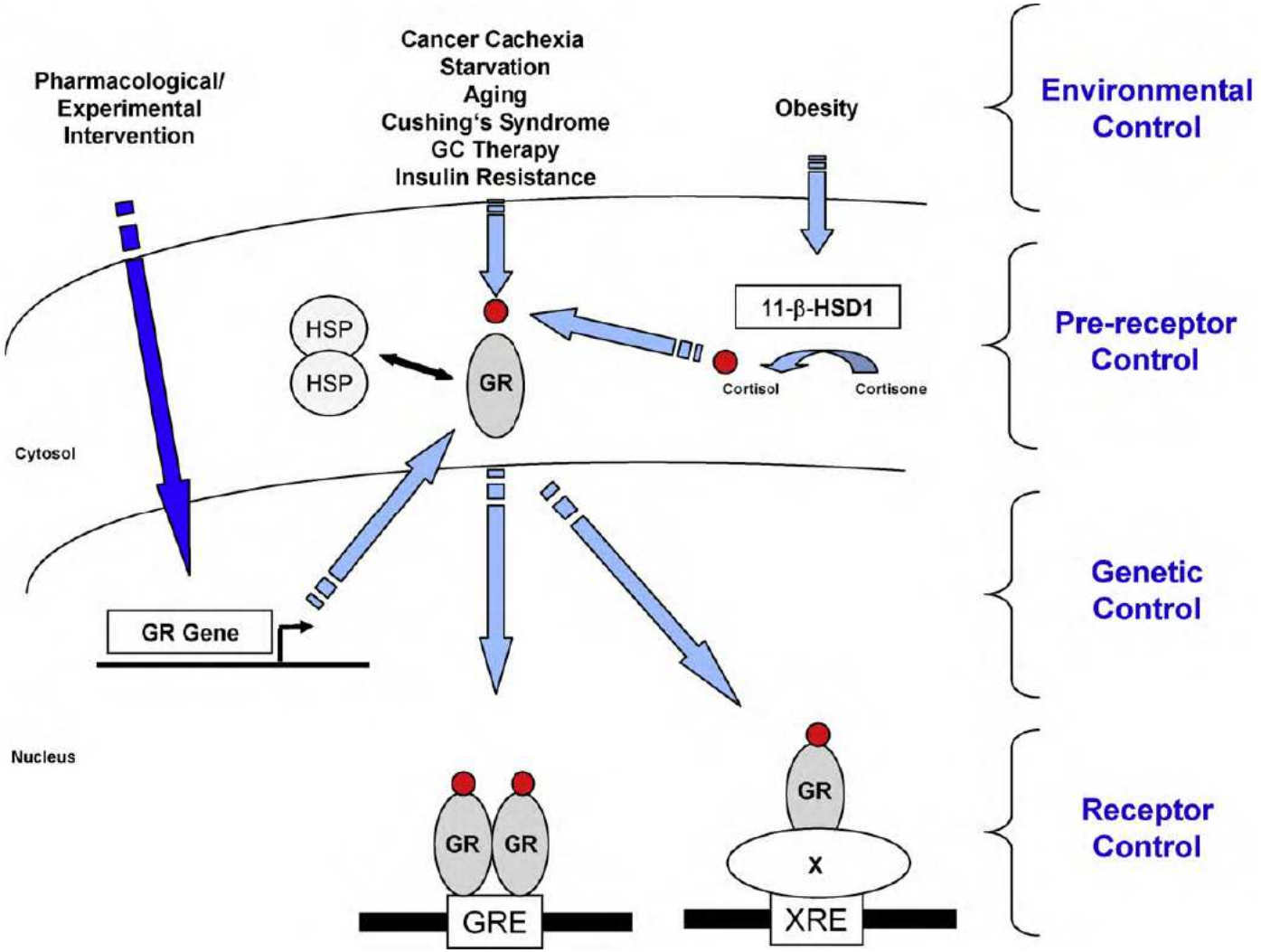
Active Cortisol

11βHSD- 1

Adipokines mediate insulin resistance and inflammation



Physiological, cellular and molecular regulation of the glucocorticoid receptor

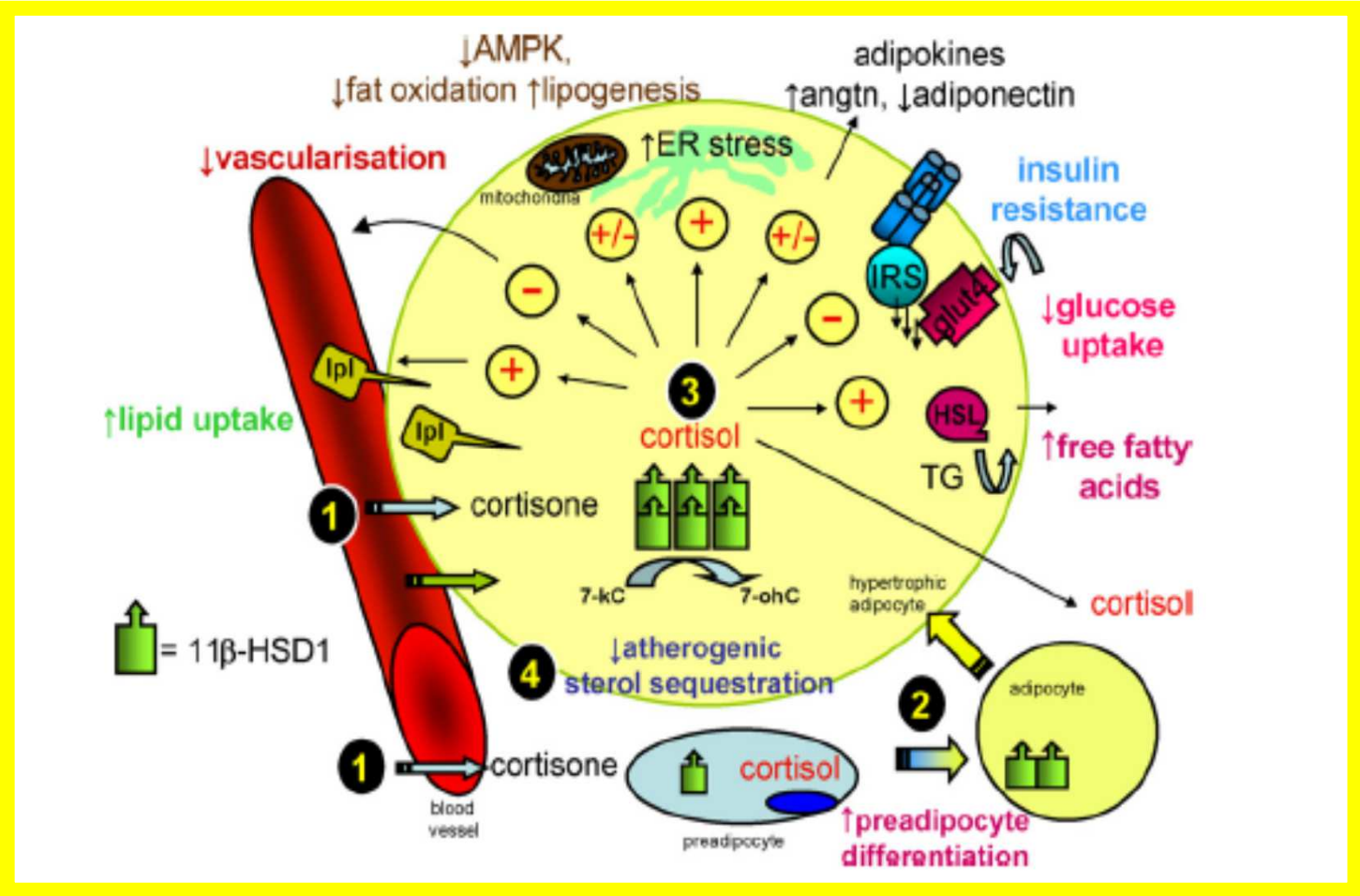


Molecular and Cellular Endocrinology

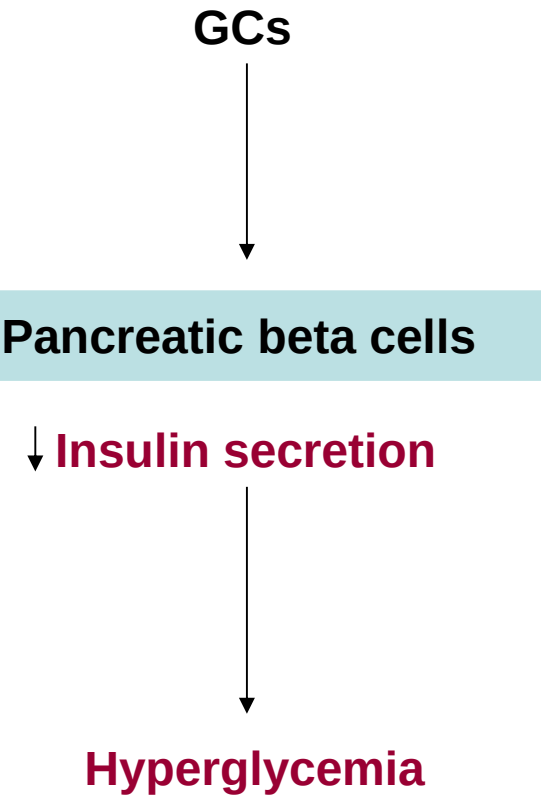
Obesity and corticosteroids: 11β-Hydroxysteroid type 1 as a cause and therapeutic target in metabolic disease

Nicholas Michael Morton*

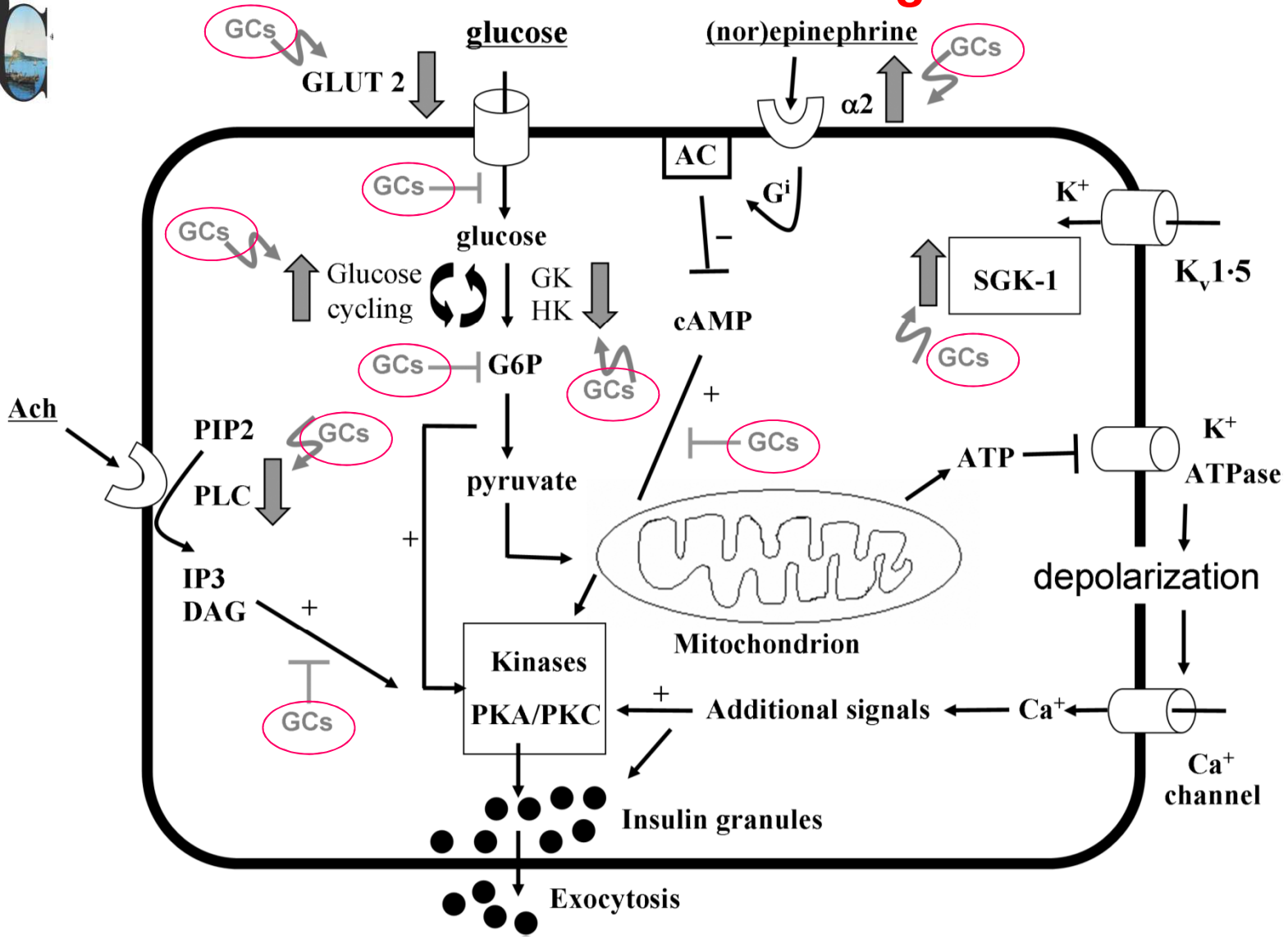
Molecular and Cellular Endocrinology 316 (2010) 154–164



Cushing & insulino-secrezione



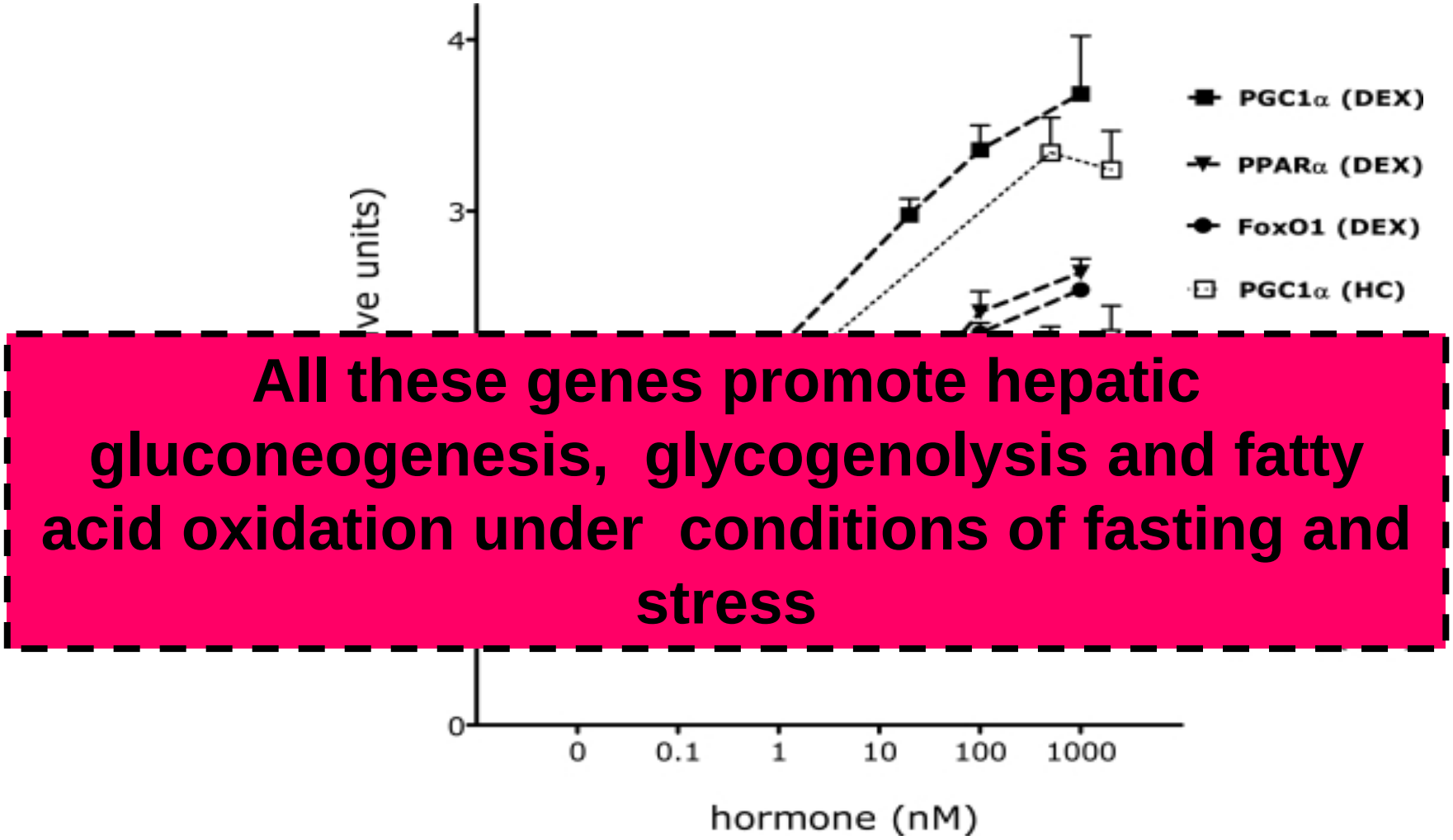
Secrezione insulinica nelle beta cellule pancreatiche e modello di interferenza dei glucocorticoidi



Van Raalte DH, European Journal of Clinical Investigation , 2009

β cell gene expression

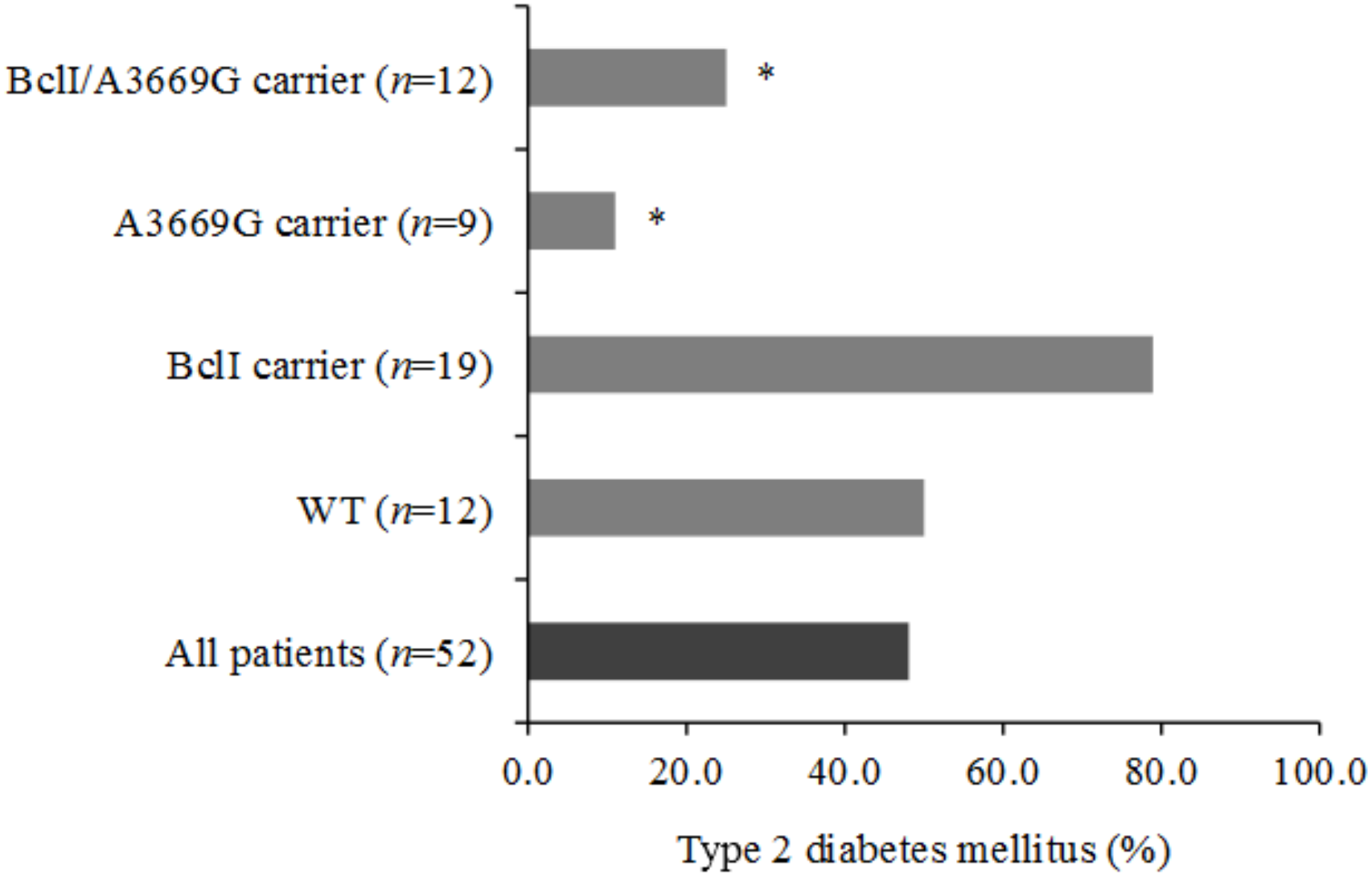
Dose-dependent effects of PRL and glucocorticoids (DEX and Hydrocortisone) on gene expression in INS-1 cells.



All these genes promote hepatic gluconeogenesis, glycogenolysis and fatty acid oxidation under conditions of fasting and stress

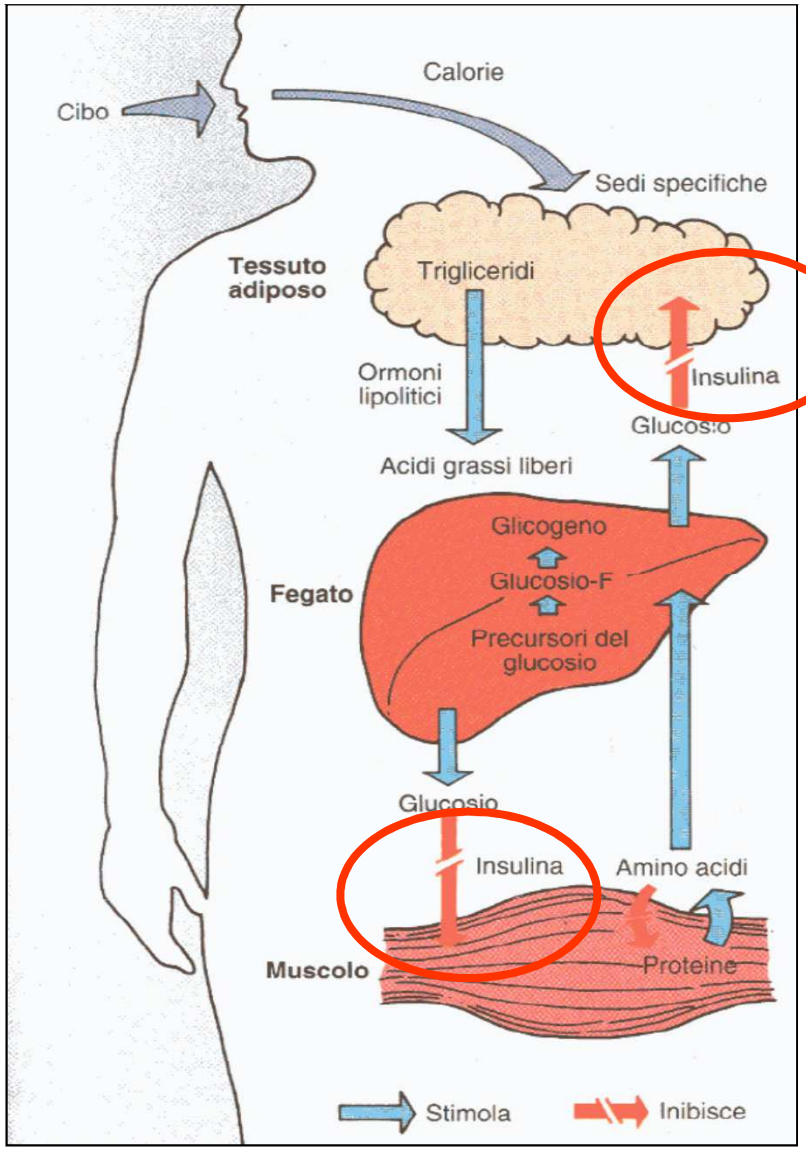
Arumugam R. et al. Endocrinology, 2008

Diabete Mellito e Cushing



Trementino L et al. EJE 2012

Ipercortisolismo & sindrome metabolica: una coppia "esplosiva"



Altogether to Beat Cushing's Syndrome

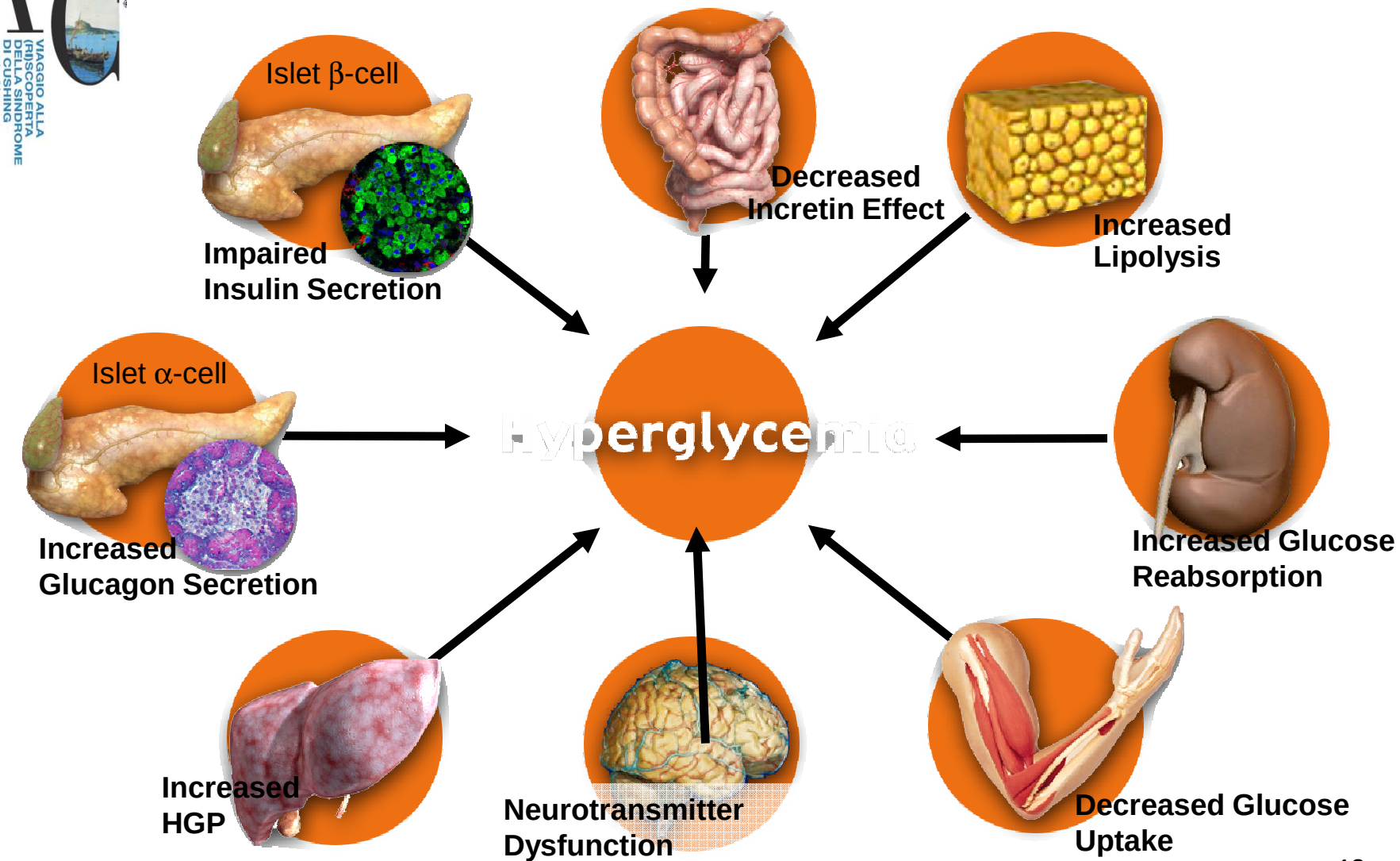
ABC

VIAGGIO ALLA (RI)SCOPERTA DELLA SINDROME DI CUSHING

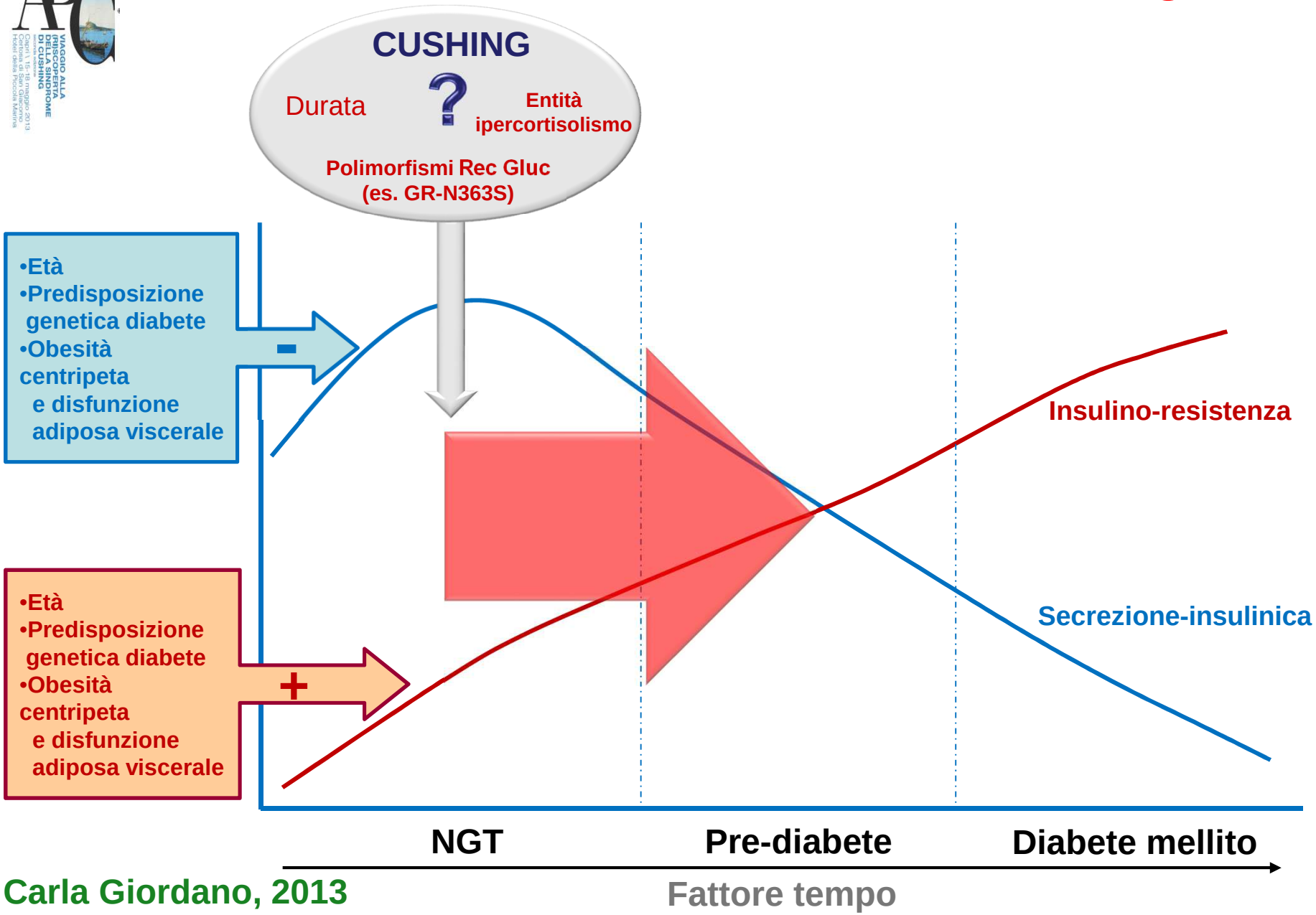
Altogether to Beat Cushing's Syndrome

VIAGGIO ALLA (RI)SCOPERTA DELLA SINDROME DI CUSHING
seconda edizione
Capri \ 15-18 maggio 2013
Certosa di San Giacomo
Hotel della Piccola Marina

8 or more actors!!!!

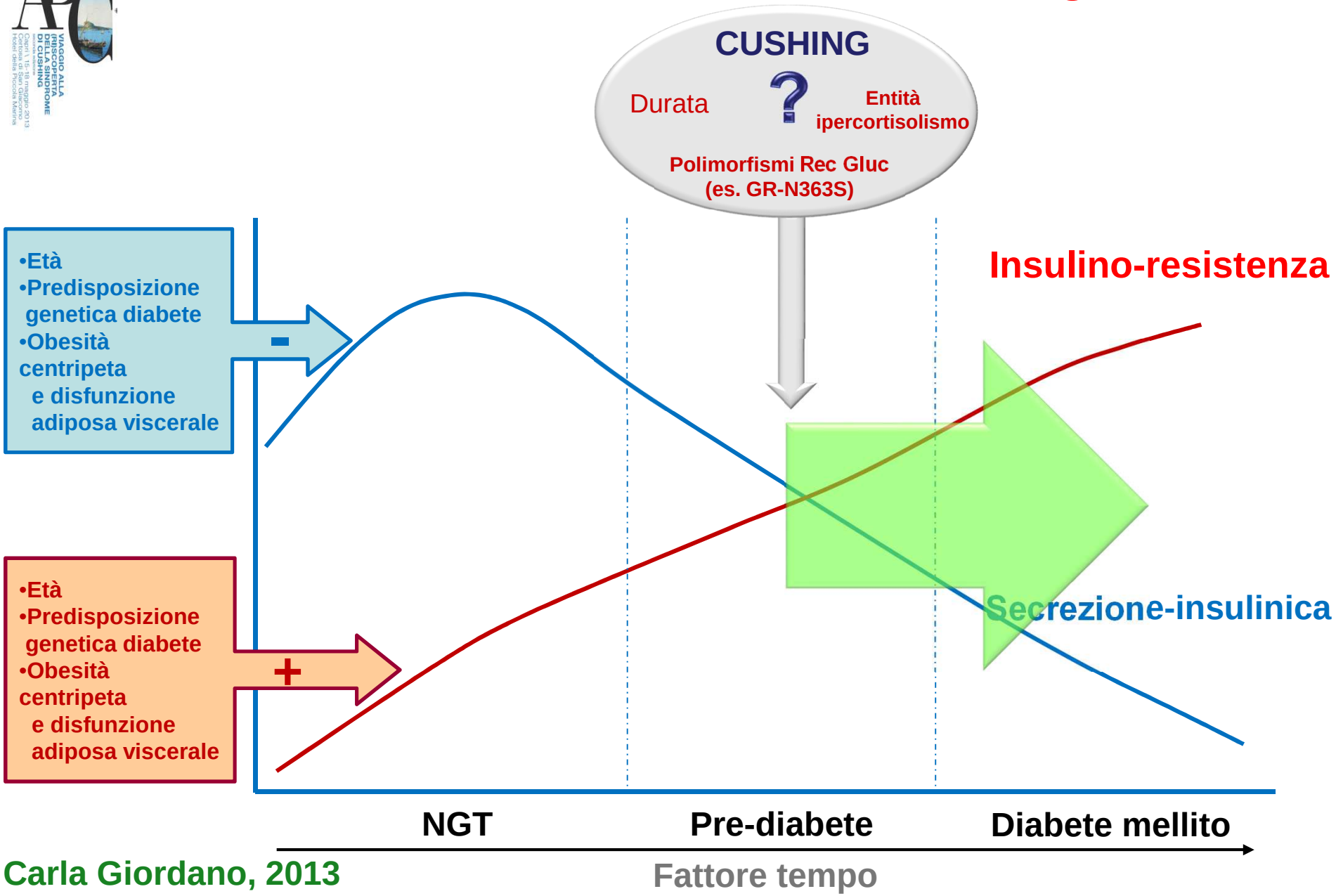


Ipotetici meccanismi fisiopatologici nella storia naturale del DM nel Cushing



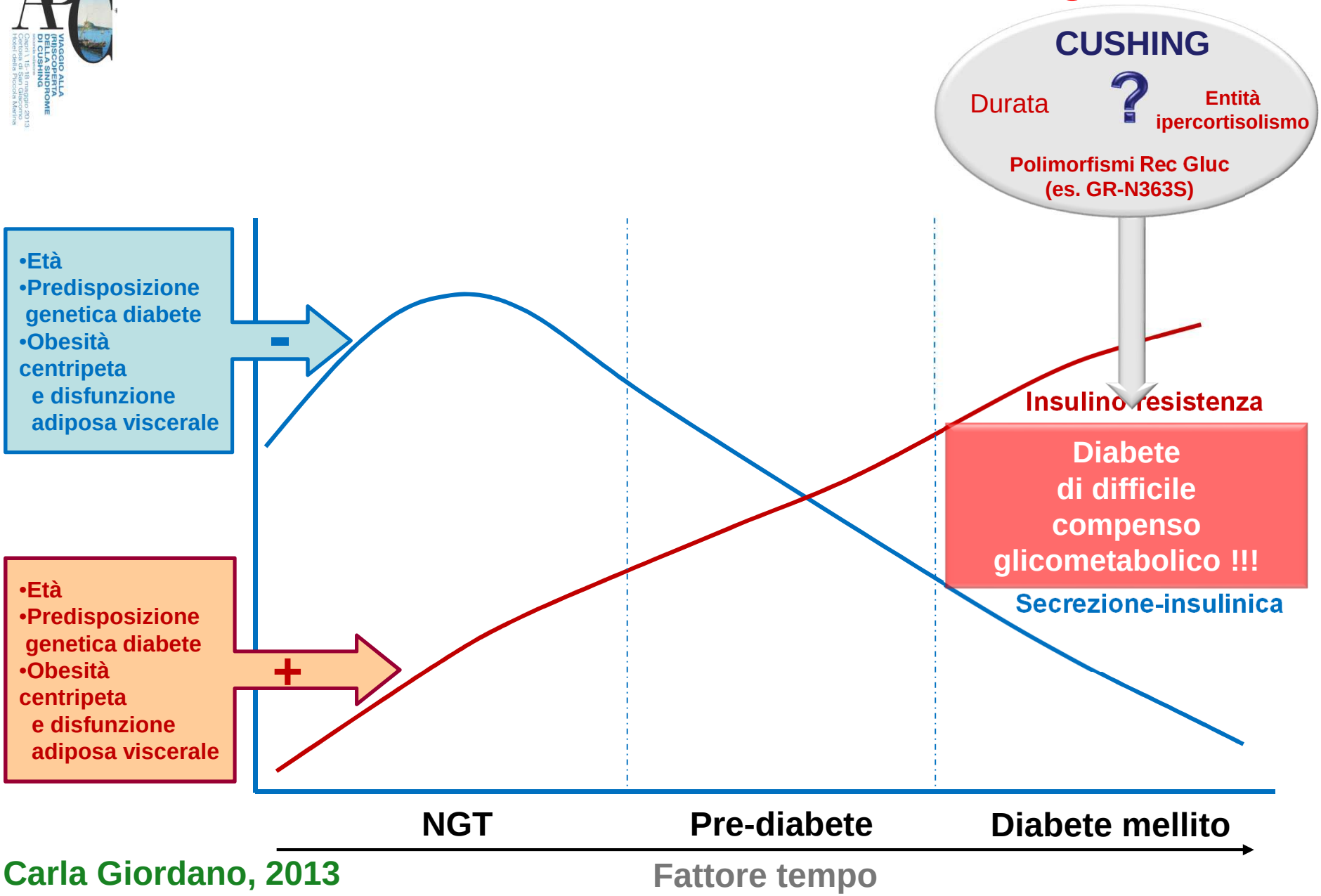
Carla Giordano, 2013

Ipotetici meccanismi fisiopatologici nella storia naturale del DM nel Cushing



Carla Giordano, 2013

Ipotetici meccanismi fisiopatologici nella storia naturale del DM nel Cushing



Carla Giordano, 2013

Grazie per la cortese attenzione

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease

Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D., for the Pasireotide B2305 Study Group*

Safety: most frequent study drug-related AEs (≥5%)

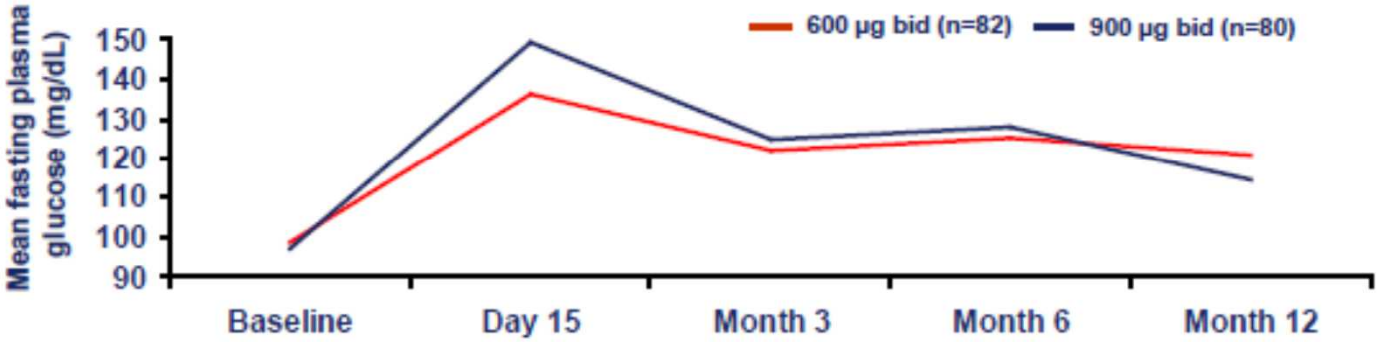
Preferred Term	Pasireotide 600µg bid N=82	Pasireotide 900µg bid N=80	Overall N=162
Diarrhea	46 (56.1)	43 (53.8)	89 (54.9)
Nausea	33 (40.2)	43 (53.8)	76 (46.9)
Hyperglycemia	31 (37.8)	32 (40.0)	63 (38.9)
Cholelithiasis	25 (30.5)	23 (28.8)	48 (29.6)
Abdominal pain	14 (17.1)	19 (23.8)	33 (20.4)
Diabetes mellitus	13 (15.9)	16 (20.0)	29 (17.9)
Fatigue	7 (8.5)	12 (15.0)	19 (11.7)
Glycosylated hemoglobin increased	10 (12.2)	7 (8.8)	17 (10.5)
Type 2 diabetes mellitus	10 (12.2)	5 (6.3)	15 (9.3)
Gamma-glutamyltransferase increased	8 (9.8)	7 (8.8)	15 (9.3)
Alanine aminotransferase increased	9 (11.0)	5 (6.3)	14 (8.6)
Decreased appetite	6 (7.3)	7 (8.8)	13 (8.0)
Headache	5 (6.1)	7 (8.8)	12 (7.4)
Lipase increased	7 (8.5)	5 (6.3)	12 (7.4)
Vomiting	2 (2.4)	8 (10.0)	10 (6.2)
Abdominal pain upper	6 (7.3)	3 (3.8)	9 (5.6)
Adrenal insufficiency	4 (4.9)	5 (6.3)	9 (5.6)
Blood glucose increased	6 (7.3)	3 (3.8)	9 (5.6)
Alopecia	4 (4.9)	5 (6.3)	9 (5.6)

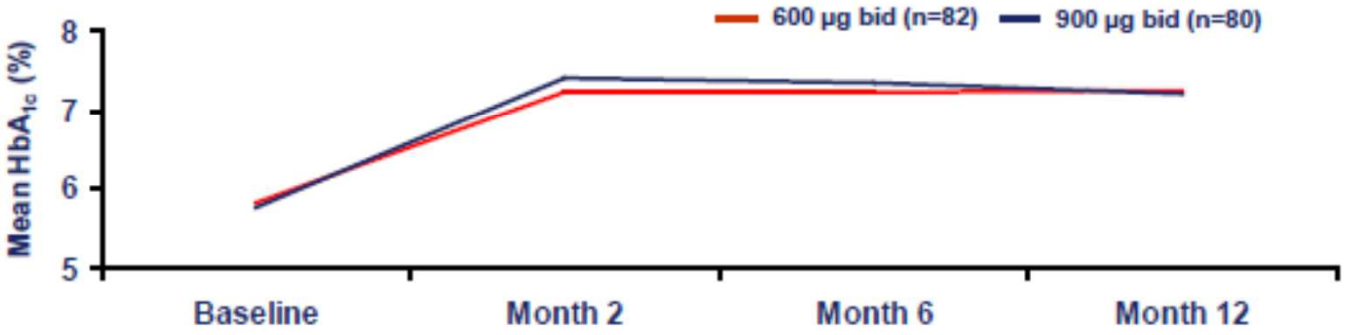
Preferred terms are presented in descending order of frequency for the overall group.
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
N = number of patients in the safety analysis set

Changes in glycemia

Visit	Pasireotide 600µg bid (N=82) n		Pasireotide 900µg bid (N=80) n	
Mean fasting plasma glucose (mg/dL)				
Baseline	79	98.6	77	97.1
Day 15	78	136.0	76	149.2
Month 3	69	122.0	66	124.7
Month 6	57	125.1	55	128.0
Month 12	39	120.9	38	114.4
Mean HbA1c (%)				
Baseline	78	5.83	76	5.76
Month 2	73	7.24	66	7.41
Month 6	59	7.24	56	7.34
Month 12	40	7.25	38	7.21

Changes in glycemia





There were no events of diabetic ketoacidosis or hyperosmolar coma

Changes from baseline in diabetes status

Baseline	Changes from baseline to last assessment, n (%)			
	Normal	Pre-diabetic	Diabetic	Missing
Normal (n=67)	14 (21)	29 (43)	23 (34)	1 (1.5)
Pre-diabetic (n=39)	1 (3)	9 (23)	28 (72)	1 (3)
Diabetic (n=55)	1 (2)	6 (11)	47 (85)	1 (2)
Missing (n=1)	1 (100)	0	0	0

Patients with pre-diabetes had a higher risk of developing diabetes
Patients with diabetes at baseline had a greater increase in glucose and HbA1c

Role of somatostatin in glucose metabolism

- Somatostatin is an inhibitor of both insulin and glucagon secretion[1]
  - Binds with high affinity to the five somatostatin receptor subtypes[2]
  - sst_2 and sst_5 are the predominantly expressed subtypes in human pancreatic islet cells
- Inhibition of insulin is mediated mainly by sst_2 and sst_5 in humans[3,4]
- Inhibition of glucagon is mediated almost entirely by sst_2[5,6]
- Pasireotide is a multireceptor-targeted somatostatin analogue with high binding affinity for $sst_{1–3}$ and sst_5

[1]Hauge-Evans AC *et al. Diabetes* 2009;58:403–411; [2]Patel YC. *Front Neuroendocrinol* 1999;20:157–198; [3]Fagan SP *et al.* Surgery 1998;124:254–258; [4]Zambre Y *et al. Biochem Pharmacol* 1999;57:1159–1164; [5]Singh V *et al.* J *Clin Endocrinol Metab* 2007;92:673–680; [6]Singh V *et al. Endocrinology* 2007;148:3887–3899

Pasireotide and glucose metabolism

- The mechanisms of hyperglycemia seen with pasireotide sc at doses of 600 and 900 µg bid are related to:
  - Decreases in insulin secretion, as observed following OGTT and HCT
  - Significantly decreased incretin response, as observed following OGTT and HCT
- Pasireotide did not affect insulin sensitivity

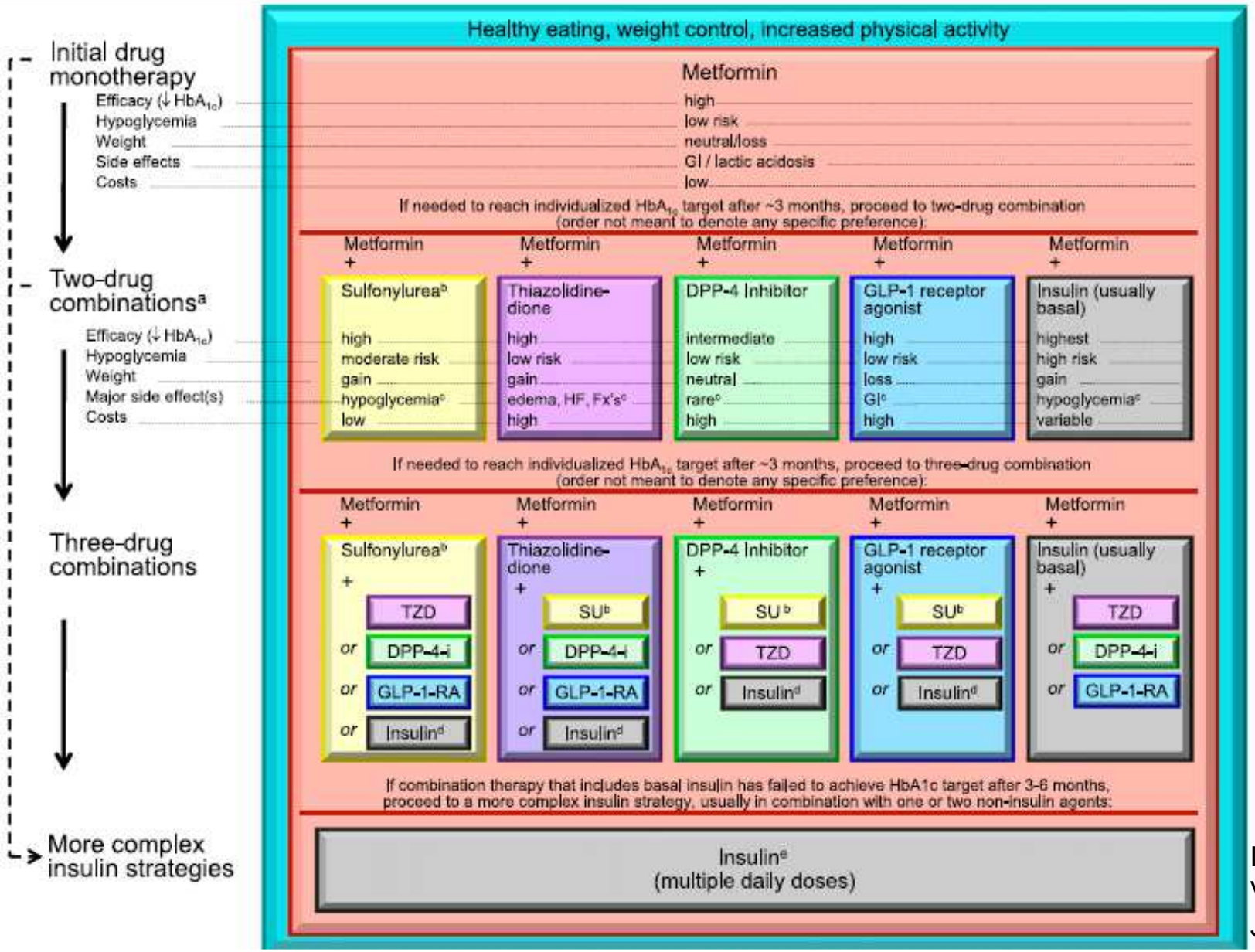
In healthy volunteers over a 7 day period:

- DPP-4 inhibitors (eg vildagliptin) and GLP-1 agonists (eg liraglutide) seemed to be the most effective drugs to ameliorate pasireotide-induced hyperglycemia
- In this study, metformin was not effective in treating the pasireotide-induced hyperglycemia

Come curare il diabete nel Cushing?

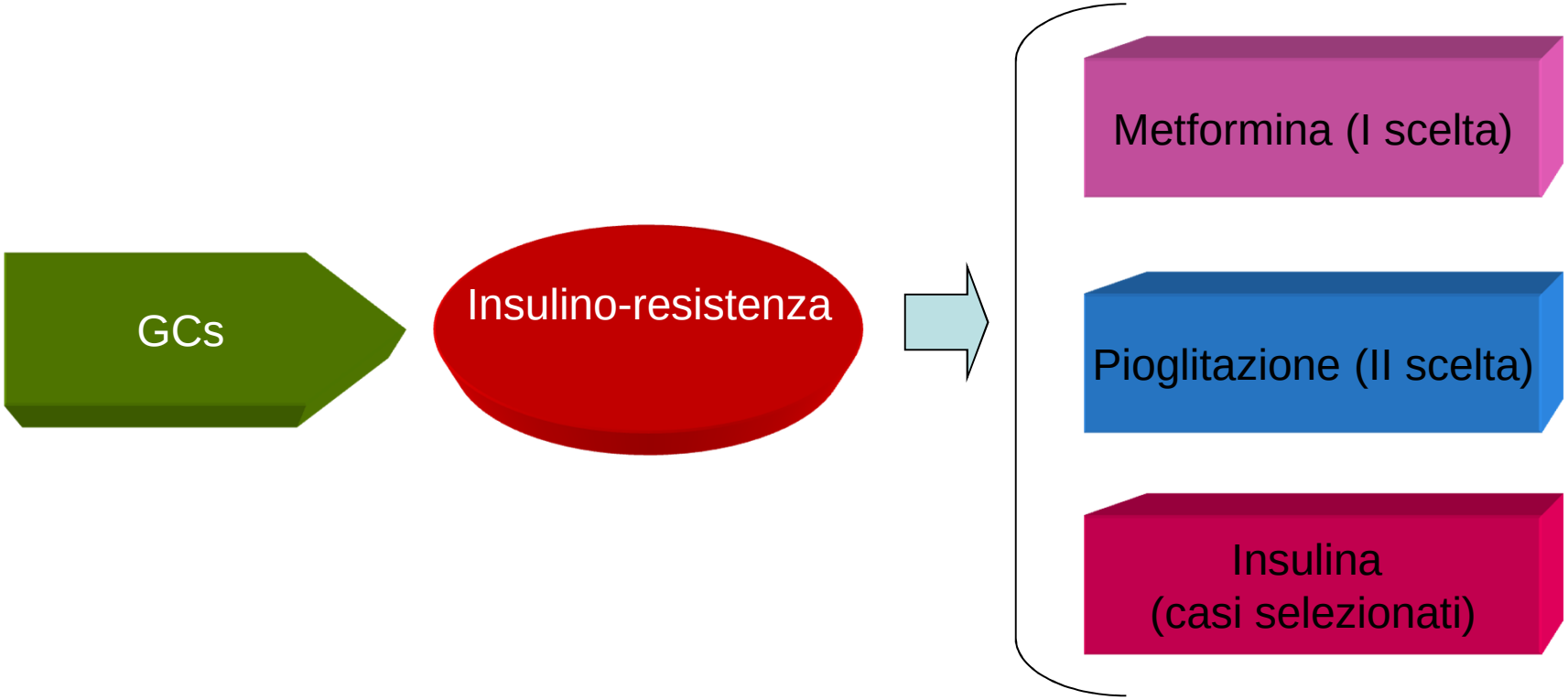
- E’ sufficiente la cura/remissione del Cushing?
- Più efficiente la terapia chirurgica o medica?
- **Occorre terapia specifica del diabete?**

Algoritmo terapia ipoglicemizzante nel DM2

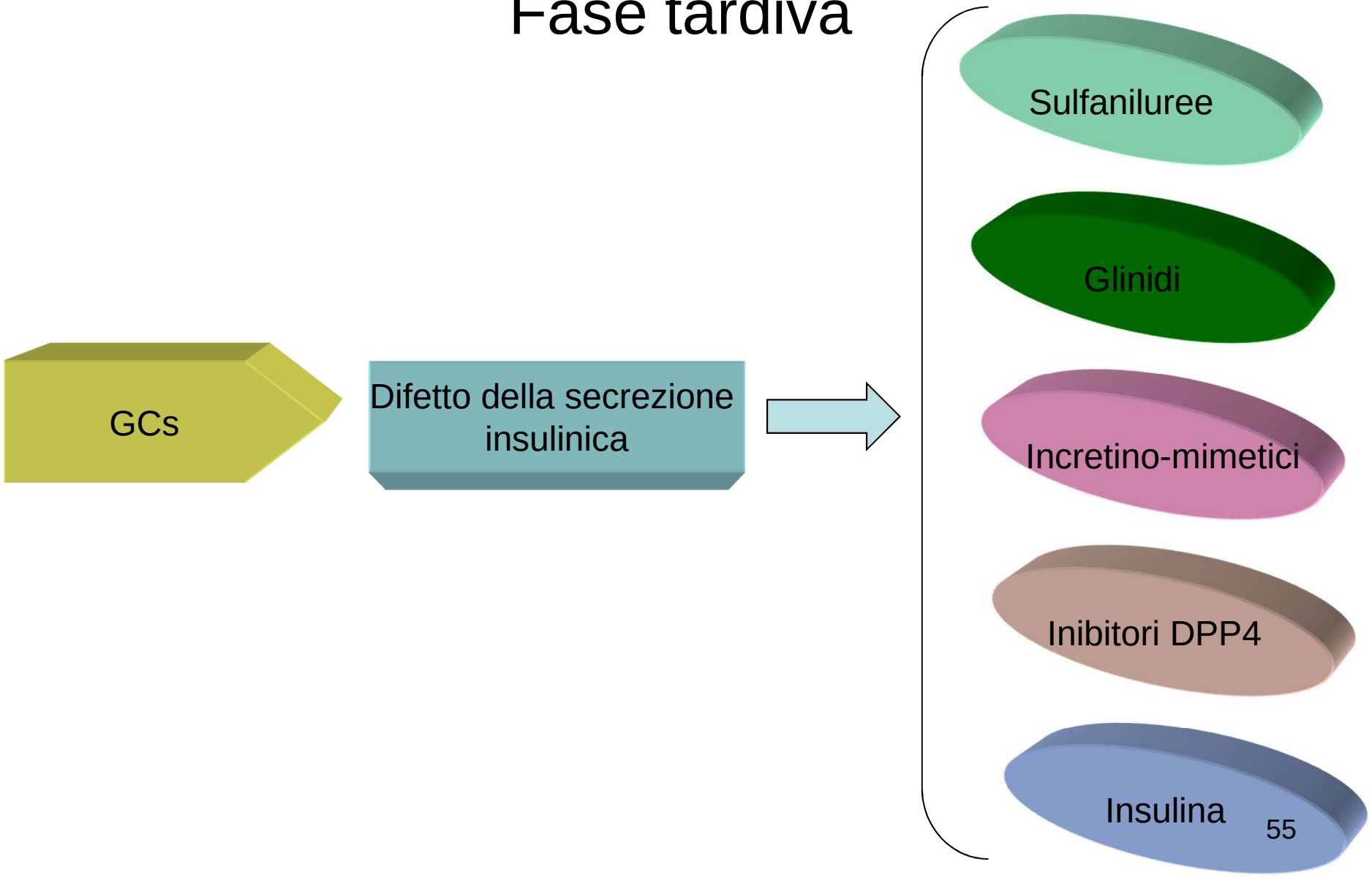


Diabetes care, Volume 35, June 2012

Trattamento del DM nel Cushing
Fase precoce



Trattamento del DM nel Cushing
Fase tardiva



11-Hydroxysteroid dehydrogenase type 1 is an important regulator at the interface of obesity and inflammation

Claudia A. Staab, Edmund Maser

Journal of Steroid Biochemistry & Molecular Biology 119 (2010) 56–72