10:30-11:30 SIMPOSIO 4

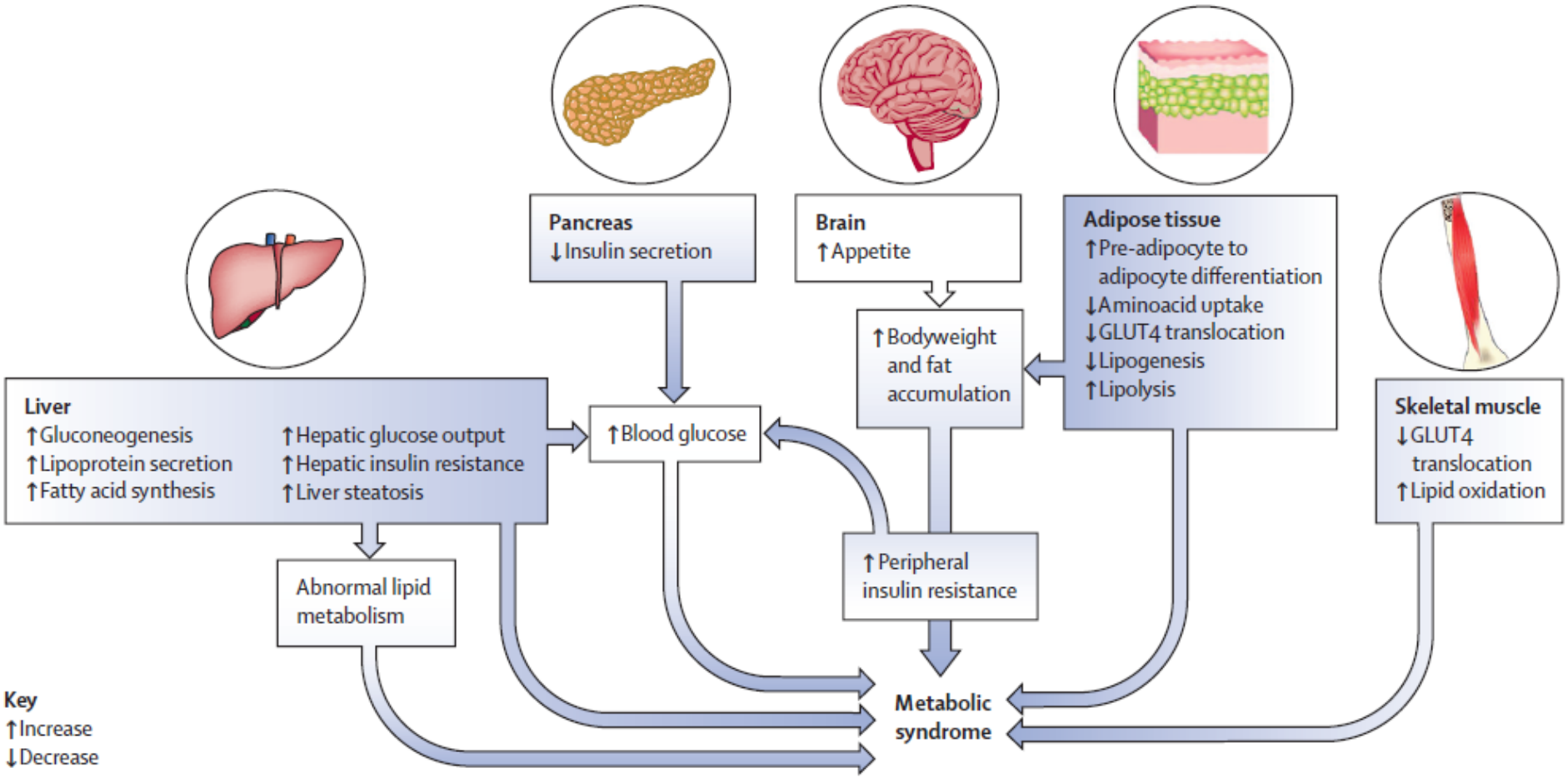
LA GUARIGIONE DALLA SINDROME DI CUSHING: EFFETTO SU COMPOSIZIONE CORPOREA E METABOLISMO

Moderatori: Renato Pasquali, Carla Giordano

IL METABOLISMO GLICIDICO E LIPIDICO

Roberta Giordano

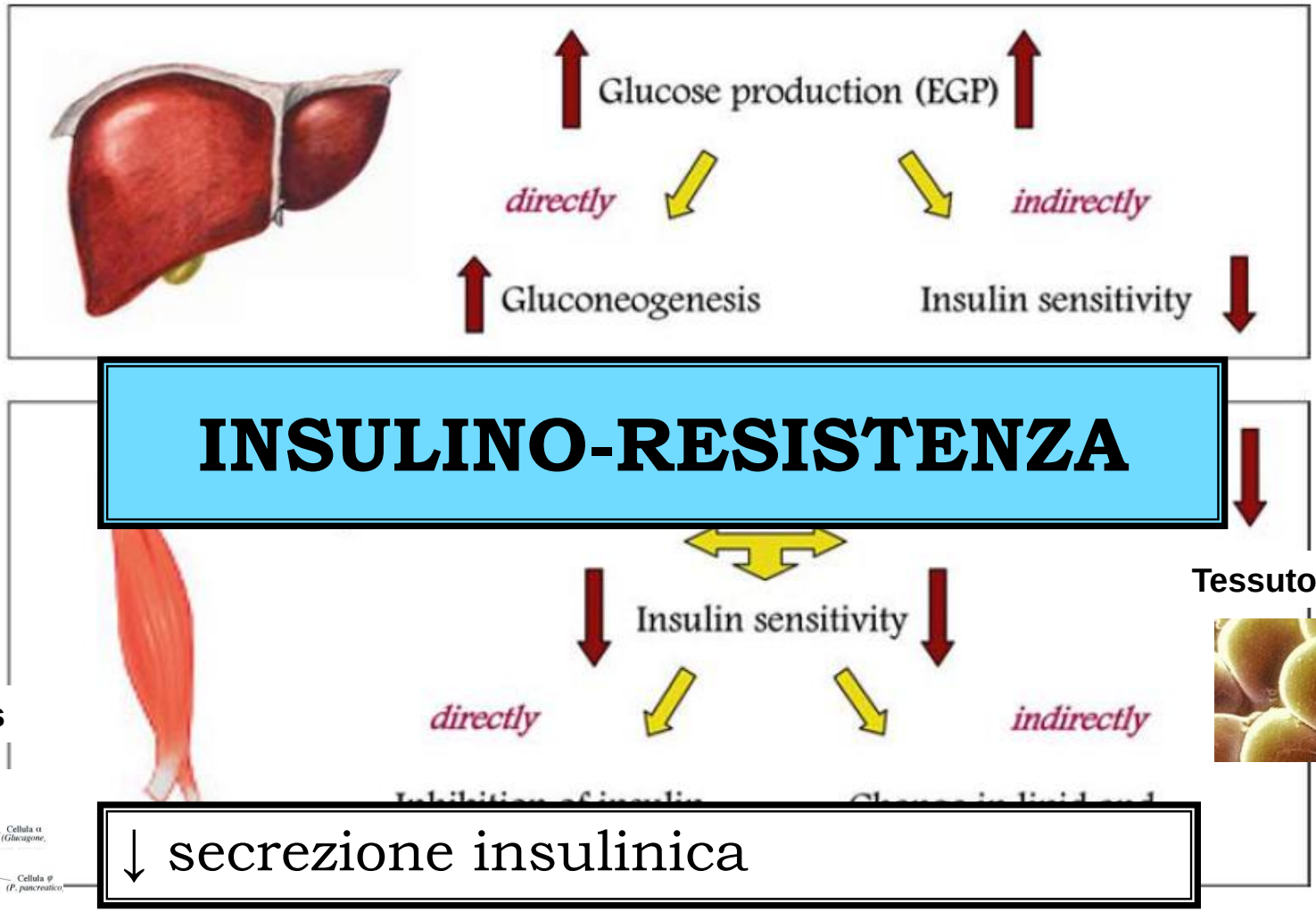
SCDU Endocrinologia, Diabetologia e Metabolismo;
Dip. Scienze Mediche; Università di Torino.



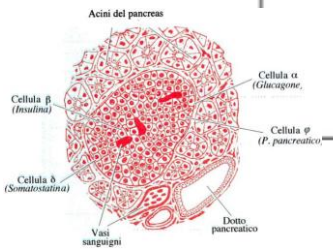
Metabolismo glicidico

Pivonello R et al., *Lancet Diabetes Endocrinol 2016; 4: 611-629*

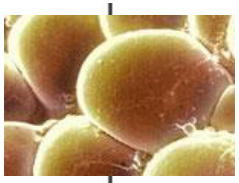
Metabolismo glicidico



Pancreas



Tessuto adiposo



Pivonello R et al., *Neuroendocrinology 2010; 92 (Suppl 1): 77-81*
Mazziotti G et al., *Trends Endocrinol Metab 2011; 22: 499-506*

Sistema incretinico ?

10 soggetti sani, prednisolone 37.5 mg/die per 12 die +physical inactivity (rest 8h/d) + hypercaloric diet

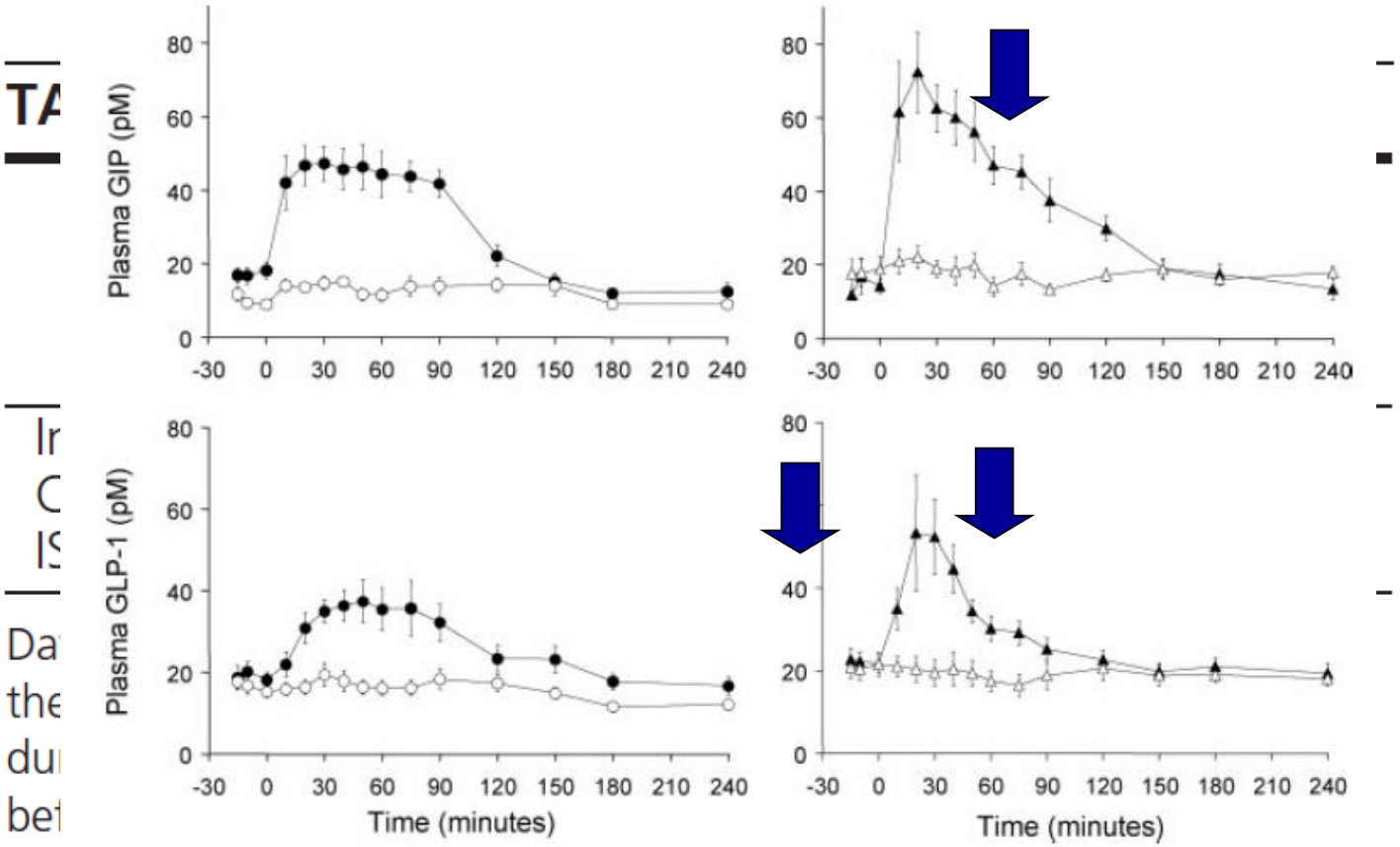
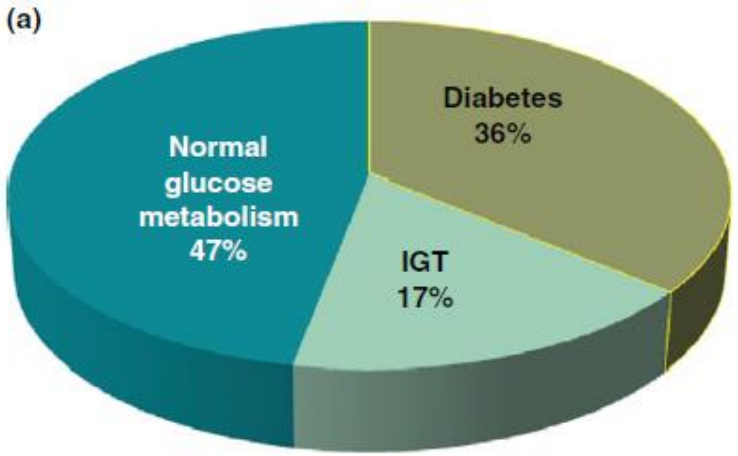


FIG. 3. Before intervention (*left*, *circles*) and after intervention (*right*, *triangles*) plasma GIP (*top*) and GLP-1 (*bottom*) concentrations in healthy subjects during a 75-g OGTT (*black symbols*) and IIGI (*white symbols*), respectively.

Hansen K et al., *J Clin Endocrinol Metab 2010; 95: 3309-3317*

s. Cushing «attiva»

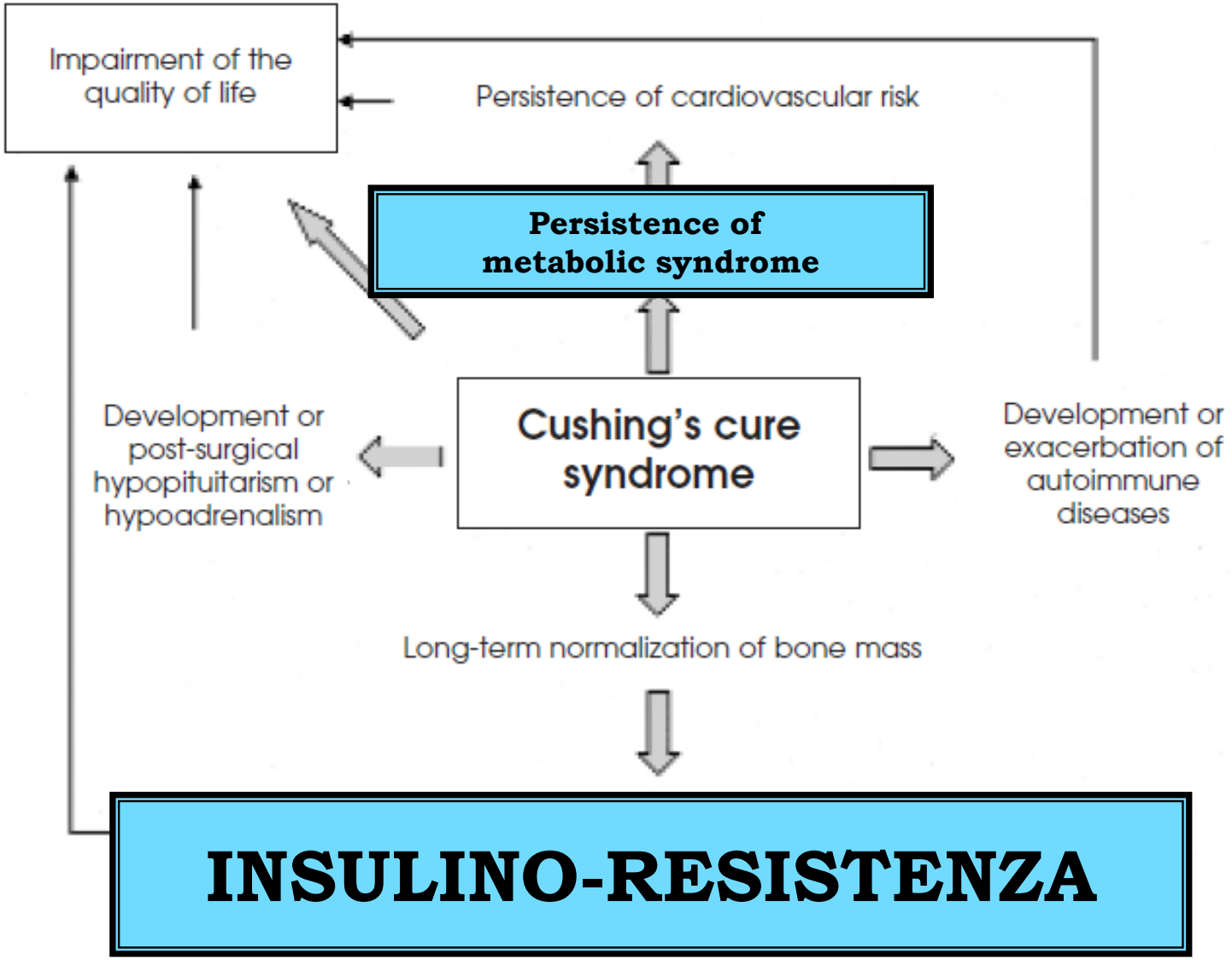


DM (11-47%)
IGT (7-64%)
IFG (6-14%)

- **Nessuna differenza tra ♀ e ♂**
- **Nessuna differenza per eziologia (>ECS)**
- **Nessuna correlazione con durata di malattia**
- **Qualche correlazione con grado di malattia**

(Mancini et al. 2004, FG e grado di ipercortisolismo)

Pivonello R et al., Neuroendocrinology 2010; 92 (Suppl 1): 77-81
Mazziotti G et al., Trends Endocrinol Metab 2011; 22: 499-506
Valassi E et al., Eur J Endocrinol 2011; 165: 383-392
Pivonello R et al., Lancet Diabetes Endocrinol 2016; 4: 61—629
Mazziotti G et al., Cur Diab Rep 2017; 17 (5): 32



Pivonello R et al., *Arq Bras Endocrinol Metab 2007; 51/8*

s. Cushing «guarita»

IGT o DM (fino 60%)

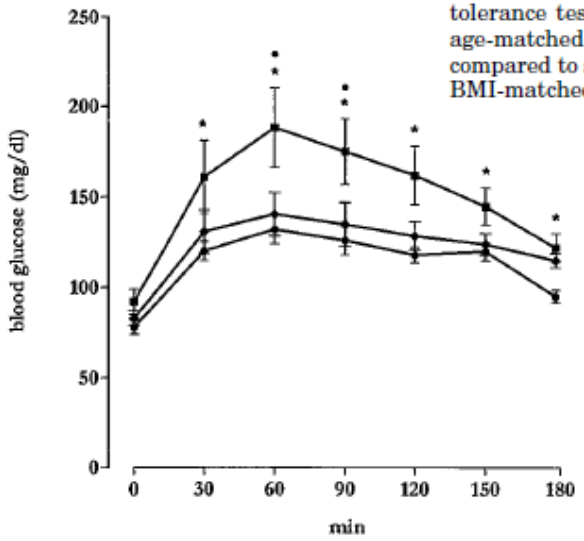
- **Alterazioni > in CD vs CS** (Giordano et al. 2011)
- **Nessuna correlazione con durata di malattia**
- **Nessuna correlazione con grado di malattia**
- **Correlazione tra WHR ed IR**

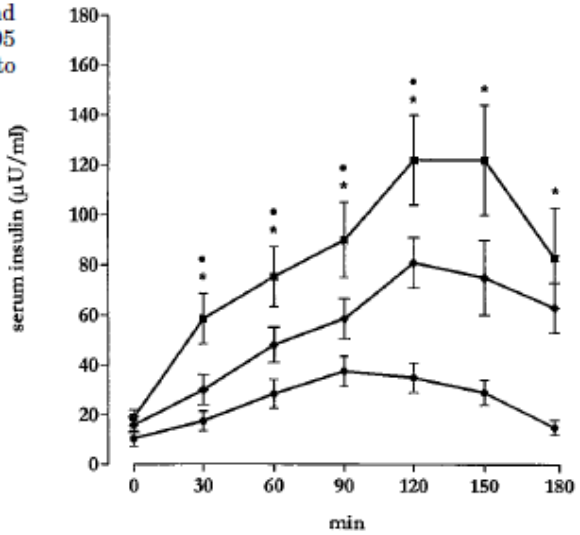
Colao A et al., J Clin Endocrinol Metab 1999; 84: 2664-26672
Faggiano A et al., J Clin Endocrinol Metab 2003; 88: 2527-2533
Webb SM et al., J Clin Endocrinol Metab 2010; 93:630-638
Espinosa-de-los Monteros A et al., Endocr Pract 2013; 2: 252-258
Giordano R et al., Clin Endocrinol 2011; 75: 354-360

m. Cushing «guarita»

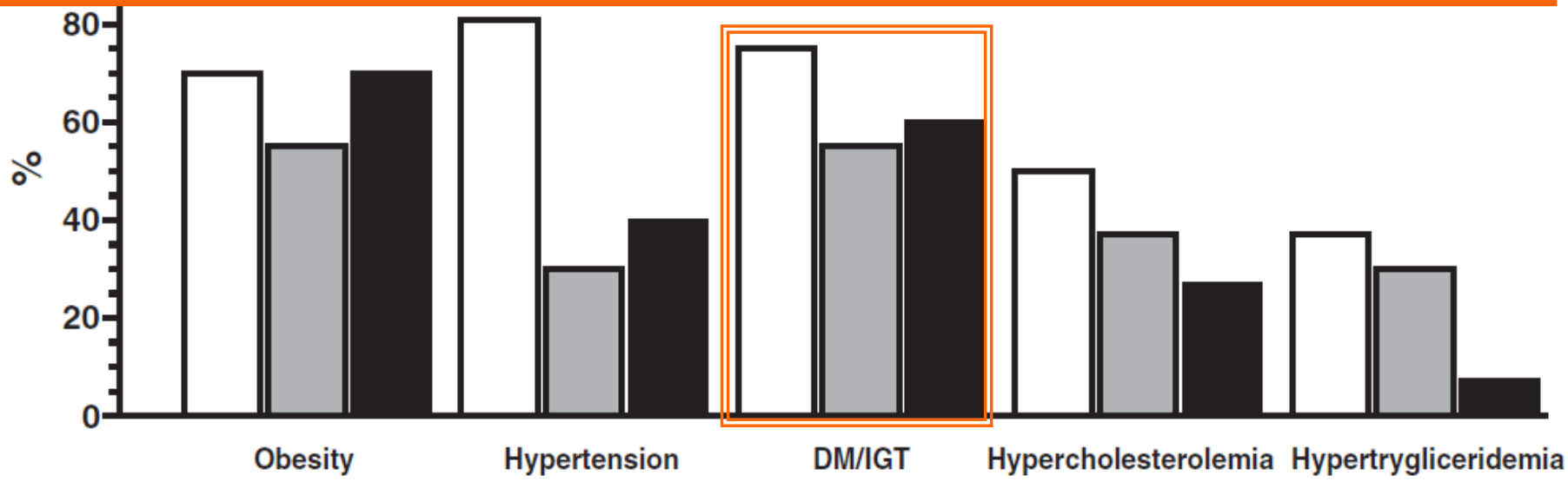
	Tipo di studio	n. Pazienti (caratteristiche)	Criteri di guarigione	Alterazioni (%)
Colao A et al. 1999	Cross-sectional (5 anni)	15 (3 M, 12 F; 20-50 aa)	UFC, ACTH, F 24, Nugent	DM (33.3%) IGT (26.7%)
Faggiano A et al. 2003	Open longitudinal (1 anno)	25 (8 M, 17F, 20-50 aa)	UFC, ACTH, F 24, Nugent	DM (40%) IGT
Webb SM et al. 2010	Post-hoc analysis observational HypoCCS (3 anni)	160 (46 M, 114 F, 46 aa)	?	DM (16.9%)
Espinosa de-los-monteros A et al. 2013	Retrospective (12-58 mesi)	29 (2 M, 27 F, 36 aa)	UFC, Nugent F8 < 5 mcg/dl	DM (31-34.4%)

FIG. 1. Blood glucose and serum insulin responses to oral glucose tolerance test in patients cured of Cushing's disease (■), sex- and age-matched controls (●), and BMI-matched controls (♦). *, $P < 0.05$ compared to sex- and age-matched controls; ●, $P < 0.05$ compared to BMI-matched controls.

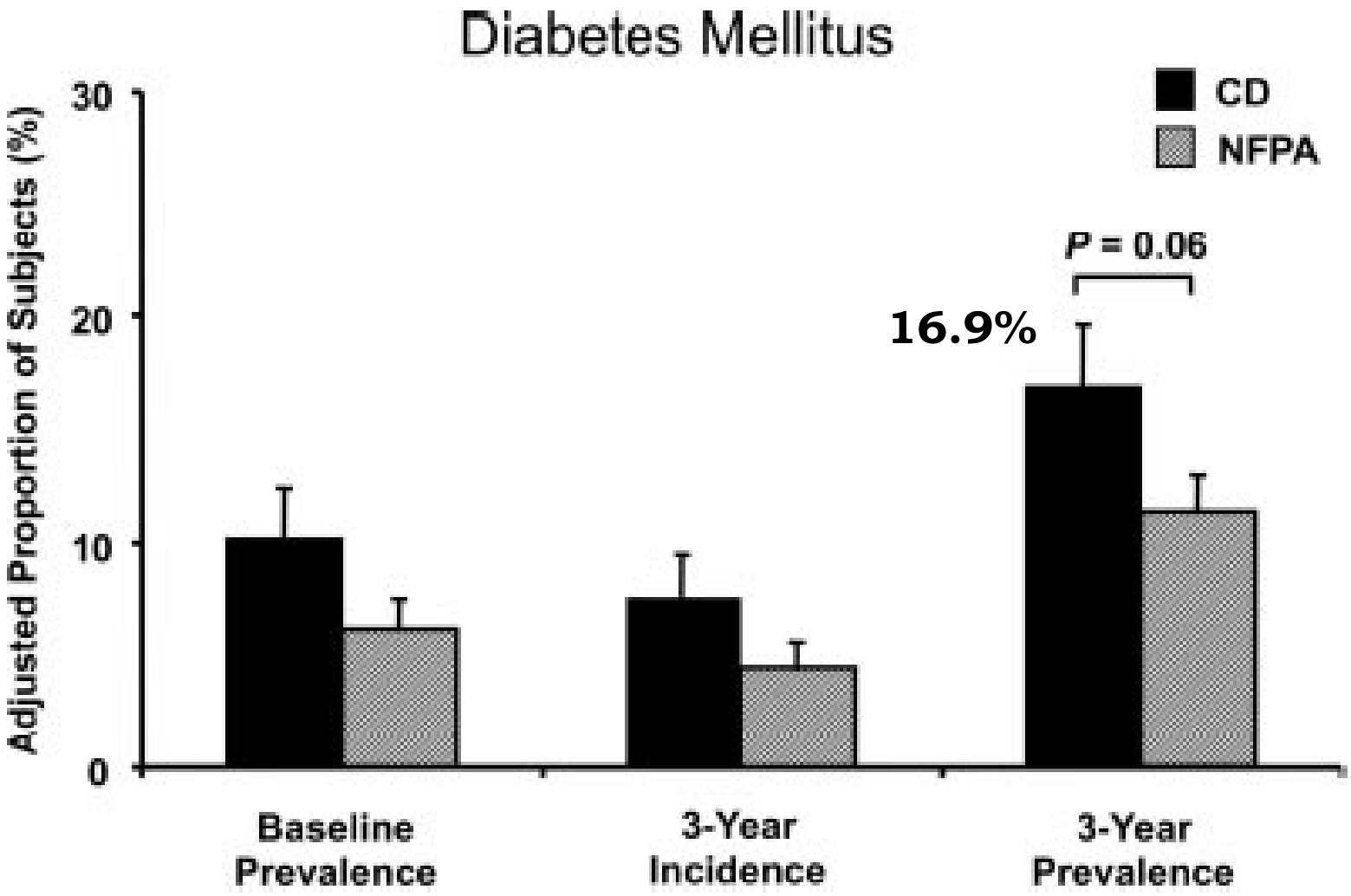




DM (33-40%), IGT (26.7%)



Colao A et al., J Clin Endocrinol Metab 1999; 84: 2664-26672
Faggiano A et al., J Clin Endocrinol Metab 2003; 88: 2527-2533



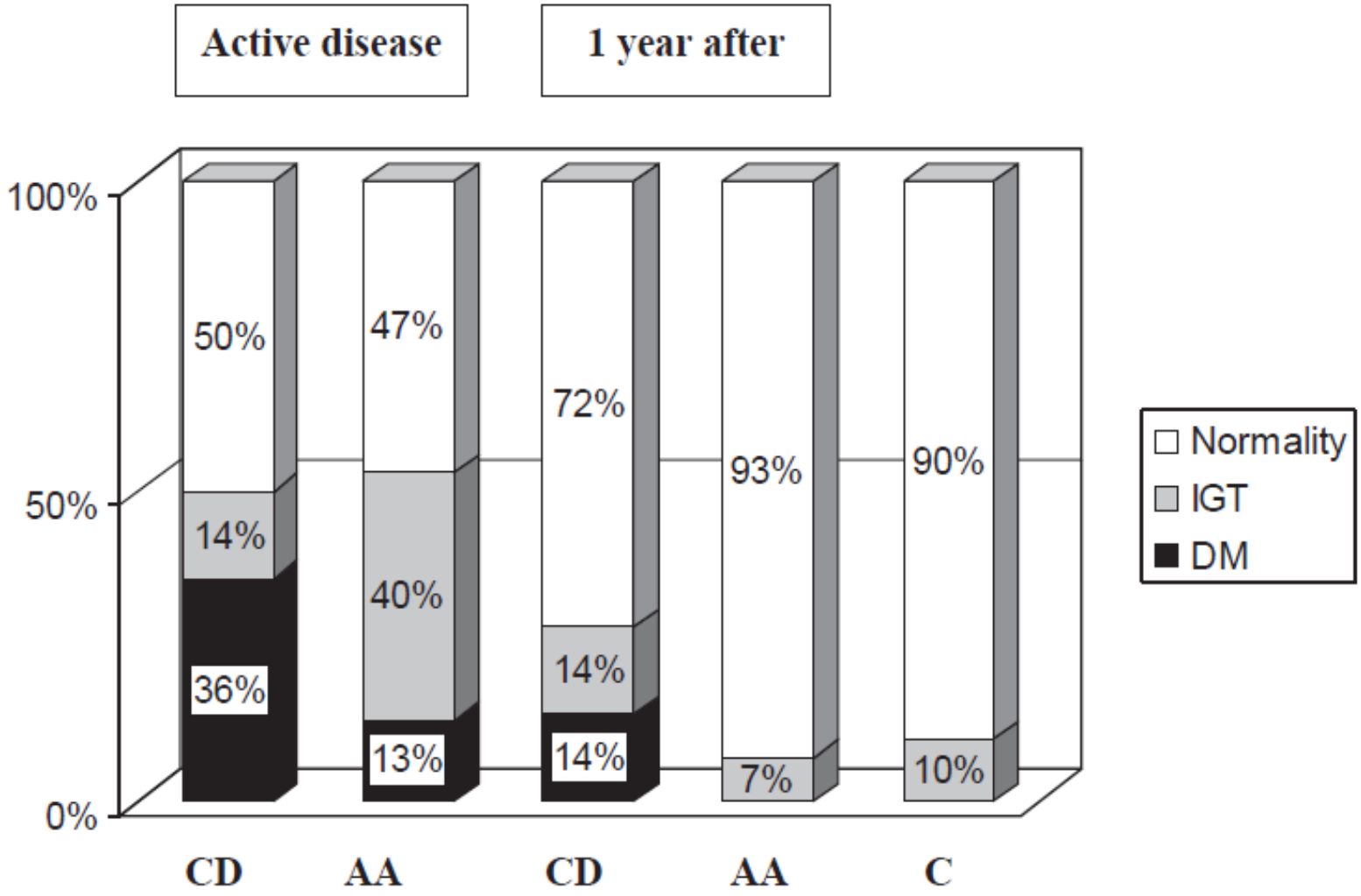
Webb SM et al., *J Clin Endocrinol Metab 2010; 93:630-638*

Table 3
Prevalence of Symptoms, Signs, and Comorbidities of CD at Diagnosis and Early and Late Evaluations

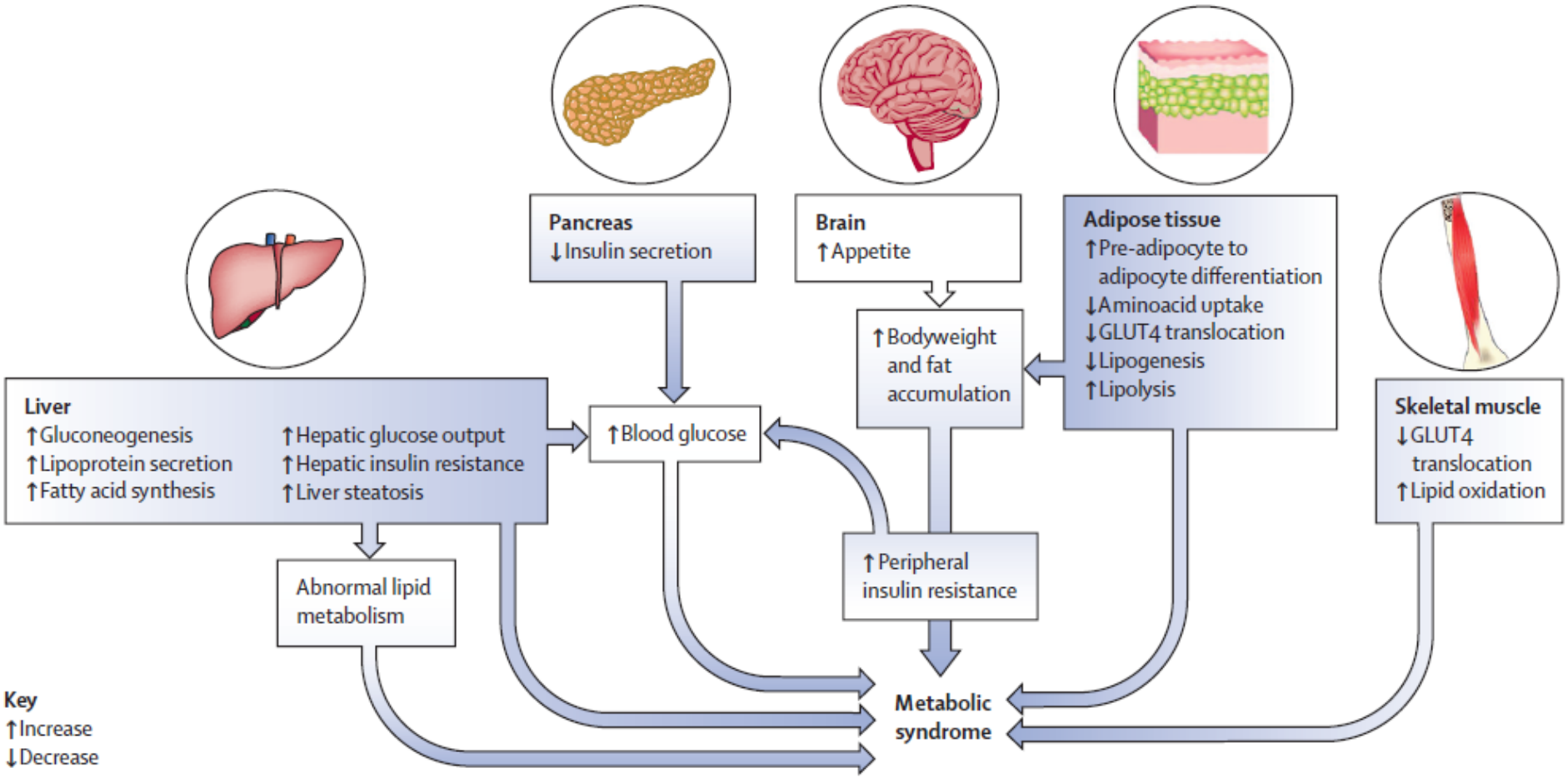
n (%)	Diagnosis	Early Evaluation	P^a	Late Evaluation	P^b
Purple striae	21 (72.4)	0	<.01	0	<.01
Hypokalemia	4 (13.8)	0	<.01	0	<.01
Acanthosis nigricans	12 (41.4)	9 (31)	.250	6 (20.7)	.031
Hirsutism	25 (86.2)	9 (31)	<.01	5 (17.2)	<.01
Acne	15 (51.7)	7 (24.1)	<.01	3 (10.3)	<.01
Fatigue	26 (89.7)	11 (38)	<.01	5 (17.2)	<.01
Depression	24 (82.8)	11 (38)	<.01	6 (20.7)	<.01
Menstrual abnormalities[c]	15 (75)	4 (20)	<.01	7 (35)	<.01
Mean BMI (mean ± SD)	32.6 ± 5.4	28.4 ± 4.3	<.01	30.1 ± 6.1	<.01
Overweight	5 (17.2)	15 (51.7)	.013	11 (38)	.04
Obesity	21 (72.4)	9 (31)	.002	13 (44.8)	.021
Overweight and obesity	26 (89.7)	24 (82.7)	.625	24 (82.7)	.625
IFG, IGT, and diabetes	20 (69)	14 (48.2)	.031	17 (58.6)	.453
Diabetes	14 (48.3)	9 (31)	.063	10 (34.4)	.219
Hypercholesterolemia	23 (79.3)	16 (55.1)	.039	19 (65.5)	.219
Hypertriglyceridemia	17 (58.6)	16 (55.1)	.99	16 (55.1)	.99
Hypertension	22 (75.9)	7 (24.1)	<.01	7 (24.1)	<.01

Espinosa-de-los Monteros A et al., Endocr Pract 2013; 2: 252-258

29 pts (14 CD, 12 F, 2 M; 15 AA, 14 F, 1 M)



... 5 year after ... only CD



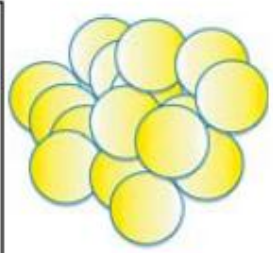
Metabolismo lipidico

Pivonello R et al., *Lancet Diabetes Endocrinol 2016; 4: 611-629*

Metabolismo lipidico

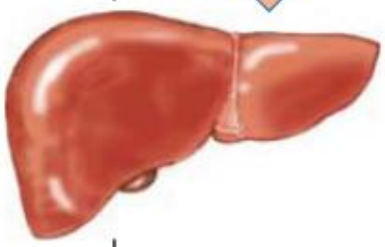
Chronic Glucocorticoid Excess

Adipose tissue
- lipoprotein Lipases (HSL and ATGL) activity and expression increased
- permissive effect on lipid mobilization by catecholamine action
- lipolysis increased
- adipogenesis activity increased (visceral fat)
- AMPK activity inhibited (visceral fat)



↑CT, LDL, TG; ↓ HDL

Liver
- insulin resistance
  - alteration of insulin signalling
    (intracellular lipids phosphorylate serine sites on IRS-1)
- gluconeogenesis increased
- trialcyglycerides (TAG) storage and VLDL secretion increased
- de novo lipogenesis increased
- FFA β-oxidation inhibited
- AMPK activity increased
- hepatic steatosis



Arnaldi et al., *Neuroendocrinology 2010; 92 (Suppl 1): 77-81*

s. Cushing «attiva»

Table 1. Prevalence of hyperlipidemia in Cushing's syndrome in relation to the cut-offs used for establishing the diagnosis

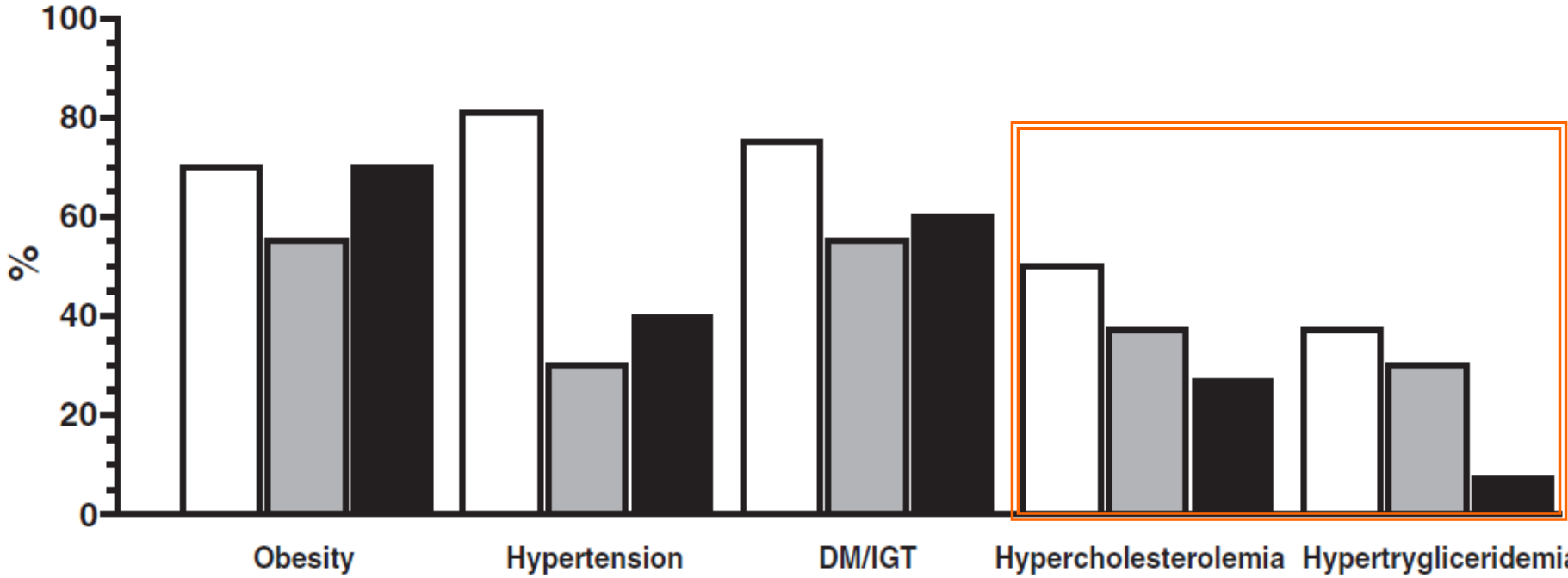
Series	High total cholesterol, mg/dl		High triglycerides, mg/dl	
	patients (%)	cut-off	patients (%)	cut-off
Colao et al. [12]	4/15 (26.7)	>240	1/15 (6.7)	>250
Faggiano et al. [13]	13/25 (52)	>240	5/25 (20)	>250
Mancini et al. [14]	12/49 (25)	>250	6/49 (12.5)	>250
Tauchmanovà et al. [5]*	10/28 (35)	>200	10/28 (35)	>160
* Patients with subclinical Cushing's syndrome.				
Espinosa-de-los Monteros A et al.	23/29 (79.3)	>200	17/29 (58.6)	>150

IperCT (26.7-79.3%), iperTG (6.7-58.6%)

Greenman Y G *et al., Neuroendocrinology 2010; 92: 91--95*

m. Cushing «guarita»

IperCT (23-26%) e iperTG (6.7-40%)



Colao A et al., J Clin Endocrinol Metab 1999; 84: 2664-26672
Faggiano A et al., J Clin Endocrinol Metab 2003; 88: 2527-2533

m. Cushing «guarita»

Table 2. Lipid parameters in patients with Cushing's disease at diagnosis and 1 year after remission, compared to healthy controls (control group 1) and to BMI-matched controls (control group 2): adapted from Faggiano et al. [13]

	Patients		Control 1 (sex and age matched)	Control 2 (BMI matched)
	active disease	1 year remission		
Number	25	25	32	32
BMI	29.2 ± 1.8	26.8 ± 1.5	22.8 ± 1.6	28.4 ± 1.8
Triglycerides, mg/dl	172 ± 35	159 ± 26	134 ± 26	182 ± 35
Total cholesterol, mg/dl	240 ± 25[a]	213 ± 23	174 ± 15	219 ± 19
LDL cholesterol, mg/dl	168 ± 23[c, d]	145 ± 19[a]	103 ± 11	149 ± 15
HDL cholesterol, mg/dl	38 ± 3[b, c]	43 ± 3.5[c]	55 ± 2.3	50 ± 2.7
Total/HDL-cholesterol ratio	6.1 ± 0.6 [b, c]	5.1 ± 0.5[c]	3.1 ± 0.3	4.3 ± 0.4

[a] $p < 0.05$ vs. control 1; [b] $p < 0.05$ vs. control 2; [c] $p < 0.01$ vs. control 1; [d] $p < 0.05$ vs. remission.

CT and LDL-C similar to those in BMI-matched controls

Greenman Y G *et al., Neuroendocrinology 2010; 92: 91--95*

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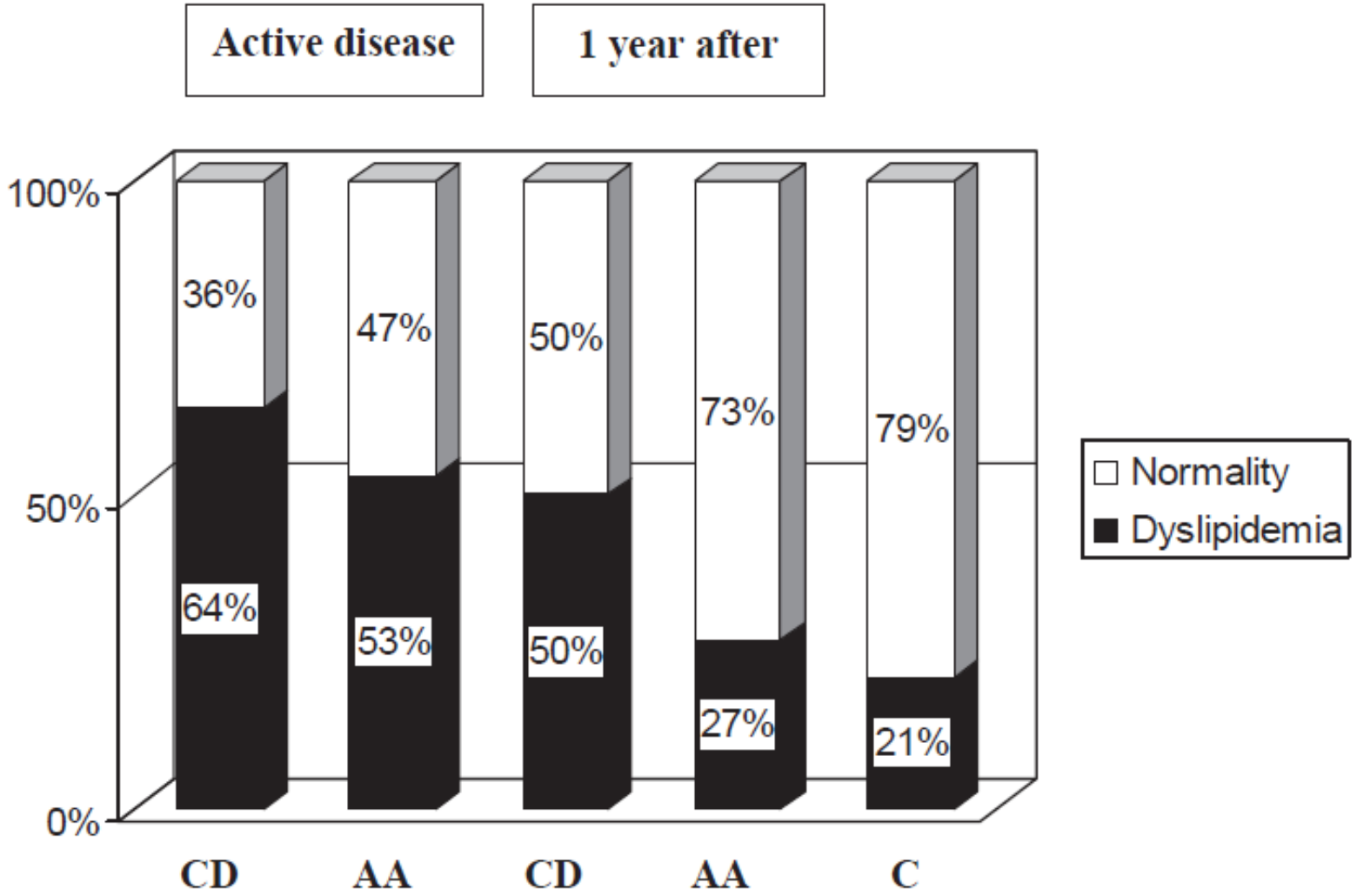
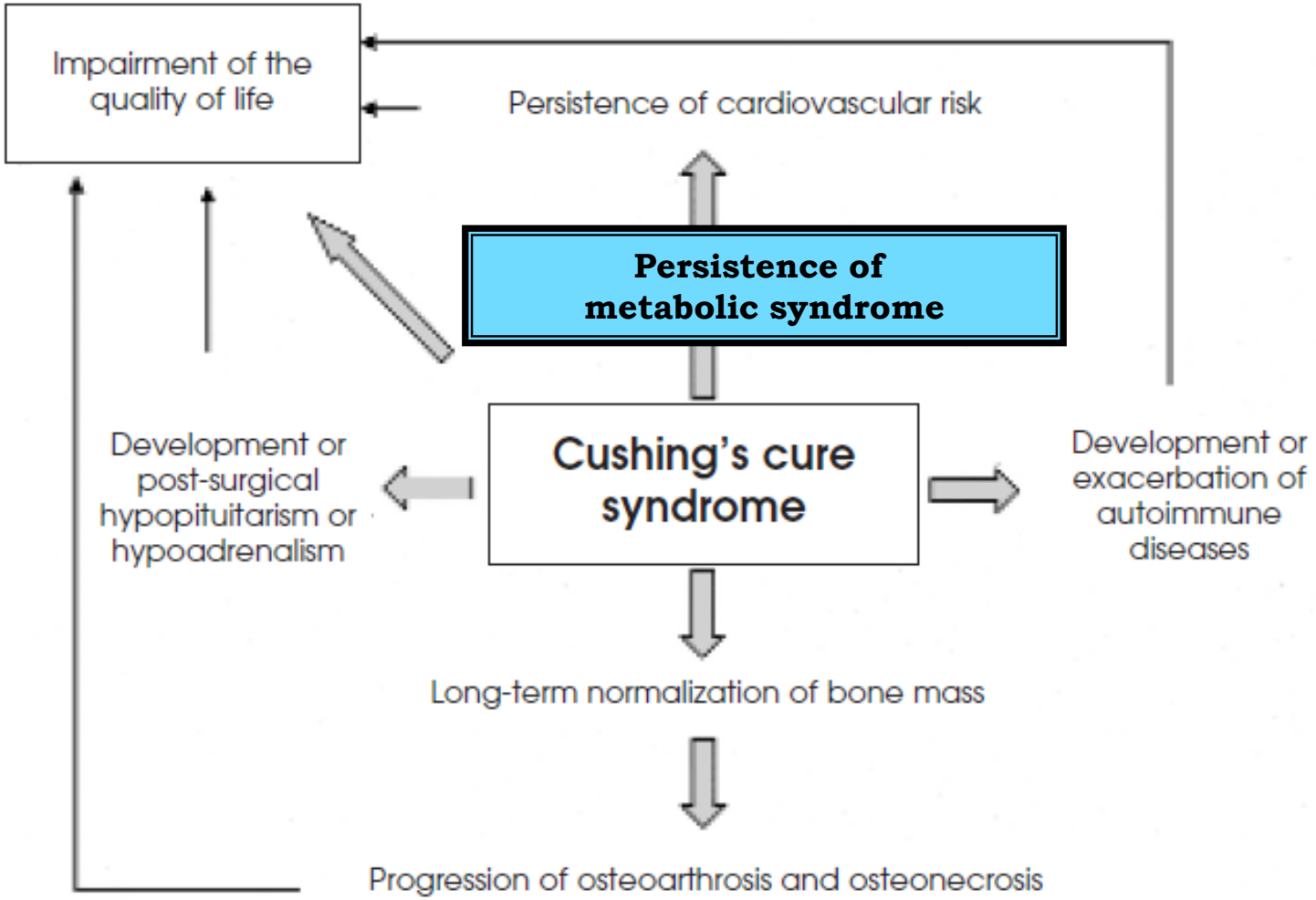
Espinosa-de-los Monteros A et al., Endocr Pract 2013; 2: 252-258



CT and LDL-C decreased in AA only…
No differences in HDL or TG …

G ***… 5 year after … CD > AA***



Cure or remission ?
Adrenal insufficiency and GC treatment
GC withdrawal syndrome

Pivonello R et al., *Arq Bras Endocrinol Metab 2007; 51/8*

… effetti dei GC dipendono da:

- ✓Livelli circolanti (90% legato CBG)
- ✓Passaggio circolo → tessuti (Mdr1a-GP)
- ✓Metabolismo pre-recettoriale (11 β-HSD1)
- ✓Legame recettoriale (GR)
- ✓Sensibilità tissutale (polimorfismo GR)

Variabilità genetica

Association of glucocorticoid receptor polymorphism A3669G with decreased risk of developing diabetes in patients with Cushing's syndrome

Laura Trementino, Gloria Appolloni, Carolina Concettoni, Marina Cardinaletti, Marco Boscaro and Giorgio Arnaldi

European Journal of Endocrinology (2012) **166** 35–42

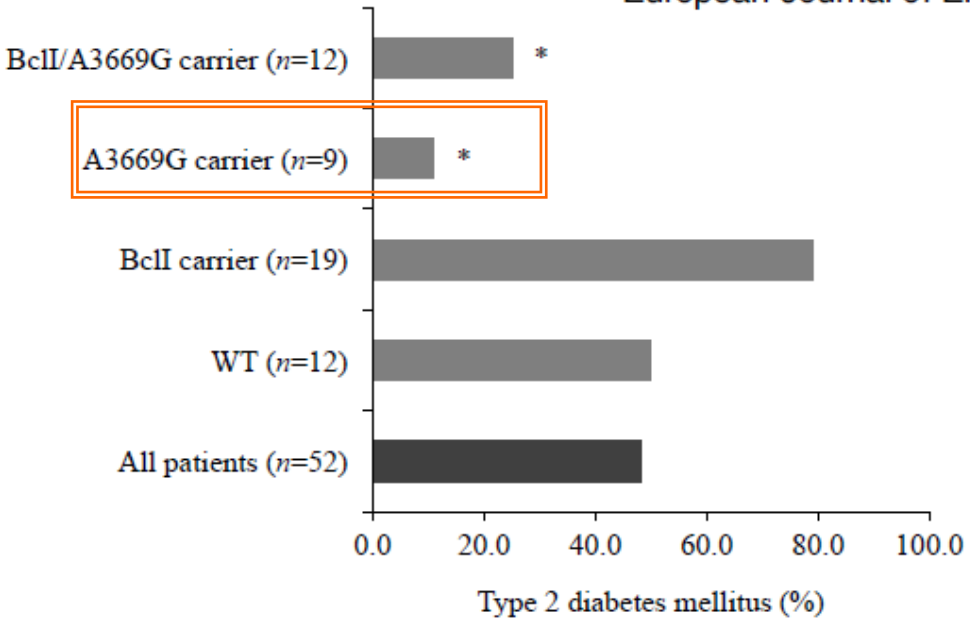


Figure 1 Type 2 diabetes mellitus frequency in patients with Cushing's syndrome (CS) according to haplotype. WT, wild type; BclI carrier, patients with heterozygous or homozygous BclI polymorphism; A3669G carrier, patients with heterozygous or homozygous A3669G polymorphism; BclI/A3669G carrier, patients coexpressing BclI and A3669 *GR* polymorphisms. *$P<0.05$ vs BclI carrier.

Remissione e non guarigione …

✓«Curare» (**NCH, CH**) ipercortisolismo = migliorare (≠curare) alterazioni metaboliche

✓**Terapia medica** se ipercortisolismo (chetoconazolo→ ipolip., interferenze su cit. P450; pasireotide → iperglic., ipolip.)

✓**Terapia sostitutiva GC** se ipocortisolismo (over-treatment, «GC withdrawal syndrome»)

Terapia alterazioni metaboliche

Table 1. Classes of drugs currently used in the treatment of diabetes mellitus, their mechanisms of action, and their application in CS

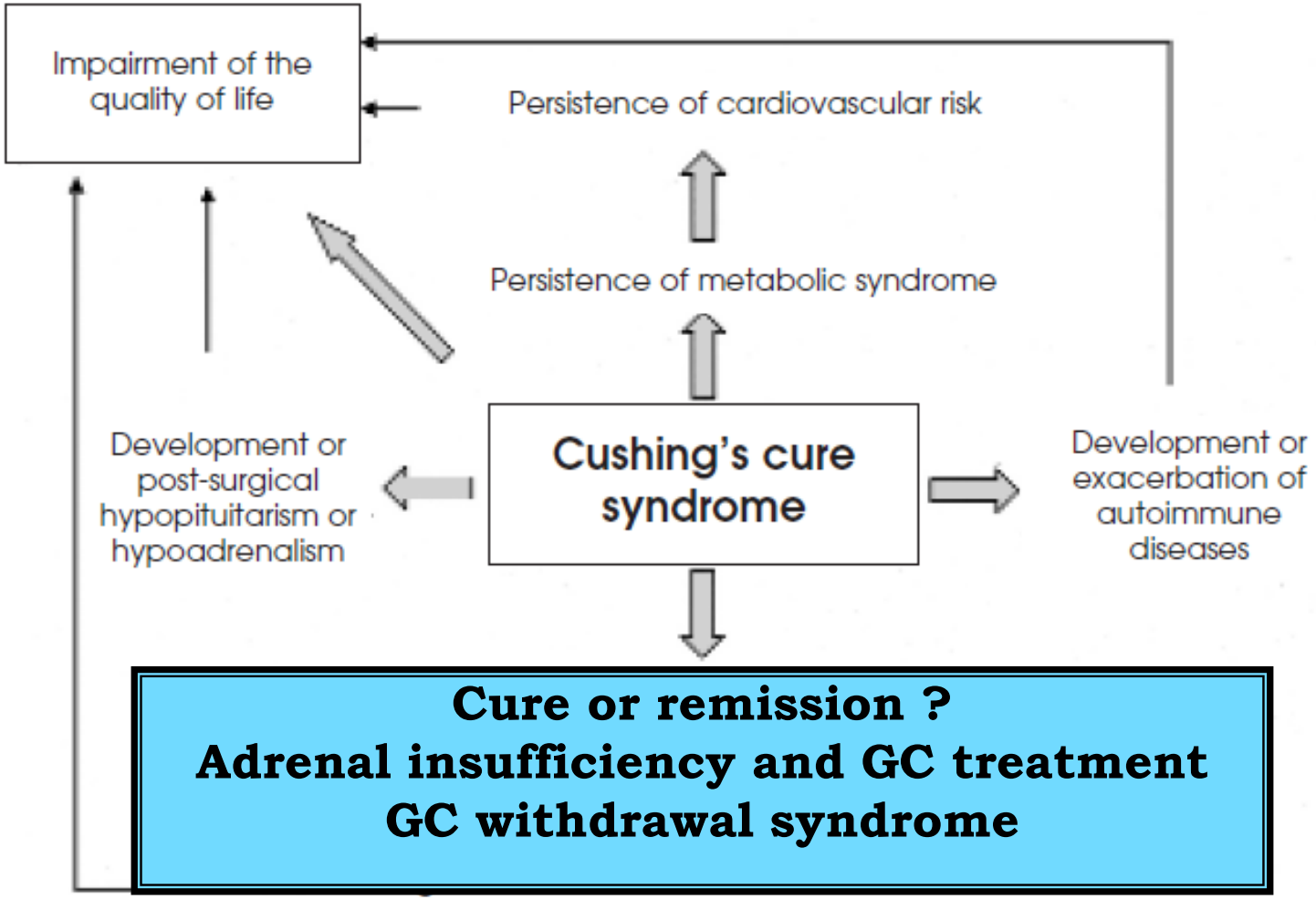
Class and examples	Main mechanisms of action	Clinical application in CS
Biguanide (metformin)	Insulin-sensitizer: improvement of insulin activity with decreased glucose output from the liver and increased glucose uptake in the muscle	First-line therapy in patients with insulin resistance.
Thiazolidinedione (pioglitazone)	Insulin-sensitizer: improvement of insulin activity which decreases the release of free fatty acids from the adipose cell by action on perixosome-proliferator-activated receptors	Second-line therapy in association to metformin, in insulin-resistant patients, when hyperglycemia is not controlled or there is intolerance to other drugs
α-Glucosidase inhibitors (acarbose, miglitol)	Inhibit intestinal carbohydrate absorption	Second-line therapy if postprandial hyperglycemic spikes are not controlled or there is intolerance to other drugs
Sulphonylureas (glimepiride, gliclazide, glibenclamide)	Increase insulin secretion	First-line therapy alone or in association with metformin
Meglitinides (repaglinide, nateglinide)	Increase insulin secretion	First-line therapy alone or in association with metformin
Dipeptidyl-peptidase-4 inhibitors (sitagliptin, vildagliptin, saxagliptin)	Increase endogenous glucagon-like peptide-1 levels	Second-line therapy if postprandial hyperglycemia is not corrected by other drugs
Glucagon-like peptide-1 mimetics (exenatide, liraglutide)	Increase glucose-dependent insulin secretion and inhibit glucagon secretion. Delayed gastric emptying	Second-line therapy if postprandial hyperglycemia is not corrected by other drugs
Rapid insulin analogs (apart, lispro, glulisine)	Correction of postprandial hyperglycemia	First-line therapy in patients receiving high glucocorticoid doses and second-line therapy if postprandial hyperglycemia is not corrected by oral hypoglycemic agents
Basal insulin analogs (glargine, detemir)	Correction of fasting hyperglycemia	Second-line therapy in patients with persistent fasting hyperglycemia
Sodium-glucose-co-transporter 2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)	Increase in urinary glucose excretion	Potential increase in urinary and genital infections

Lipid-Lowering Drugs (pravastatin and rosuvastatin)

Mazziotti G et al., *Trends Endocrinol Metab 2011; 22: 499-506*
Mazziotti G. et al., *Curr Diab Rep 2017 May; 17 (5): 32*

Greenman Y G *et al., Neuroendocrinology 2010; 92: 91--95*

Conclusioni



- ✓ Correggere le alterazioni metaboliche
- ✓ Trattare con dosi e GC «adeguati»


Altogether
to Beat
Cushing's
Syndrome
ABC
5ª Edizione
Viaggio alla (ri)scoperta
della Sindrome di Cushing
Napoli, 10-12 Aprile 2017
Centro Congressi Federico II - Via Partenope, 36

… Grazie …