16.30-17-30 **SESSION 2: A PECULIAR ASPECT OF COMPLICATIONS: HYPERGLICAEMIA AND DIABETES MELLITUS IN CUSHING'S SYNDROME**
Chairs: **Carla Giordano, Paola Loli**
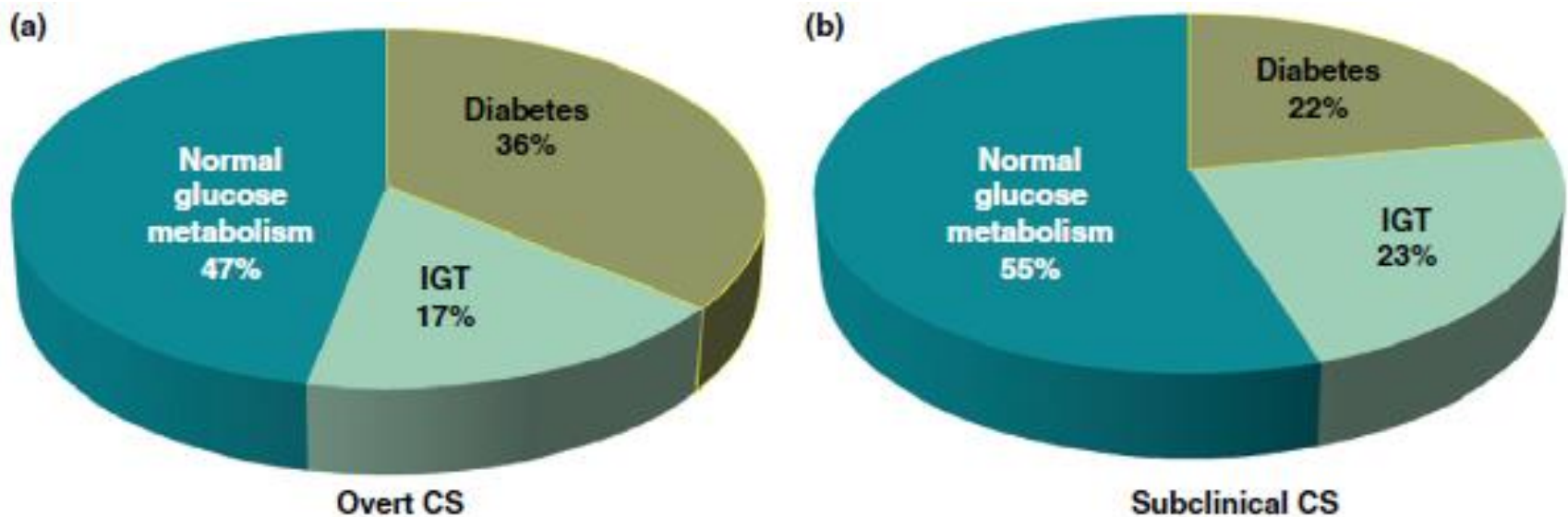
The Diabetes associated with Cushing's syndrome

Monica De Leo

Altogether to Beat Cushing's Syndrome

AB C

DIPARTIMENTO DI MEDICINA CLINICA E CHIRURGIA UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

Viaggio alla (ri)scoperta della Sindrome di Cushing 4ª Edizione / 4th Edition

Journey to the (re)discovery of Cushing's Syndrome

Napoli, 5–7 May 2015
Hotel S. Lucia

Scientific Coordinators
Annamaria Colao, Rosario Pivonello

# Prevalence of Diabetes mellitus and Impairment Glucose Tolerance (IGT) in patients with overt and subclinical CS

The mean prevalence was calculated from data published on 476 patients with overt CS and 655 patients with subclinical CS

(a) Overt CS — Normal glucose metabolism 47%, Diabetes 36%, IGT 17%

(b) Subclinical CS — Normal glucose metabolism 55%, Diabetes 22%, IGT 23%

Mazziotti G et al .*Trends Endocrrinol Metab* 2011; 22(12):499-506

Presence of signs and symptoms in male and female patients

Sign/symptom	Women (n=233) %	Men (n=47) %
Obesity	86.2	85.1
Moon facies	81.1	89.4
Hypertension	67.4	68.1
Buffalo hump	53.6	51.1
Purple striae	50.6	72.3*
Impaired glucose tolerance/diabetes	45.4	42.8
Muscle atrophy	45.5	63.8*
Psychiatric disturbances	34.3	25.5
Osteoporosis	31.6	46.8*
Ecchymoses	32.2	21.3
Acne	27.5	19.1
Hypokalaemia	21.8	32.6
Nephrolithiasis	6.4	21.3

*$P<0.05$ versus women

Prevalence of Diabetes mellitus and Impairment Glucose Tolerance (IGT) in patients with overt and subclinical CS
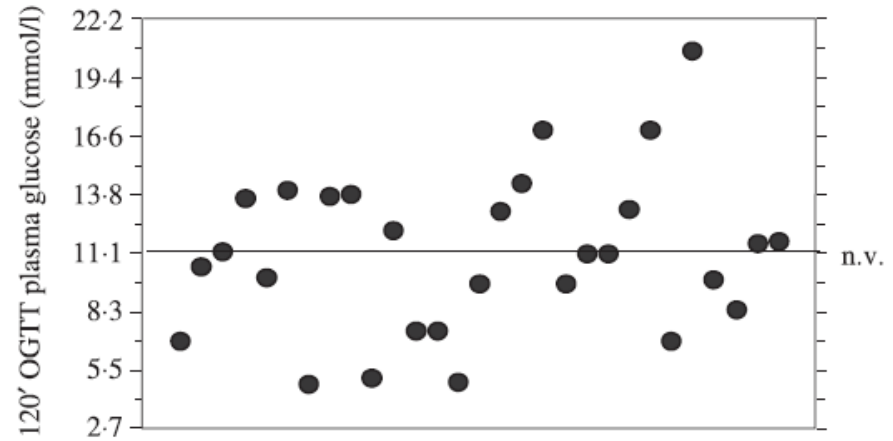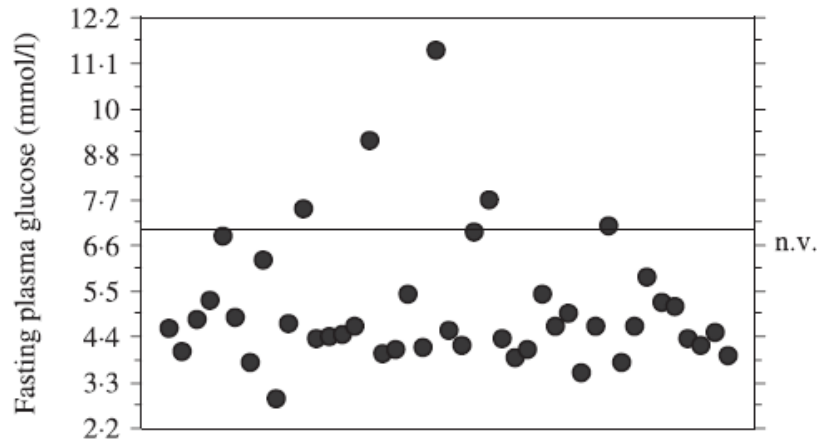
- 49 patients with CS (27 CD, 15 adrenal CS); 49.8% diabetes, 21.3% IGT

- Sixty-four per cent of diabetic patients had basal glucose level < 6.1 mmol/L and the diagnosis was made only after OGTT

- No difference in basal and post OGTT glucose and insulin levels between patients with pituitary adenomas and adrenal CS

- Fasting glucose was positively correlated with 0800 h plasma cortisol levels and UFC levels

- HOMA index and ISI were not significantly different in obese-overweight compared with normo-weight patients

Mancini T et al. *Clin Endocrinol* 2004;61;768-777;
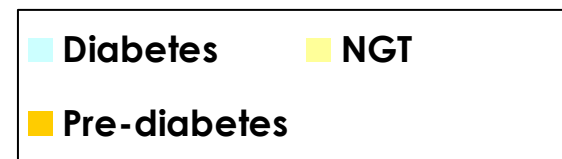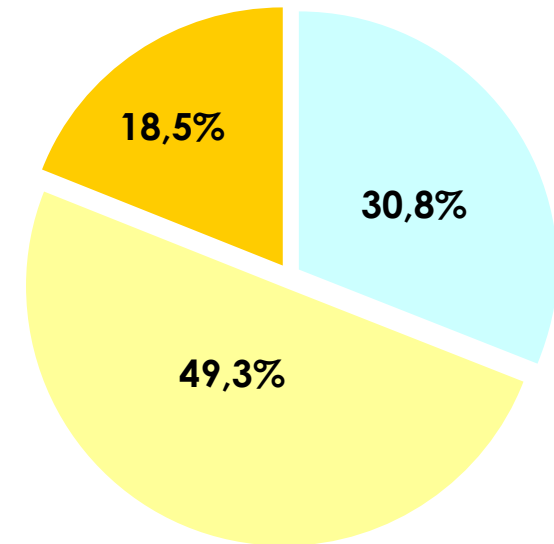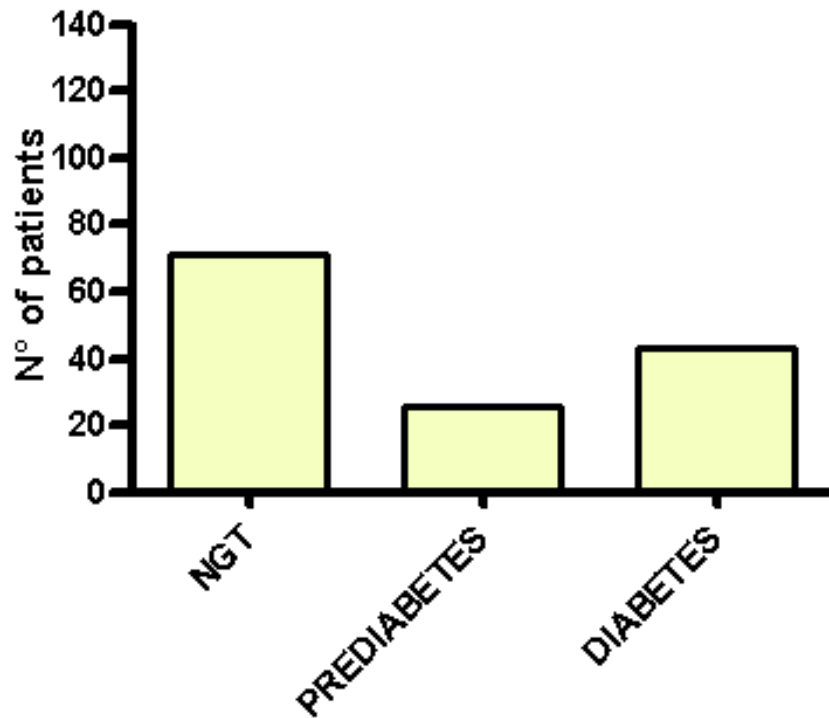CD: Cushing's disease
OGTT: oral glucose tolerance test ; UFC: urinary free cortisol ; HOMA index: homeostasis model assessment; ISI: insulin sensitivity index

Issues on the assessment of the true prevalence of diabetes in CS

The prevalence of Diabetes Mellitus in CS may be actually underestimated:

- More than one half of patients with CS and diabetes were shown to have normal fasting glucose

- OGTT is the diagnostic gold standard to identify the impairment of glucose metabolism in CS

- Glycate haemoglobin may be helpful in the clinical setting of CS being an integrated measure of glucose homeostasis

- The use of glycate haemoglobin for diagnosis of diabetes is not yet a standard practice

- Surrogate markers of peripheral insulin activity could be also useful for the early identification of patients with insulin resistance before the development of the overt diabetes

Mancini T *et al. Clin Endocrinol* 2004;61;768-777; Resmini E et al . *Acta Diabetol* 2009;46;85-95; American Diabetes Association *Diabetes Care* 2011;34;S62-S69; Malkani S et al. *Am J Med* 2011;124;395-401; Matthews DR et al . *Diabetologia* 1985;28;412-419

Prevalence of diabetes in CS

Giordano et al. *Eur J Endocrinol* 2014;170:311-319
NGT: normal glucose tolerance
Prediabetes: patient with impairment fasting glucose, impairment glucose tolerance or both

Prevalence of diabetes in CS

	CS/NGT (n=71)	CS/PREDIABETS (n=26)	CS/DIABETES (n=43)	*P*
Age (years)	35.05 ±16.34	41.27 ± 12.97	50.58 ± 14.64	<0.001
Metabolic syndrome[a]	28 (39.4)	20 (76.9)	40 (93)	<0.001
HOMA-β	170.65±43.7	163.46±77.52	87.11±76.94	<0.001
DIo	3.04±3.68	0.87±1.12	0.7±1.07	0.002
ISI-Matsuda	4.25±1.93	3.35±1.95	4.33±5.38	0.947
HOMA2-IR	1.97±0.79	2.57±1.19	1.83±1.05	0.671

Pathophysiology of Diabetes Mellitus in CS

Geer et al *Endocrinol Metab Clin North Am* 2014; 43:75-102

Pathophysiology of Diabetes Mellitus in CS

Van Raalte et al . *Eur J Clin Invest* 2009;39 (2):81-93
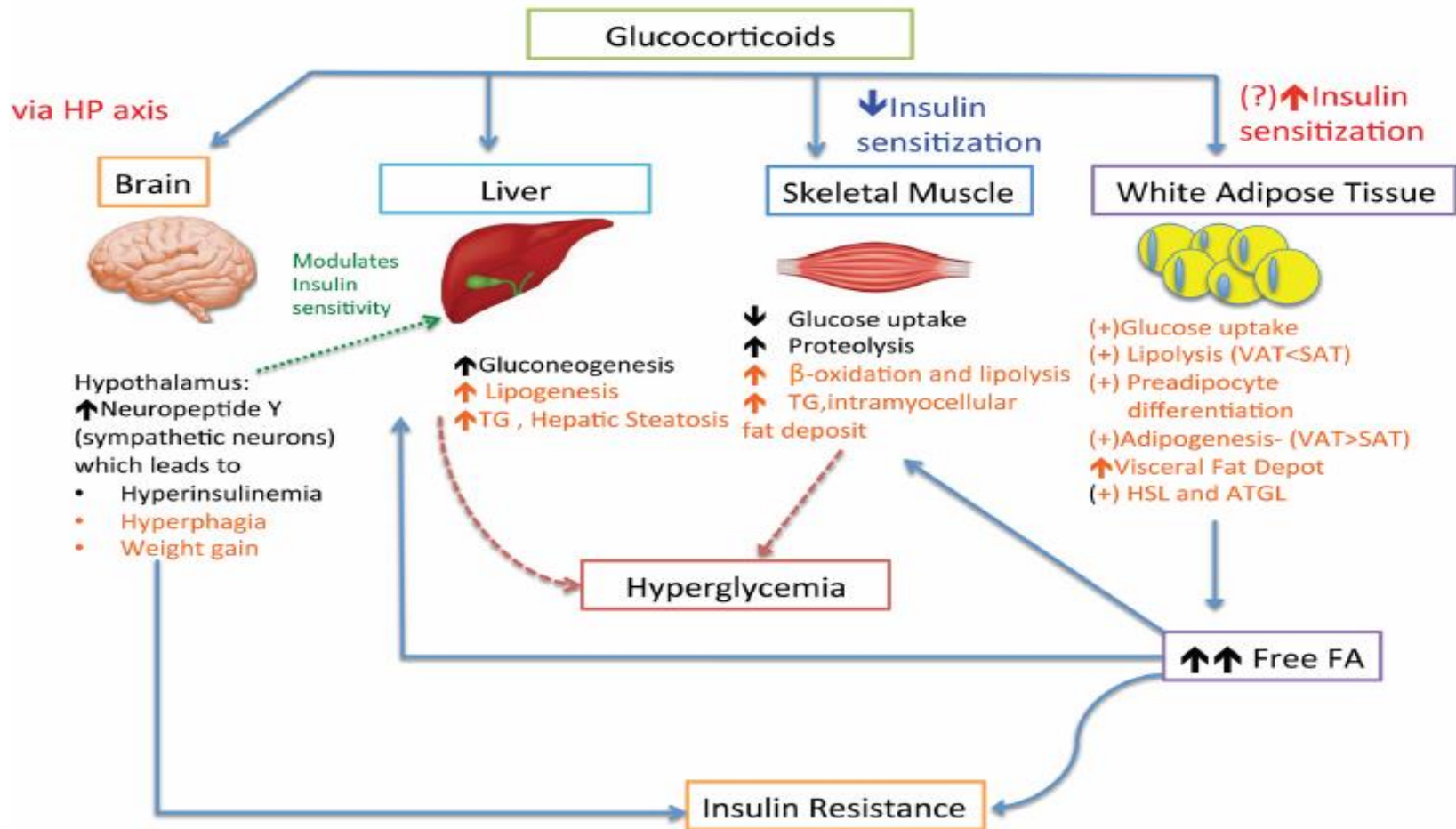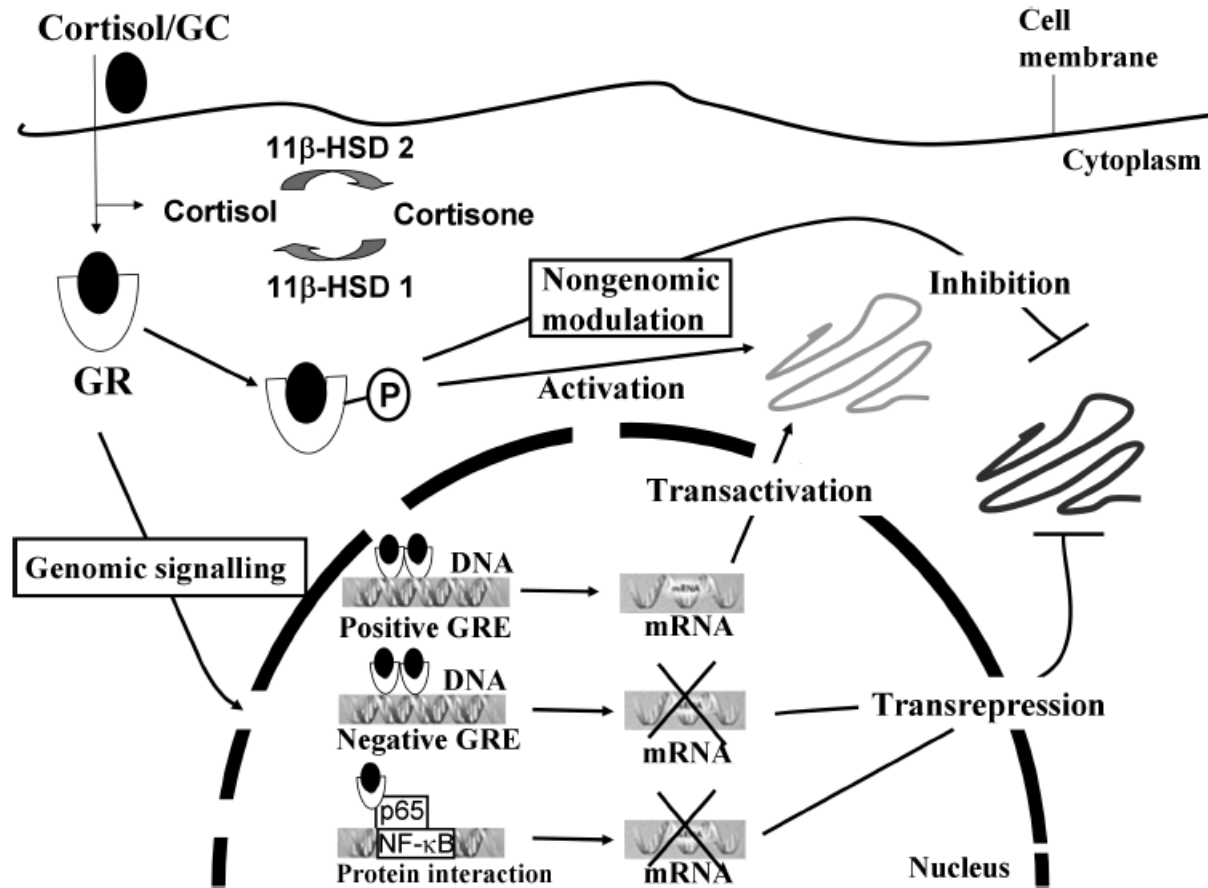
**Figure 3 Insulin secretory process in pancreatic beta cells and the proposed modes of interference by glucocorticoids.** GCs induce beta-cell dysfunction by inhibiting several pathways. Most notably, GCs impair beta-cell glucose uptake and oxidation, decrease protein kinase A and C activation, and reduce calcium fluxes by permitting repolarizing potassium currents. Abbreviations: AC, adenyl cyclase; Ach, acetylcholine; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; G6P, glucose-6-phosphatase; G^i. G-coupled inhibitory protein; GC, glucocorticoid; GK, glucokinase; GLUT2, glucose transporter 2; HK, hexokinase; IP3, inositol triphosphate; $K_v1.5$, voltage-dependent K channel; PIP2, phosphatidylinositol biphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; SGK-1, serum- and glucocorticoid inducible kinase-1.

Van Raalte et al . *Eur J Clin Invest* 2009;39 (2):81-93
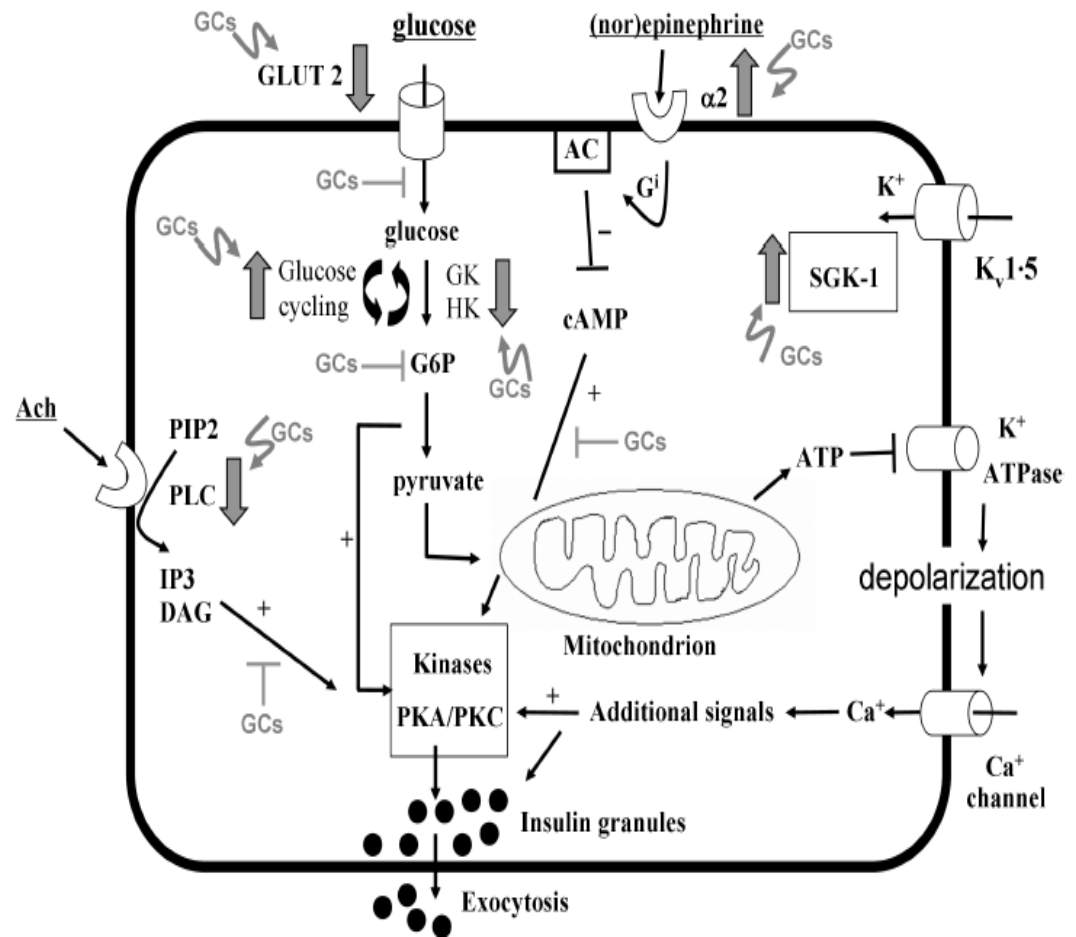
Potencial mechanisms involved in pathogenesis of Diabetes Mellitus in CS

Giordano et al. *Eur J Endocrinol* 2014;170:311-319
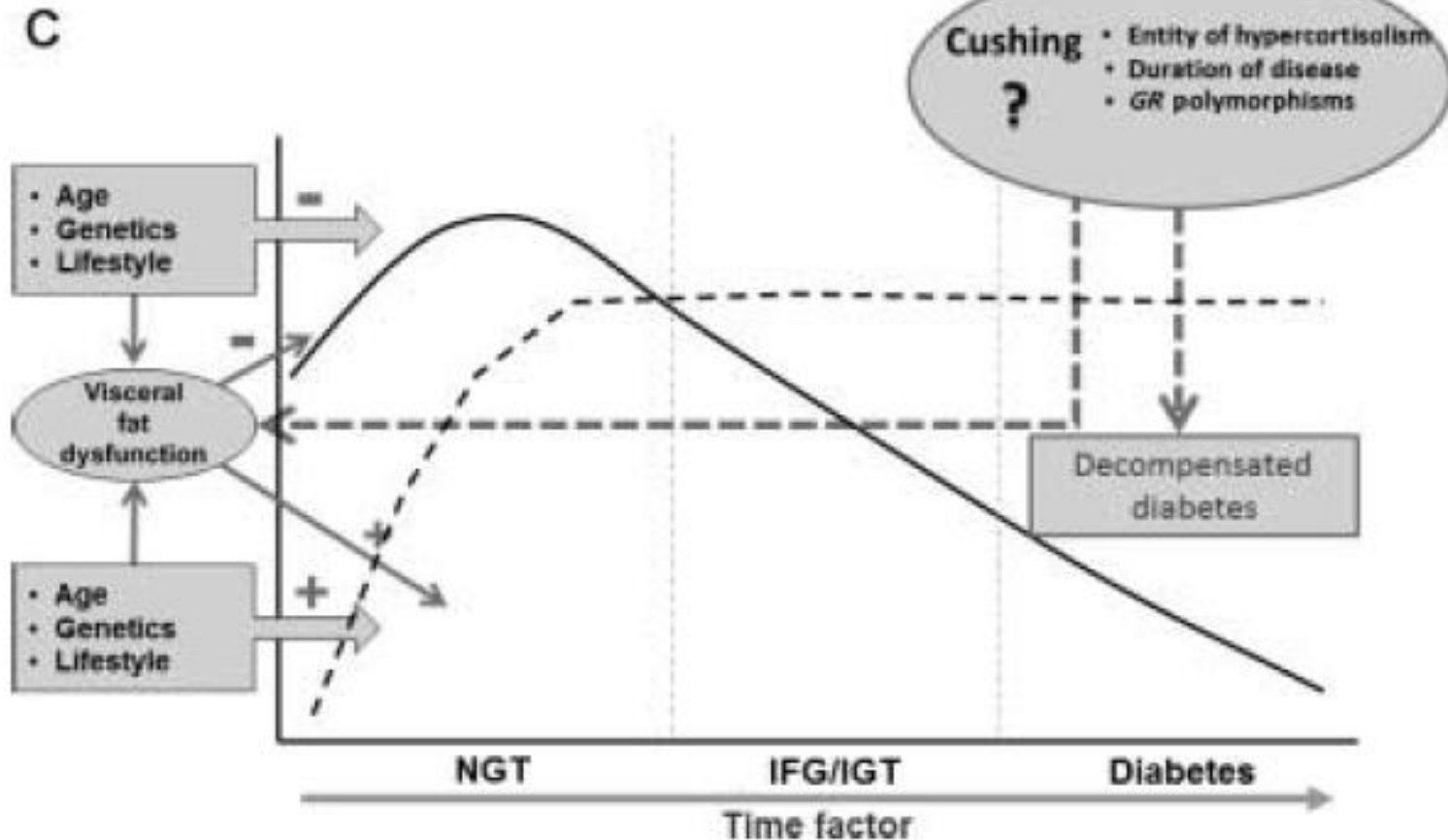
Pathophysiology of Diabetes Mellitus in CS
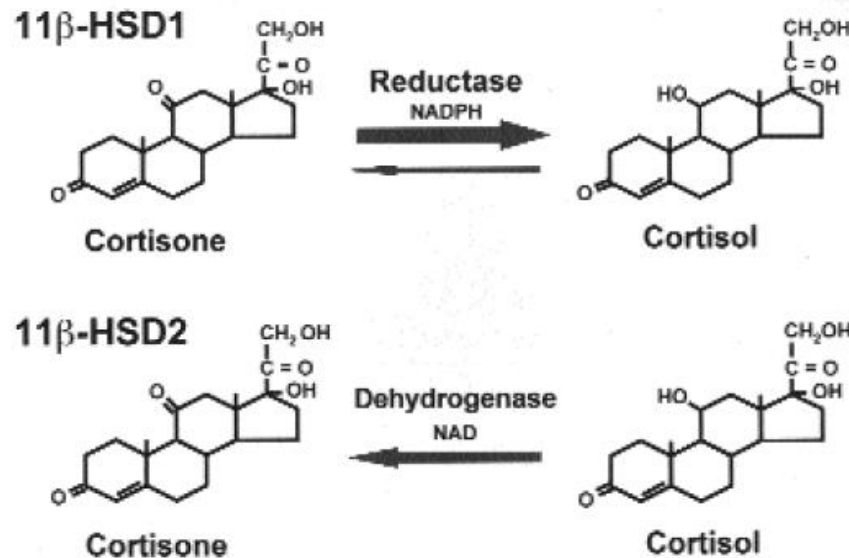
- 11βHSD1 is a NADPH dependent reductase (that converts inactive cortisone to active cortisol) and a dehydrogenase (that converts cortisol to cortisone), expressed in the liver, adipose, gonadal and central nervous system tissues. 11βHSD1 functions mostly as a reductase in intact cells and organs.

- 11βHSD2 is a NADPH dependent dehydrogenase enzyme that is highly expressed in the kidney and colon and catalyzes the inactivation of cortisol in cortisone. This not only protects the mineralcorticoid receptor from the occupancy by cortisol but also crucially provides substrate for 11βHSD1 in peripheral tissue.

Kater et al . *Arq Bras Endocrinol Metab* 2007;51/8:1397-1403
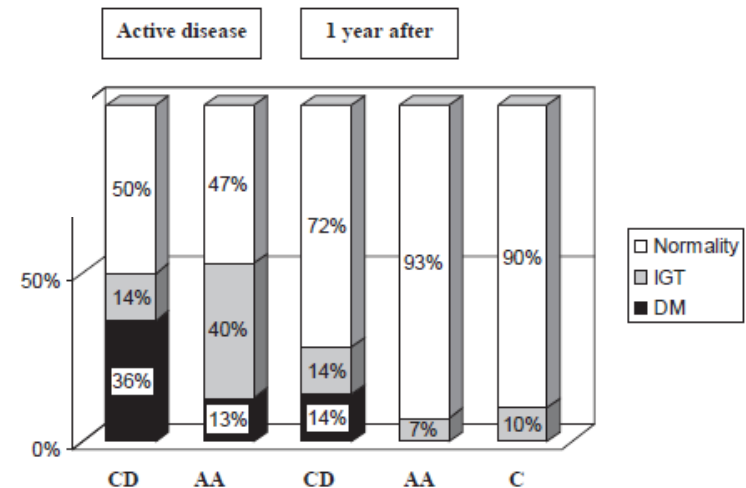
Pathophysiology of Diabetes Mellitus in CS

- Glucocorticoids availability and action depend not only upon circulating levels, but also on tissue-specific intracellular metabolism by 11βHSD

- 11βHSD1 functional defect protects patient with Cushing's disease from the classic metabolic phenotype

- 11βHSD1 KO mice with circulation glucocorticoids excess are protected from glucose intolerance, hyperinsulinemia, hepatic steatosis and adiposity

- Whereas liver-specific 11βHSD1 KO mice developed a full Cushingoid phenotype, adipose specific 11βHSD1 KO mice were protected from hepatic steatosis and fatty acid excess

- INCB13739, a 11βHSD1 inhibitor, improved hyperglycemia in patients with type 2 diabetes inadequately controlled by metformin

Tomlison et al. *J Clin Endocrinol Metab* 2002; 87(1)57-62; Morgan et al. *Proc Natl Acad Sci U S A*. 2014 ;111(24):E2482-91; Rosenstock et al. *Diabetes Care* 2010;33:1516-1522

Metabolic outcome in patients with CS after remission

- A persistent higher prevalence of metabolic syndrome and atherosclerosis as well as cardiovascular risk has been described in patients in remission from CS compared to controls, even after 5 years of desease remission.
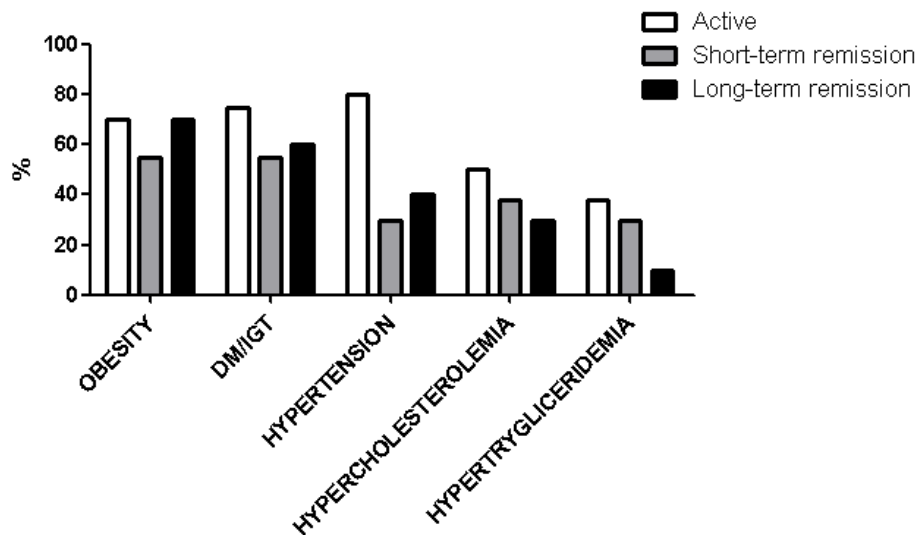
- 1 year after remission, metabolic and cardiovascular abnormalities persist in patients with adrenal and pituitary CS, as well as a more marked decrease in adrenal adenoma

Colao al . *J Clin Endocrinol Metab* 1999;84:2664-2672, Pivonello et al . *Endocrinol Metab Clin N Am* 2005 3;327-339; Giordano et al. *Clin Endocrinol* 2011;75;354-360

Conclusion 1

- **Real prevalence of Diabetes Mellitus in CS is actually underestimated**

- **OGTT is the diagnostic gold standard to identify the impairment of glucose metabolism in CS**

- **Surrogate markers of peripheral insulin activity could be also useful for the early identification of patients with insulin resistance before the development of the overt diabetes**

- **Diabetes in CS is due to complex and heterogeneous pathophysiological mechanism only in part linked to insulin resistance**

- **Persistent tissue hypercortisolism, also after the normalization of glucocorticoid circulating levels, could explain persistence of metabolic abnormalities**

- **The use of selective 11βHSD1 inhibitors, as adjuvant therapy, to limit CS associated metabolic effects, could be an intriguing possibility**

Prevalence of subclinical CS in diabetic populations

Author	N° of patients	Inclusion criteria	Method of screening	Prevalence of CS (%)
Leibowitz et al[1]	90	BMI 25 kg/m^2, HbA1c > 9%	1 mg overnight DST	3
Catargi et al[2]	200	BMI 25 kg/m^2, HbA1c> 8%	1 mg overnight DST	2
Chiodini et al[3]	294	Age >30 yr at diagnosis, BMI 19-49 kg/m^2, hospitalized	1 mg overnight DST	9,4
Reimondo et al[4]	100	New T2DM	1 mg overnight DST	1
Newsome et al[5]	171	Age 18-80yr, BMI >25kg/m^2 T2DM >1 yr	1 mg overnight DST	0
Mullan et al[6]	201	HBA1c <7%, BMI>25kg/m^2, history of hypertension or BP >140/90mmHg	Midnight salivary cortisol	0

[1]Leibowitz et al. *Clin Endocrinol (Oxf)* 1996;44:717–722; [2]Catargi et al. *J Clin Endocrinol Metab* 88:5808–5813; [3]Chiodini et al. *Eur J Endocrinol* 2005;153:837–844; [4]Reimondo et al. *Clin Endocrinol (Oxf)* 2007;67:225–229; [5]Newsome et al. *Intern Med J* 2008;38:178–182 [6]Mullan et al. *J Clin Endocrinol Metab* 2010;95;2262-2265
BMI: body mass index; HbA1C: glycate hemoglobin; T2DM: type 2 diabetes mellitus; BP: blood pressure

Conclusion 2

- The analysis of the recently published data has given a prevalence rate of CS from 0 to 9,4% (2,5%) among diabetes patients

- The *a priori* possibility of having subclinical CS is estimated to be lower than that of a false positive result

- Available data do not support the cost-effectiveness of the CS screening in diabetes patients in clinical practice

- Test screening inclusion in future guidelines for the diagnosis of CS would not be justified

[1]Leibowitz et al. *Clin Endocrinol (Oxf)* 1996;44:717–722; [2]Catargi et al. *J Clin Endocrinol Metab* 88:5808–5813; [3]Chiodini et al. *Eur J Endocrinol* 2005;153:837–844; [4]Reimondo et al. *Clin Endocrinol (Oxf)* 2007; 67:225–229; [5]Newsome *et* al. *Intern Med J* 2008;38:178–182 [6]Mullan et al. *J Clin Endocrinol Metab* 2010;95;2262-2265

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