Terapia corticosteroidea e diabete

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Agenda

- Effects of glucocorticoids
- Steroid-induced diabetes mellitus
- Epidemiology and diagnosis
- Risk factors for steroid-induced diabetes mellitus
- Pathophysiology
- Clinical approach and management
- Steroid-Induced diabetes mellitus in special settings (*cancer patients*)
- Conclusions and take home message

The Nobel Prize in Physiology or Medicine 1950

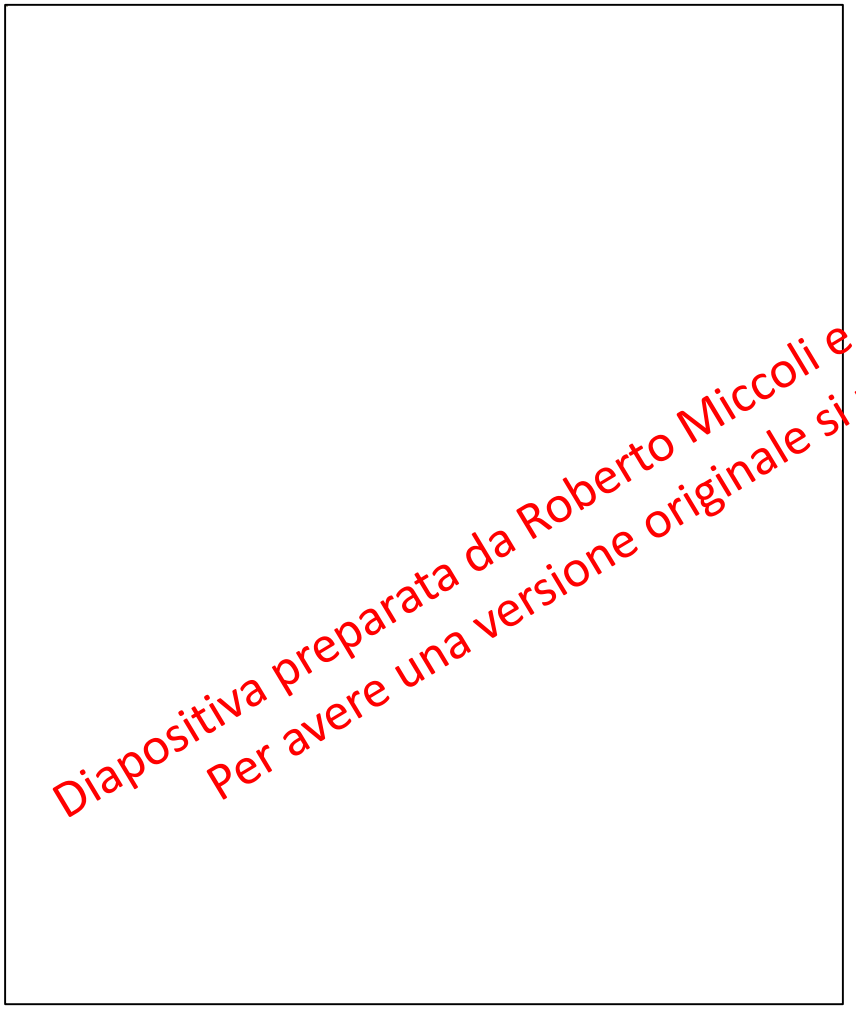
"for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"

"Dr. Hench, Professor Kendall, and Professor Reichstein. The Caroline Institute has decided to award this year's Nobel Prize in Physiology or Medicine to you jointly, for your discoveries regarding the hormones of the adrenal cortex, their structure, and biological effects.

*Your work is a splendid example of close co-operation between representatives for physiology, biochemistry, and clinical medicine, as well as between scientists belonging to different countries. Once again it emphasizes the international character of scientific research".**

*From the speech of the Professor G. Liljestrand, member of the Staff of Professors of the Royal Caroline Institute

Glucocorticoids (GCs) and the stress response



Pathways of communication among the Immune system, the hypothalamic–pituitary–adrenal axis, and other tissues influenced by immune signals and glucocorticoids

Red lines denote inhibition, and blue and black arrows activation.

Turk Rhen et al. N Engl J Med. 2005

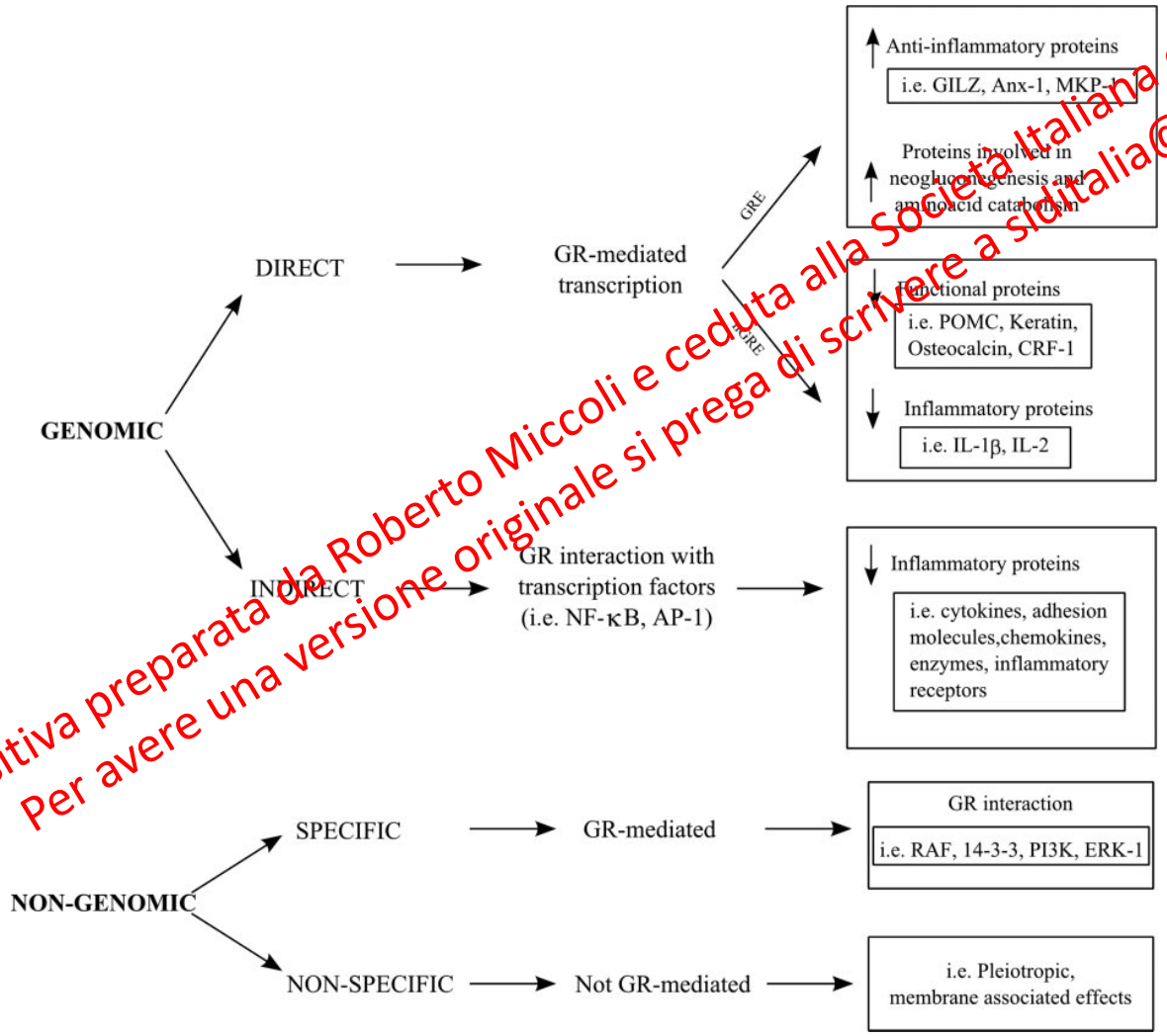
General mechanisms of action of glucocorticoids

Three general mechanisms:

1. DNA-dependent regulation
2. Protein intreference mechanisms (e.g. NF-kB elements)
3. Non-genomic activation through membrane-associated receptors and second messengers

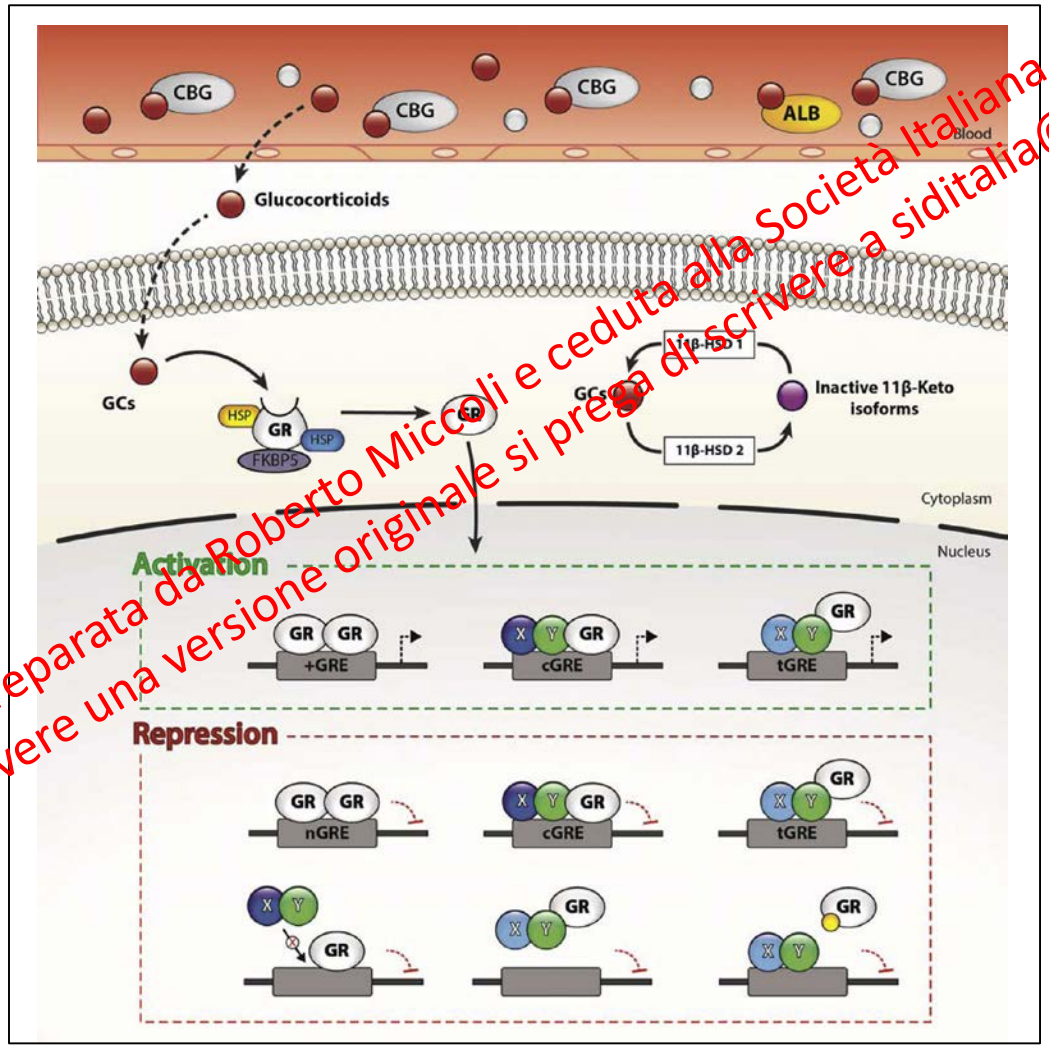
Turk Rhen et al. N Engl J Med. 2005

Genomic and nongenomic glucocorticoid molecular mechanisms



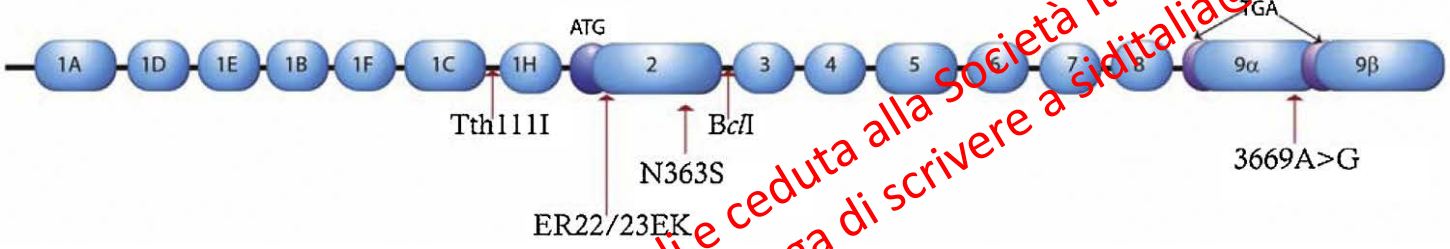
Ayroldi E et al. FASEB J. 2012

Glucocorticoid receptors'role in the regulation of gene transcription



Moraitis AG et al. J Steroid Biochem Mol Biol. 2016

Glucocorticoid receptor gene and single nucleotide polymorphisms



The generic variations may account for the diversity in patient presentations and responses to GCs. Moreover, it has been speculated that the polymorphism of the GR locus might be related to adverse effects of GCs

Moraitis AG et al. J Steroid Biochem Mol Biol. 2016

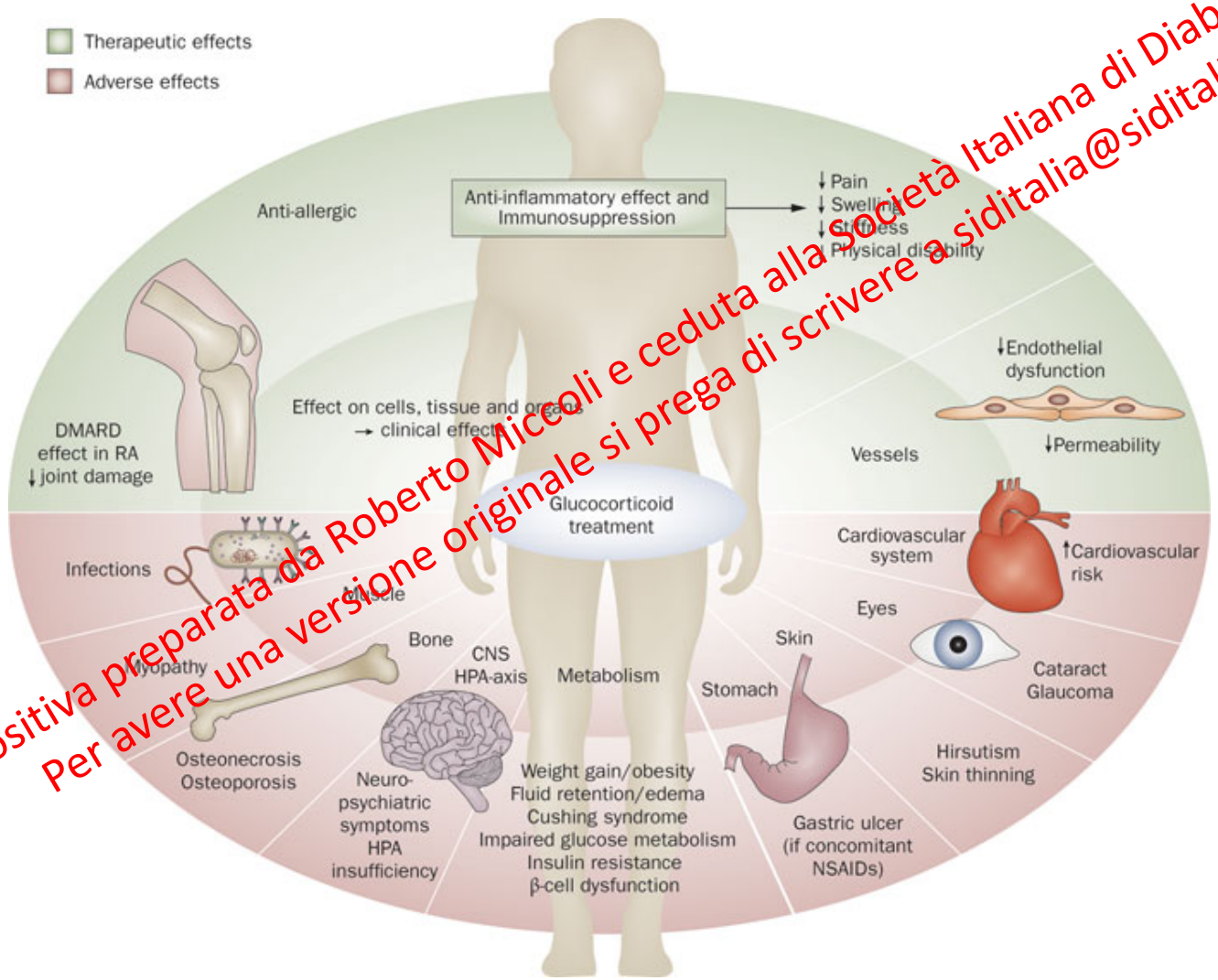
Characteristics of the different systemic glucocorticoid preparations

Compound	Equivalent dose (mg)	Anti-inflamatory potency*	Sodium retention power*	Half-life† (h)
Short acting				
Cortisone	25	0.8	0.8	8–12
Hydrocortisone	20	1	1	8–12
Intermediate acting				
Prednisone	5	4	0.8	12–16
Prednisolone	5	4	0.8	12–16
Methylprednisolone	4	5	0.5	12–16
Deflazacort	7.5	4	0.5	12–16
Fludrocortisone	2	10	125	12–24
Triamcinolone	4	5	0	12–24
Long acting				
Betamethasone	0.75	25	0	20–36
Dexamethasone	0.75	25	0	20–36
Intra-articular administration				
Triamcinolone acetonide	4	5	0	36–72
Methylprednisolone acetate	4	5	0.5	36–72
Paramethasone	2	10	0	36–72

*Relative to hydrocortisone. †Duration of the estimated biological action of the glucocorticoid.

Perez A et al. J Diabetes. 2014

Multiple adverse effects of glucocorticoids



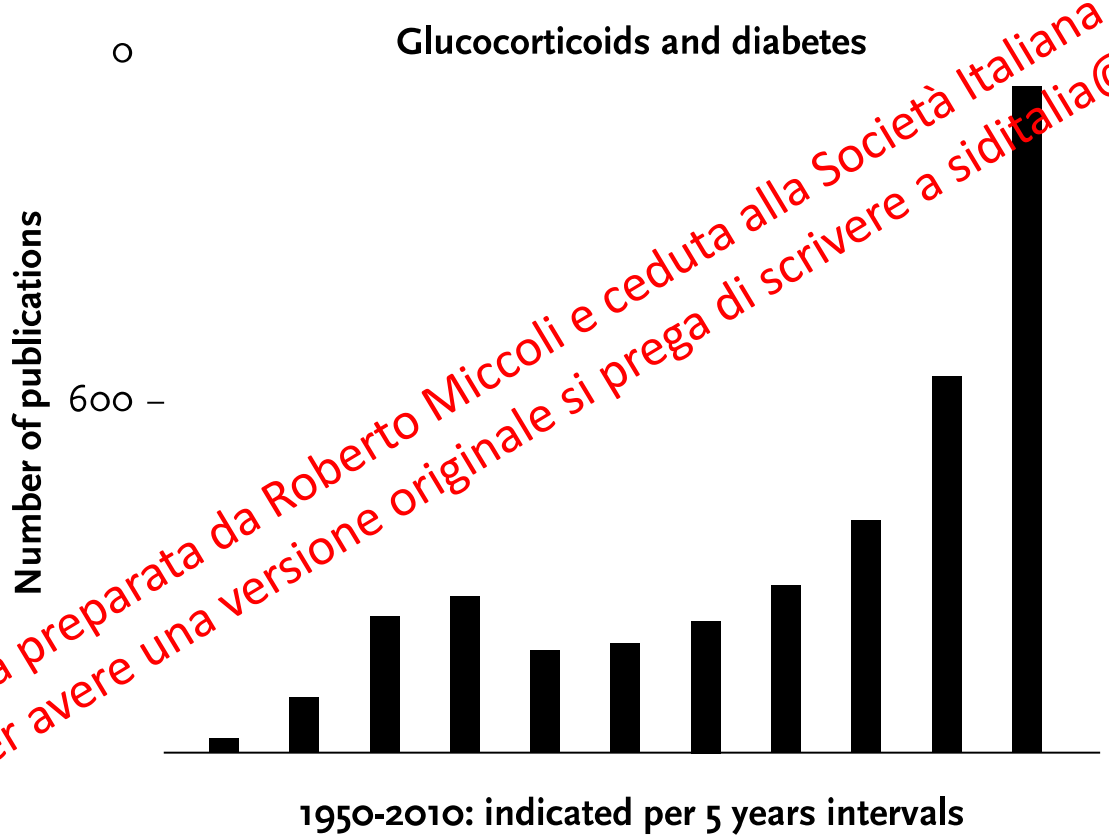
Hoes JN et al. Nat Rev Rheumatol. 2010

Side-effects of short term and long term glucocortcoid use

Short-term glucocorticosteroid therapy	Long-term glucocorticosteroid therapy	
Gastrointestinal intolerance	**Musculoskeletal**	**Metabolic**
Increased predisposition to infections	Growth retardation	Hyperglycemia
Delayed wound healing	Osteoporosis	Truncal obesity
Increased appetite Hyperglycemia	Myopathy	Hyperlipidemia
Fluid and sodium retention	Avascular necrosis of bone	Hypokalemia
Mood changes	**HPA axis**	Hypocalcemia
Weakness	Suppression	**Cutaneous**
Insomnia	Withdrawal syndrome	Hirsutism
Amenorrhea	Adrenal crisis	Atrophy
Acne	**Ophthalmologic**	Hyperpigmentation
	Cataracts	Acne
	Glaucoma	**Nervous system**
	Gastrointestinal	Mood and personality changes
	Gastritis	Psychosis
	Peptic ulcer disease	Pseudotumor cerebri
	Pancreatitis	
	Intestinal perforation	

Aulakh R et al. Indian J Pediatr. 2008

Glucocorticoids and their metabolic effects: renewed interest



D.H. van Raalte et al. The Netherlands Journal of Medicine. 2014

Steroid-induced diabetes mellitus. Definition

Steroid-induced diabetes mellitus (SIDM) is defined as an abnormal increase in blood glucose associated with the use of glucocorticoids in a patient with or without a prior history of diabetes mellitus.

American Diabetes Association. Diabetes Care. 2016

Diagnosis

The criteria for diagnosing diabetes by the American Diabetes Association is an 8 h fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL), 2 h post 75 g oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L (200 mg/dL), HbA1c ≥ 48 momol/mol (6.5%) (or in patients with symptoms of hyperglycemic, a random plasma glucose of ≥ 11.1 mmol/L (200 mg/dL)

American Diabetes Association. Diabetes Care. 2016

Postprandial plasma glucose are useful for detecting glucocorticoid-induced DM
The postprandial glycemia after lunch offers the greatest diagnostic sensitivity, especially when intermediate-acting glucocorticoids are administred in a single morning dose.

Iwamoto T et al. Pharmacotherapy. 2004
Uzu T et al. Nephron Clin Pract. 2007

La diagnosi di diabete mellito indotto da steroidi dovrebbe essere effettuata clinicamente sulla base della glicemia 2 ore dopo il pranzo.
(Livello della prova VI, Forza della raccomandazione A)

Epidemiology

- DM incidence in patients without a prior history of hyperglycemia to steroid use varies from 34.3% to 56%
- In the hospital setting, more than half of the patients receiving high-dose steroids develop hyperglycemia, with an incidence of 86% of at least one episode of hyperglycemia and 48% of patients presenting a mean blood glucose ≥ 140 mg/dL
- Up to 40% of patients with neuropathy without a known glycemic disorder developed DM after taking corticosteroids
- In patients with respiratory diseases, the prevalence of Steroid Induced Diabetes Mellitus was 14.7%
- In transplant patients, given the concomitant use of other immunosuppressive drugs that also affect glucose metabolism, the incidence of new DM ranges between 2% and 53%, and reaches 19% in cases of functioning pancreas transplant after 39 months follow-up

Kasiske BL et al. Am J Transplant. 2003; Donihi A et al. Endocr Pract. 2006; Uzu T et al. Nephron Clin Pract. 2007; Kim SY et al. J Korean Med Sci. 2011; Montori VM et al. Diabetes Care. 2002; Chan HW et al. Nephron Dial Transplant. 2008; Bonato V et al. Transplant Proc. 2008; Fong AC et al. Diabetes Res Clin Pract. 2013

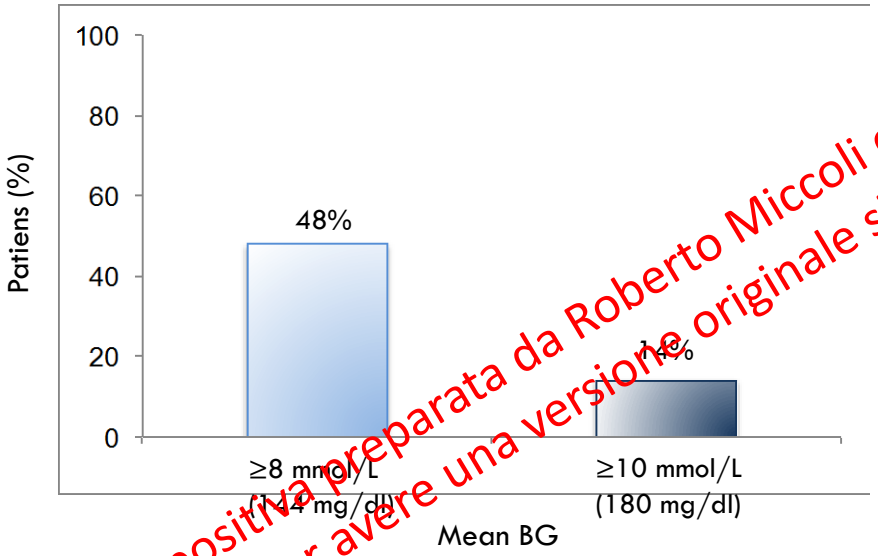
The odds ratio for presenting new diabetes after taking steroids in various studies ranges from 1.36 (*low-dose oral GCs*) to 2.31 (*among the elderly*)

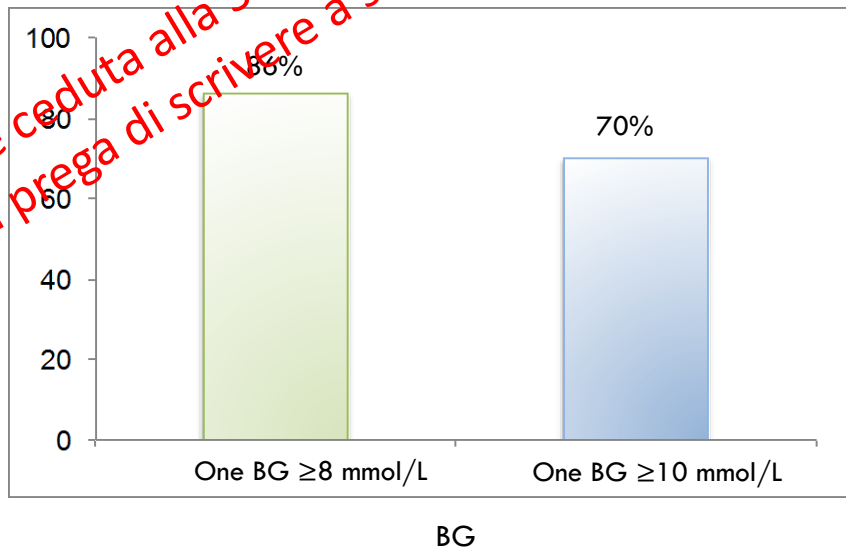
Kwan S et al. Am J Med Sci. 2013

The incidence of steroid-induced hyperglycaemia in hospital

Aim: to systematically evaluate the incidence of steroid-induced hyperglycaemia in 80 non-diabetic patients admitted to a tertiary referral hospital

Method: routine fingerprick glucose monitoring for patients commencing high-dose steroid for a minimum of 48 h





Conclusions: steroid-induced hyperglycaemia is common in hospital. Patients should be monitored for hyperglycaemia upon commencement of high-dose steroid therapy

Fong AC et al. Diabetes Res Clin Pract. 2013

Risk factors for the development of steroid-induced diabetes mellitus

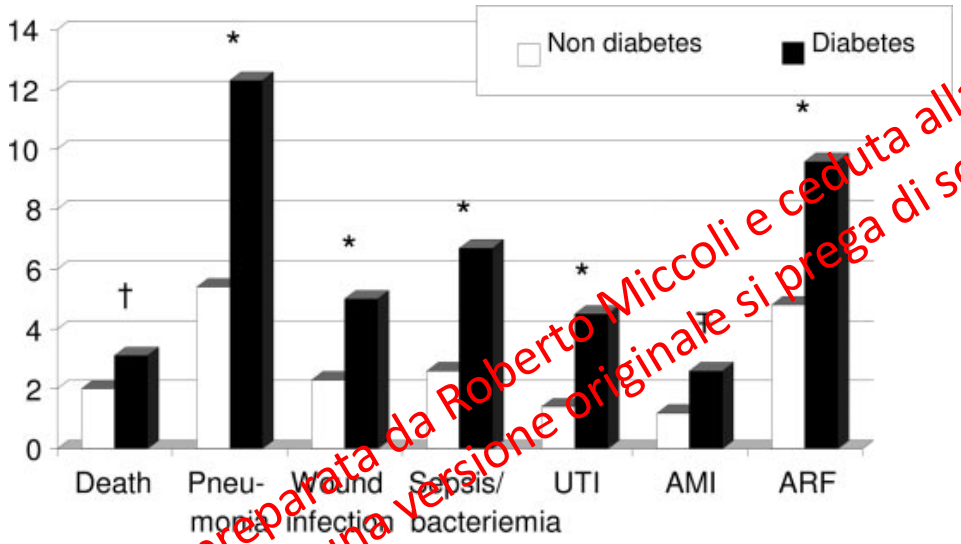
Dose and type of steroid	History of GDM
Duration of steroid treatment	Family history of diabetes
Continuous GC scheme	IFG, IGT
Age (*older*) and race (*African Americans*)	High burden of comorbidities
BMI	Concurrent immunosuppression

Gender does not seem to be a predictor and, conversely, the early withdrawal of corticosteroids is a protective factor

Tamez-Pérez HE et al. World J Diabetes. 2015

Effects of steroid induced hyperglycemia

Clinical Outcome of hyperglycemia



Thirty-day mortality and inhospital complication rates in patients with and without diabetes: blood infection (combined bacteriemia and sepsis); urinary tract infection (UTI), acute myocardial infarction (AMI), and acute renal failure (ARF).
*p < 0.001; †NS; ‡p <0.017

Acute hyperglycemia is associated with:

- increased hospital stay
- repeated emergency room visits
- risk of admission to intensive care
- higher risk of infection rates
- poor wound healing
- higher hospital mortality rates

In susceptible populations such as the elderly, **persistent hyperglycemia** associated with GC use can precipitate hyperglycemic hyperosmolar states

Frisch A et al. Diabetes Care. 2010
Donihi AC et al. Endocr Pract. 2006
Hwang JL et al. Diabetes Metab Res Rev. 2014
Fong AC et al. Diabetes Res Clin Pract. 2013
Umpierrez GE et al. J Clin Endocrinol Metab. 2002

The tangled effects of GCs on metabolism

⇧PEPCK/G6Pase

⇧TG synthesis

Impairs insulin signaling

** ↓ insulin secretion

* Insufficient ↑ in insulin release

Alters beta cell function

Fat accumulation

⇧gluconeogenesis

⇧ [GCs]

FFA release
(↑ HSL activity)

Fat accumulation
(↑ LPL activity)

Impairs insulin and lipases signaling
(↓ glucose uptake)

Visceral adipose tissue
(cytokine production profile and diabetogenic activity)

Subcutaneous adipose tissue

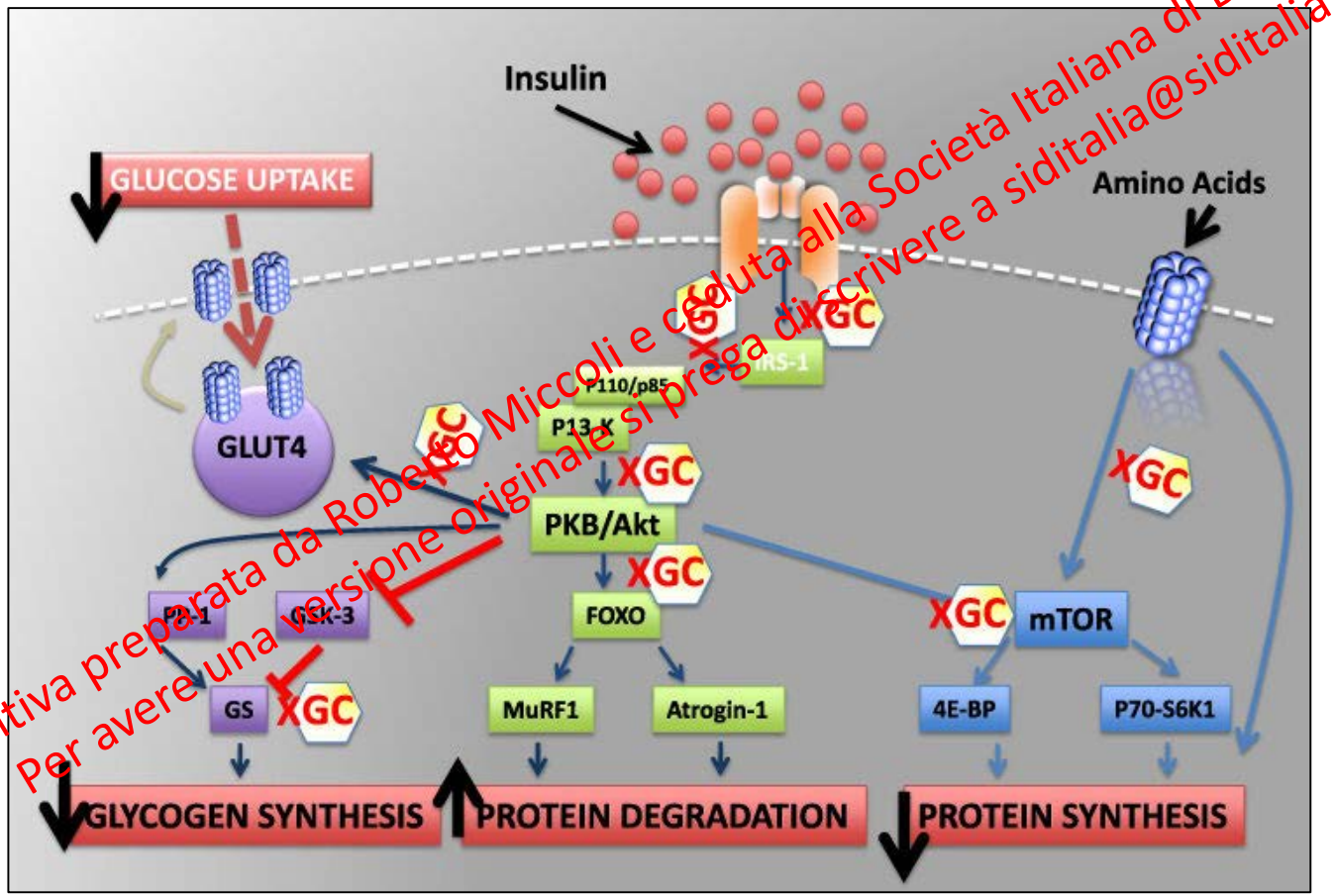
Muscle wasting
(corticosteroid myophathy)

Fat accumulation

Impairs insulin signaling
(↓ glucose uptake)

Modified from Pasieka AM et al. Metabolities. 2016

Molecular basis of glucocorticoid action



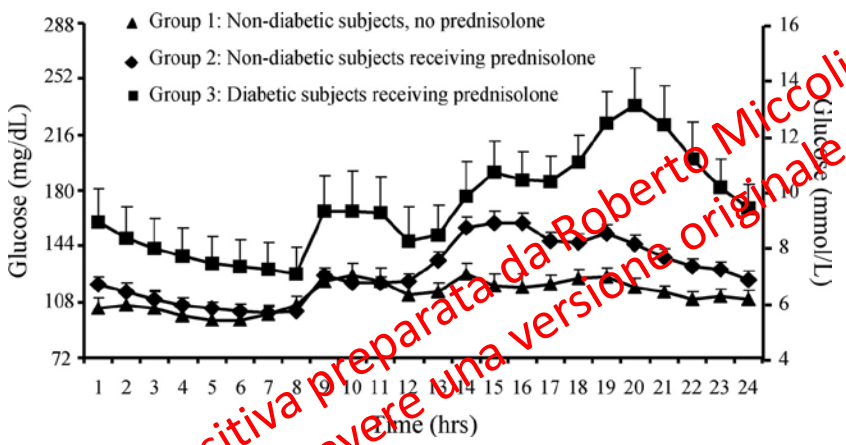
Hwang JL et al. Diabetes Metab Res Rev. 2014

Pattern of hyperglycemia induced by prednisolone

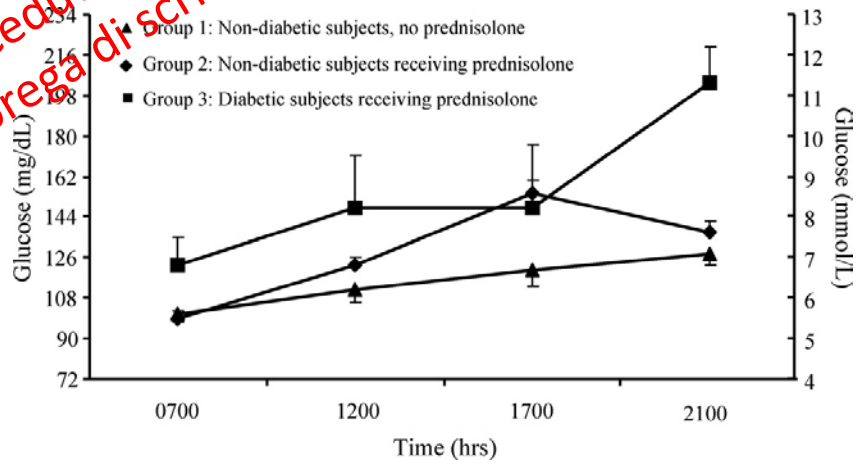
Design and Setting: cross-sectional study in 60 consecutive subjects with **chronic obstructive pulmonary disease** admitted to hospital: group 1, pts without known diabetes and not treated with glucocorticoids; group 2: pts without known diabetes and treated with prednisolone (30 ±6 mg/d); group 3: pts with known diabetes treated with prednisolone (26 ±9 mg/d).

Main Outcome Measure: Interstitial glucose concentration was assessed during continuous glucose monitoring.

Continuous glucose monitoring



Routine finger-prick blood glucose levels



Conclusions: Prednisolone predominantly causes hyperglycemia in the afternoon and evening. Treatment of prednisolone-induced hyperglycemia should be targeted at this time period

Burt MG et al. J Clin Endocrinol Metab. 2011

Pharmacokinetic and pharmacodynamic of GCs

- Following oral administration of the most commonly used steroids (prednisone and prednisolone), **peak plasma concentration** is approximately **1 hour later** , with a half-life of 2.5 hours
- The impact on glucose tolerance is more prolonged (**genomic action**)
- Glucose levels after prednisone and prednisolone reach a peak after 4-8 hours and last for about 12-16 hours, while data on dexamethasone suggest a more prolonged effect
- These drugs may cause hyperglycemia when administered at supraphysiological doses by any route (topical, oral, inhaled, intramuscular, intravenous or intra-articular), although, from the population perspective, there is either minimal or no association of incident diabetes with prescribing of glucocorticoid-containing inhalers, topical preparations, eye drops, or infrequent glucocorticoid injections for musculoskeletal disorders*

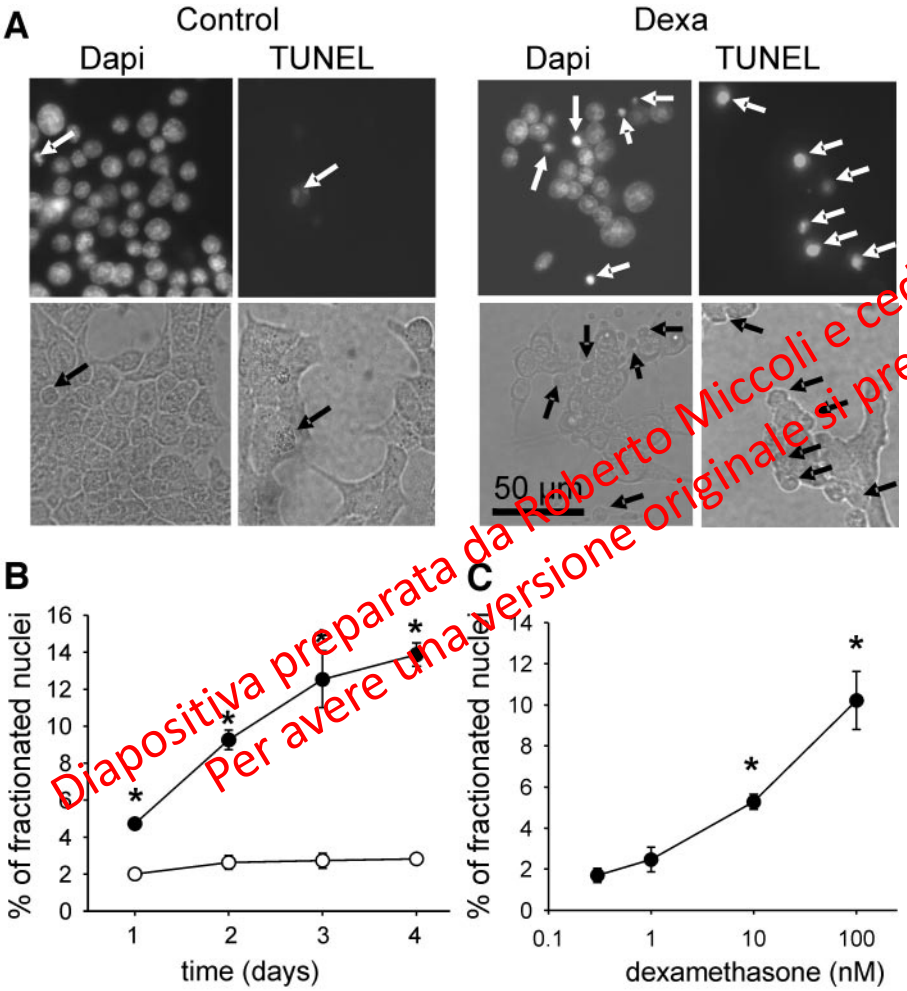
Magee MH et al. J Clin Pharmacol.
Toth GG et al. Drug Monit. 1999
*Gulliford MC et al. Diabetes Care. 2006

Glucocorticoids, bone and insulin resistance

Ferris HA et al. J Clin Invest. 2012

GCs and beta-cell function. Studies *in vitro* and *in vivo*

Dexamethasone (Dexa)-induced cell death in INS-1 cells incubated with 100 nmol/l Dexa



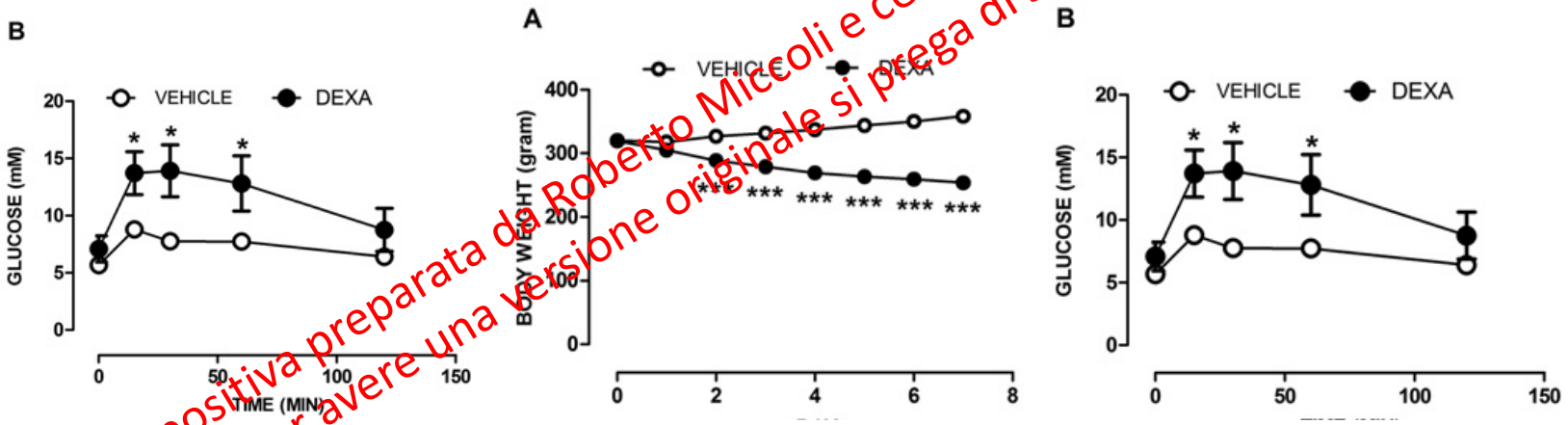
The amount of condensed nuclei in control INS-1 cell culture was almost constant over 4 days (2.0 ±0.2 to 2.8 ±0.2%; Fig. B). Treatment with dexamethasone (100 nmol/l) increased the number of condensed nuclei twofold after 1 day to sevenfold after 4 days of treatment (to 4.7 ±0.12 and 13.9 ±0.6%, respectively; Fig. A and B). In parallel, the number of TUNEL- stained cells increased dramatically after dexamethasone treatment but not in control INS-1 cells (Fig. A). The effect of dexamethasone was dose-dependent and significant at 10 nmol/l (Fig. C).

Ranta F et al. Diabetes. 2006

Direct inhibitory actions of GCs on GLP-1

Male Wistar rats treated with once-daily intraperitoneal injections of dexamethasone (1.0 mg/kg of body weight, DEXA) or saline (vehicle) for 7 consecutive days.

On the day of the final injection, rats were starved for 6 h and then subjected to an OGTT (2 g/kg of body weight). Blood glucose (B) and serum insulin (C) levels were monitored at the indicated time points. (D) At the end of the OGTT, a larger blood sample was collected to measure serum GLP-1 levels. Results are means±S.E.M. (n = 8–11). *P<0.05, **P<0.01, ***P<0.001 compared with vehicle.



Daily injections of dexamethasone to Wistar rats for 7 consecutive days induce **glucose intolerance** and **hyperinsulinaemia and reduce circulating levels of GLP-1**

Kappe C et al. Clin Sci (Lond). 2015

Pathophysiology of steroid induced diabetes mellitus: Summary

Increase in insulin resistance with increased glucose production and inhibition of the production and secretion of insulin by pancreatic β-cells
GCs increase endogenous glucose production, increment in gluconeogenesis and antagonizing the metabolic actions of insulin
Enhance the effects of other counterregulatory hormones, such as glucagon and epinephrine, which increase the endogenous synthesis of glucose
GCs reduce peripheral glucose uptake at the level of the muscle and adipose tissue
GCs also inhibit the production and secretion of insulin from pancreatic β-cells and induce β-cell failure indirectly by lipotoxicity
Impairment of gut islet axis (impaired insulinotropic effects of GLP-1)

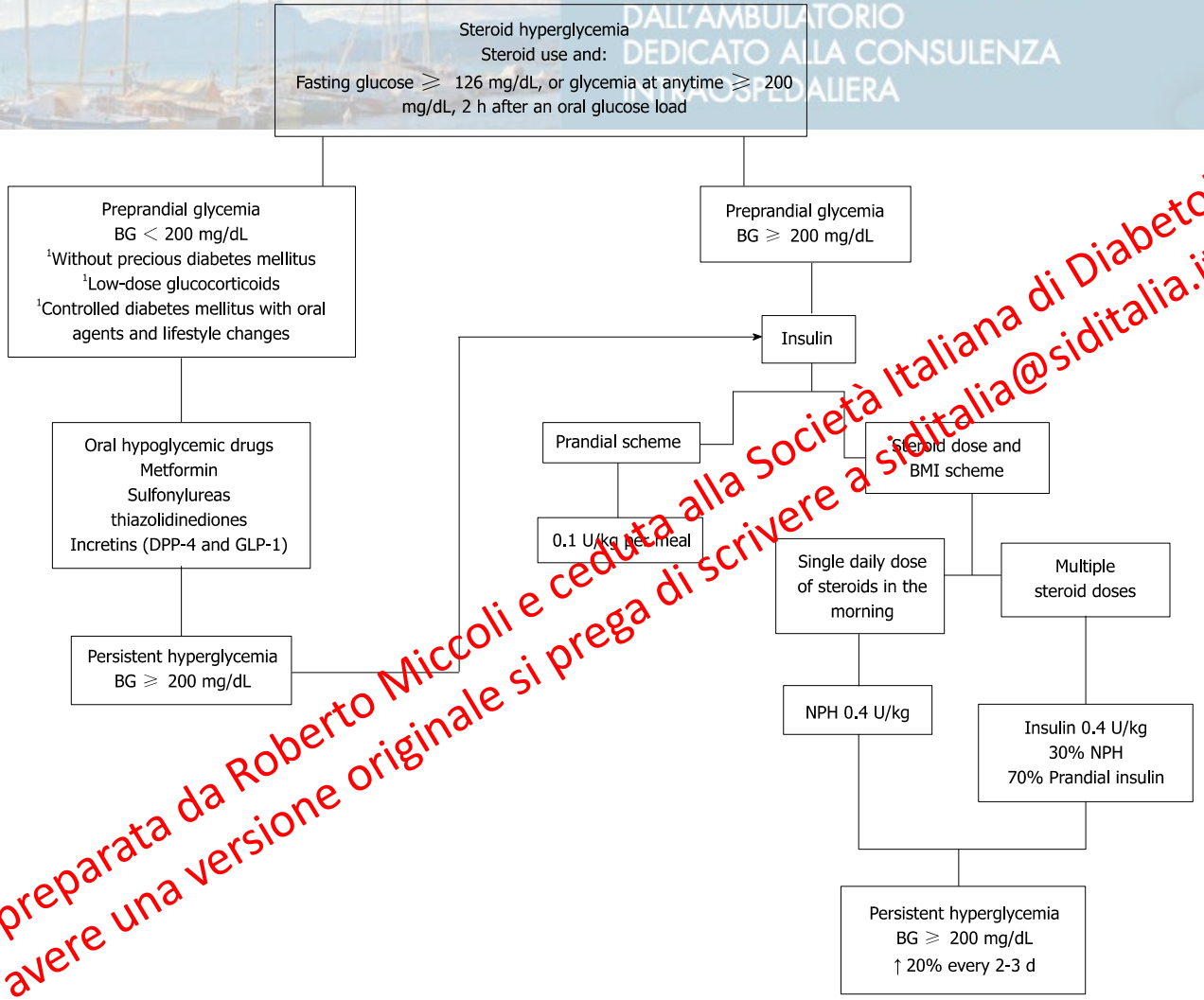
Tamez-Pérez HE et al. World J Diabetes. 2015

Steroid-induced diabetes treatment options

What is important to keep in mind when treating diabetes:

- Due to differences in steroid dose and the scheme used, the approach to hyperglycemia should always be individualized.
- A complete evaluation of the degree of pre-existing glucose intolerance, the patient's clinical condition, the degree of hyperglycemia, the type, dose and frequency of administration of the corticosteroid compound and the mechanism of action, pharmacokinetics and pharmcodynamics of the different hypoglycemic drugs must be made in order to determine the best treatment approach in each patient.
- When selecting the best treatment the first consideration to make is whether to use oral hypoglycemia drugs or insulin

Tamez-Pérez HE et al. World J Diabetes. 2015



Tamez-Pérez HE et al. World J Diabetes. 2015

Treatment of steroid-induced or steroid-exacerbated hyperglycaemia with insulin

PRANDIAL SCHEME

- The prandial insulin scheme is based on the observation that even though normal levels of fasting glucose can be present; serum **glucose gradually increases throughout the day** reaching a maximum concentration after meals, with a gradual reduction at night.

- The scheme is based on the patient's weight, the total calories consumed during the meal, and the establishment of a food pattern

- **The initial dose is calculated at 0.1 U/kg per meal**, and is then modified depending on the glycemic response and the amount of **supplementary insulin** required to correct the pre-prandial hyperglycemia.

Tamez-Pérez HE et al. World J Diabetes. 2015

Multiple dose injection (MDI) therapy

The use of basal insulin, in addition to prandial insulin, is usually considered when using high doses of steroids are used or in those patients with characteristics of diabetes prior to the start of the steroid.

Estimation of the initial dose of basal insulin in GCs-induced hyperglycemia

Prednisone dose (mg/day)	Dexamethasone dose (mg/day)	Insulin glargine/detemir dose (IU/kg per day)
≥40	≥8	0.4
30	6	0.3
20	4	0.2
10	2	0.1

Modified from Clore JN et al. Endocr Pract. 2009

Insulin therapy in steroid induced diabetes: practical and clinical consideration

In-hospital dose calculation is similar to outpatient doses, with some modifications. In patient with **previous diagnosis of diabetes** and treated with insulin prior to admission, the dose should be increased 20%. On the other hand, if high doses of steroids are used and the dose must be calculated empirically, the insulin dose will be calculated based on weight 0.7 U/kg per day.

In hospitalized patients receiving **high doses of steroids** with glucose levels above 400 mg/dL, an insulin infusion pump should be indicated. This indication is particularly important in patients receiving intravenous steroids pulses in which insulin requirements are difficult to predict

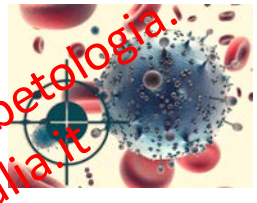
The insulin dose must be adjusted according to capillary glycemias every 2-3 d, with increases and/or decreases around 20%. Additionally, insulin doses should be adjusted based on changes in steroid dose to prevent hyperglycemia and/or hypoglycemia. The percentage of insulin adjustment corresponds to half the percentage in steroid change; for example, **if the steroid dose is reduced or increased by 50%, the insulin dose will be reduced or increased 25%**, respectively

Tamez Perez HE et al. Rev Assoc Med Bras. 2012
Hirsch IB et al. *Endocrinol Metab Clin North Am.* 1997
Umpierrez GE et al. J Clin Endocrinol Metab. 2012
Hwang JL et al. Diabetes Metab Res Rev 2014
Tamez-Pérez HE et al. World J Diabetes. 2015

Steroid-Induced diabetes mellitus in special settings

How to manage steroid diabetes in patient with cancer

Steroid-induced hyperglycemia in patients undergoing cancer therapy



- Patients undergoing cancer therapy are frequently treated with GCs that may be used in anti-emetics regimes, to reduce oedema, aid with nutrition or to help in pain management
- Some Haematological malignancies (i.e. haematological malignancies) respond well to high dose GCs and these drugs are integral to the management of such malignancies.
- Managing pre-existing or newly diagnosed diabetes in patients with cancer can be challenging.
- Many patients undergoing treatment may be struggling with multiple comorbidities and the adverse effects of their cancer therapy.
- Nevertheless, pragmatic management of hyperglycaemia appears to be important to reduce hyperglycaemia-related symptoms. Moreover, observational evidence suggests that poor glycaemic control may lead to poorer outcomes in cancer therapy

Jacob P et al. Q J Med 2015
Harris D et al. Curr Oncol. 2013
Swerdlow AJ et al. Br J Cancer. 2005

Is steroid-induced hyperglycemia predictable for patients undergoing cancer therapy?

Variables significantly and positively correlated with hyperglycemia

Patient group	*Characteristic*							
	Age	*Sex*	*BMI*	*History of DM*		*GC dose*	*Hours since*	
				Personal	*Family*		*GC dose*	*Meal*
Bone marrow transplantation (n=16)								
r	0.11	0.25	0.16	0.16	–0.13	0.19	0.21	0.27
p	0.20	0.81	0.70	0.13	0.23	0.04[a]	0.02[a]	0.02[a]
Chemotherapy (n=50)								
r	0.19	–0.14	0.41	0.26	–0.16	0.62	0.49	0.05
p	0.40	0.60	0.07	0.32	0.54	0.79	0.04[a]	0.83
Radiation therapy (n=24)								
r	0.04	0.00	0.29	0.13	0.00	0.21	0.04	0.20
p	0.84	1.00	0.13	0.55	1.0	0.32	0.82	0.25

[a] Statistically significant (defined as $p < 0.05$).
BMI = body mass index; DM = diabetes mellitus; GC = glucocorticoid.

The Authors recommend that all patients with cancer who are being treated with GCs should undergo routine glucometer testing, with CBG measurements being taken at least 4–6 hours after ingestion of GCs.

Harris D et al. Curr Oncol. 2013

Hyperglycaemia in patients with cancer: when to treat

- For outpatients with only a few days of mild steroid hyperglycemia, therapy may not be needed. Treatment would require patients to learn to test their glucose, take pills, or give insulin, all with no proven benefit.

- In the hospital, however, this type of management is possible and should be considered for even brief episodes of hyperglycemia. If the patient has only a few days of steroid therapy, and hyperglycemia is not causing symptoms, no therapy is indicated. However, patients in the hospital for 3 days or more with a fasting glucose level over 110 mg/dL or a postprandial glucose level over 140 mg/dL would be candidates for therapy.

Oyer DS et al. J Support Oncol. 2006

Hyperglycaemia in patients with cancer: options for therapy

	Pros	Cons
Sulfonylureas	?	Potential side effects (hypo), lack of flexibility
Thiazolidinediones	Insulin sensitization through PPAR-gamma agonist effect	Not useful in the acute setting as slow onset of action. Adverse effects (bone)
Incretin-based therapies	The incretin effect helps to regulate postprandial glucose levels	Not widely used, due to gastrointestinal side effects. Lack of randomized controlled trials
Alpha-glucosidase inhibitor	?	Not widely used, due to gastrointestinal side effects
Metformin	Insulin sensitization leading to increased glucose uptake in muscle and reduced hepatic gluconeogenesis	It needs to be stopped if renal function deter orates (estimated GFR < 30) or iodinated contrast media required for imaging
Insulin		Treatment of choice for acute hyperglycaemia

The challenge of managing diabetes in patients with cancer is best approached using a multi-disciplinary team of oncology and diabetes specialists managing the patient on an individualized basis

General principles for minimizing glucocorticoid toxicity

- There should be definite indication to start GC treatment
- Use short- and intermediate-acting GCs in preference to longer acting ones
- Use minimum necessary dose and duration of treatment
- Once-a-day morning administration should be preferred over divided dose therapy
- During treatment monitor for body weight, height, blood pressure, serum lipids, blood glucose and ocular pressure and development of cataract
- Careful withdrawl after long term steroid administration
- Education and preventive measures

Aulakh R et al. Indian J Pediatr. 2008

Conclusions

- GCs are drugs that have been widely used in a variety of medical conditions. Despite their medical efficacy, steroid-induced hyperglycemia remains as a common potentially harmful problem that has significant clinical implications in patients with and without diabetes mellitus

- A proper understanding of the mechanisms involved in steroid hyperglycemia is needed, since this will allow early detection and effective treatment in these patients.

- In most cases insulin must be the treatment of choice, especially in cases of serum glucose > 200 mg/dl. Nevertheless an individualized approach must be taken in each patient in order to consider lifestyle modifications and oral hypoglycemic drugs as alternative therapeutic

- Appropriate guidelines that establish the recommendations for the diagnosis and treatment of steroid diabetes are needed in order to prevent all the complications associated with the hyperglycemic state.

Unite for Diabetes - World Diabetes Day 2016

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