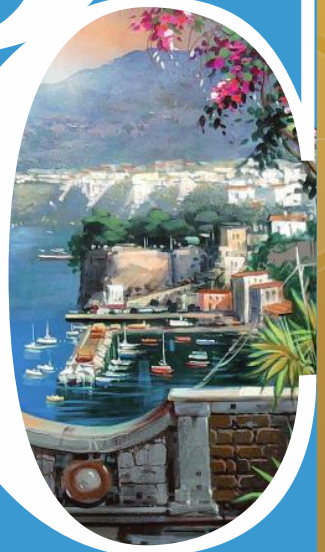
Altogether to Beat Cushing's Syndrome

ABC



Viaggio alla (ri)scoperta della Sindrome di Cushing

Terza Edizione

Sorrento, 27-30 maggio 2014

CUSHING IATROGENO:

L'APPROCCIO TERAPEUTICO ED IL FOLLOW-UP

Alberto G. Ambrogio

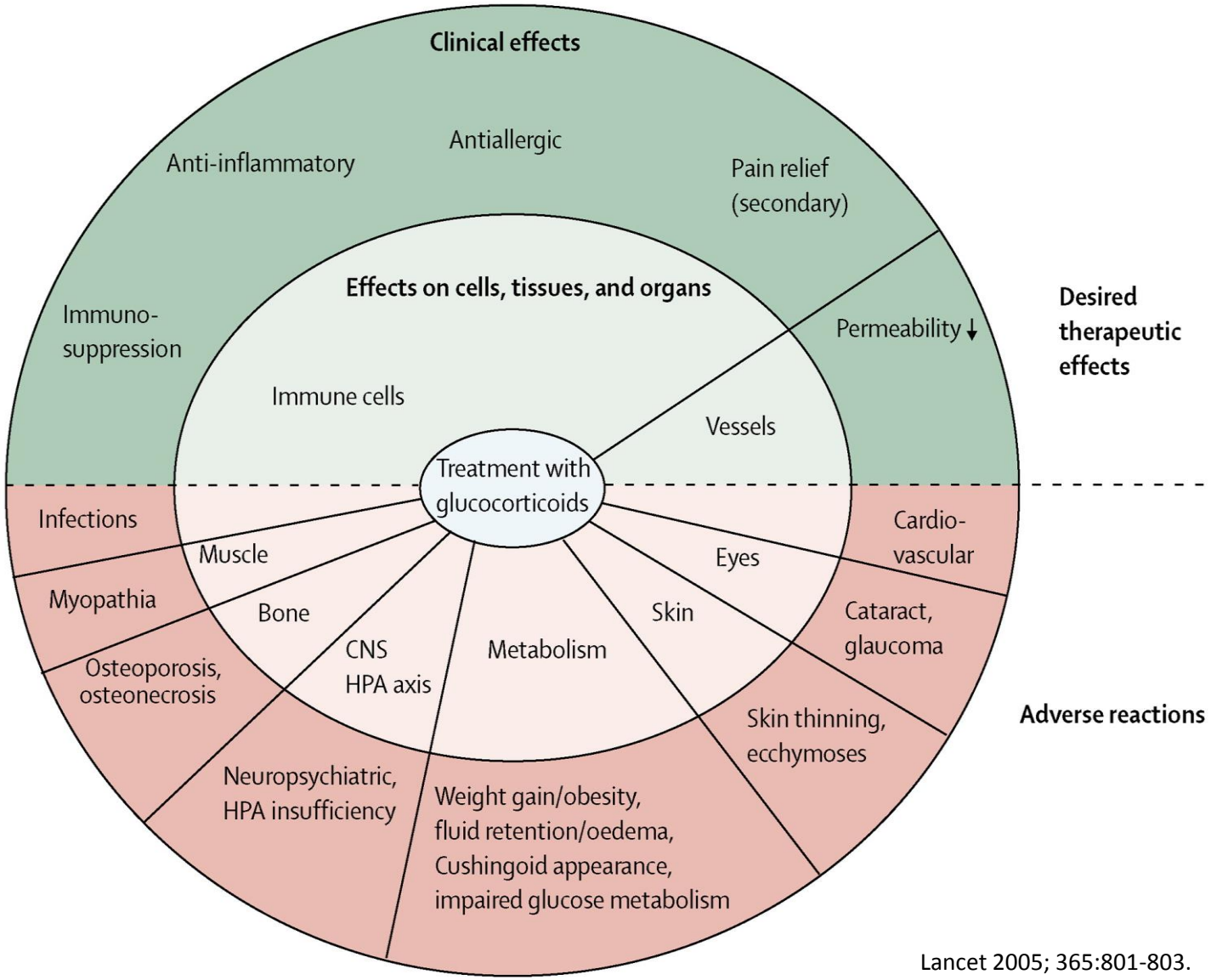
Anniversary: 50 years of glucocorticoid treatment in rheumatoid arthritis

The impact of this event has been captured [2] by dividing the history of rheumatology into 'BC' and 'AC' (before cortisol and after cortisol).

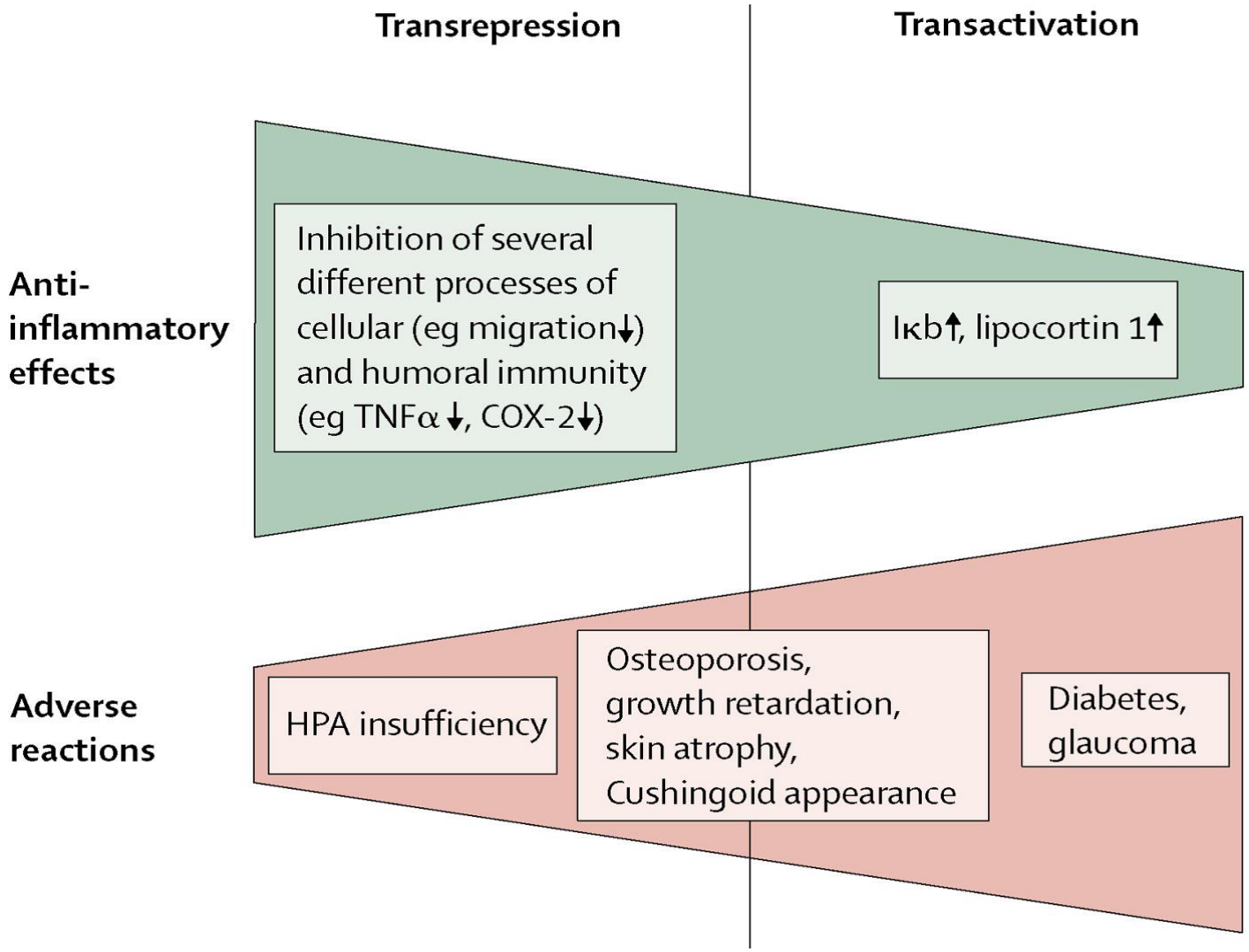
FIG 1. Professor Philip Showalter Hench, drawn by Dr J. M. H. Moll [26]. Reprinted with permission.

A few sceptical voices were raised. Russel Cecil's was one of them: '... hypoadrenalism is not the answer to the rheumatoid arthritis problem ... Hench and Kendall have only given us two more drugs to fumble with' [9].

Rheumatology 1999; 38:100-2.

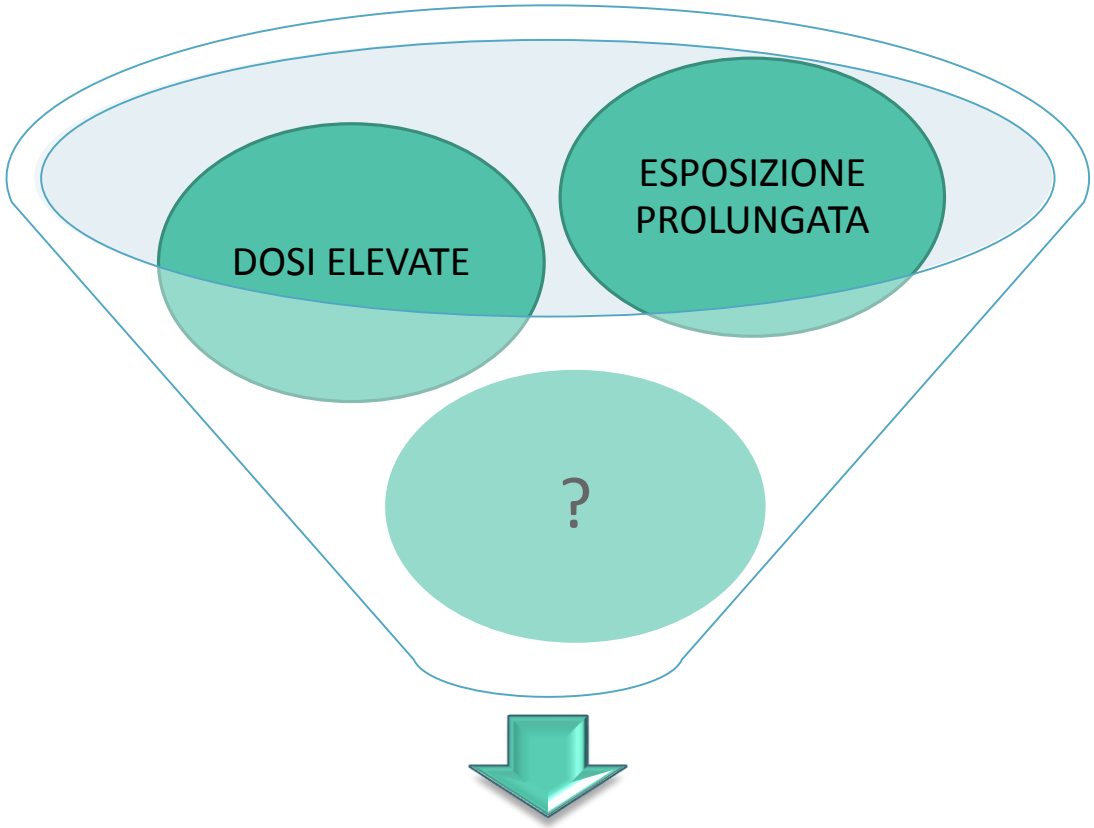


Lancet 2005; 365:801-803.



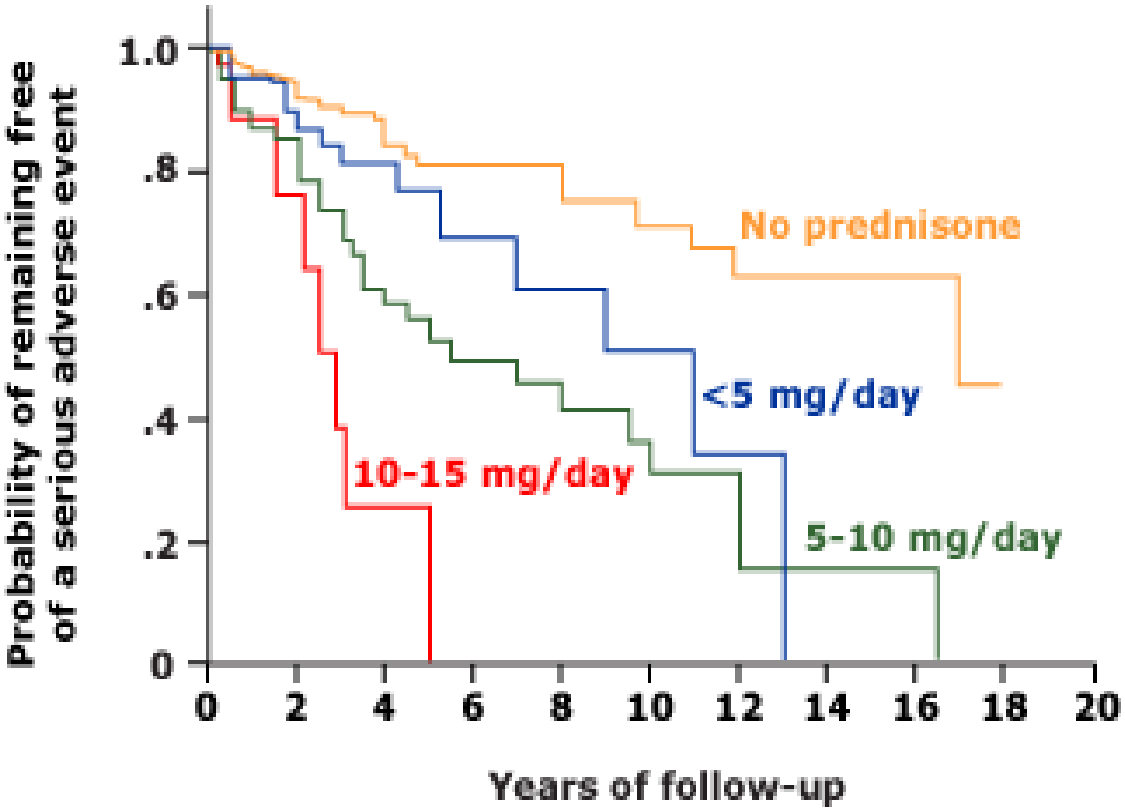
Lancet 2005; 365:801-803.

Terapia con glucocorticoidi



Cushing iatrogeno

Time course of steroid side effects



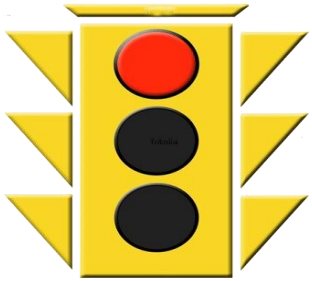
Am J Med. 1994; 96:115-23.

Approccio terapeutico agli effetti collaterali indotti dai glucocorticoidi

Dove possibile

Scalare gradualmente la terapia steroidea fino alla sua completa sospensione

Se impossibile



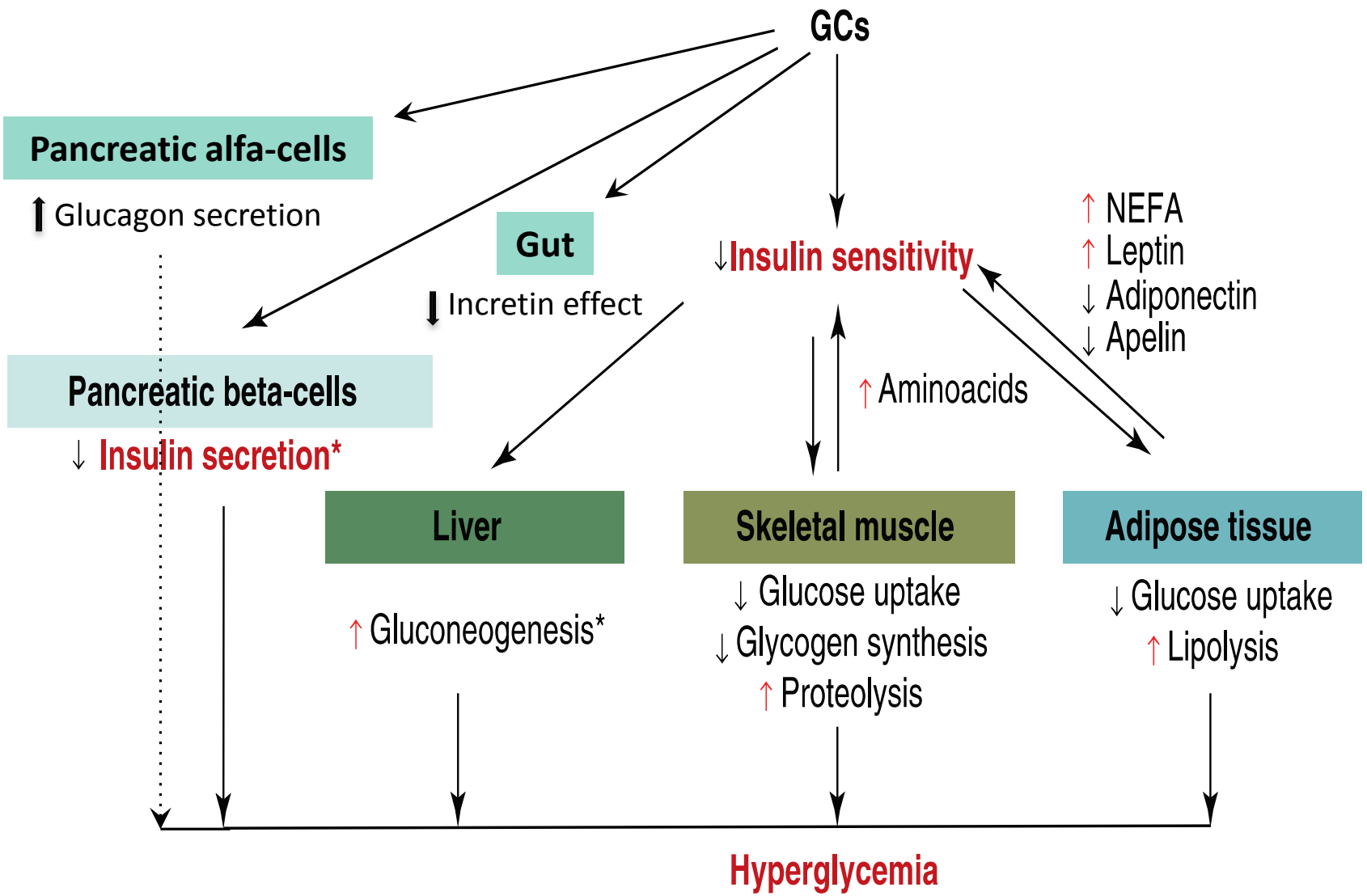
Quanto necessario ma il meno possibile

Effetti collaterali della terapia con glucocorticoidi

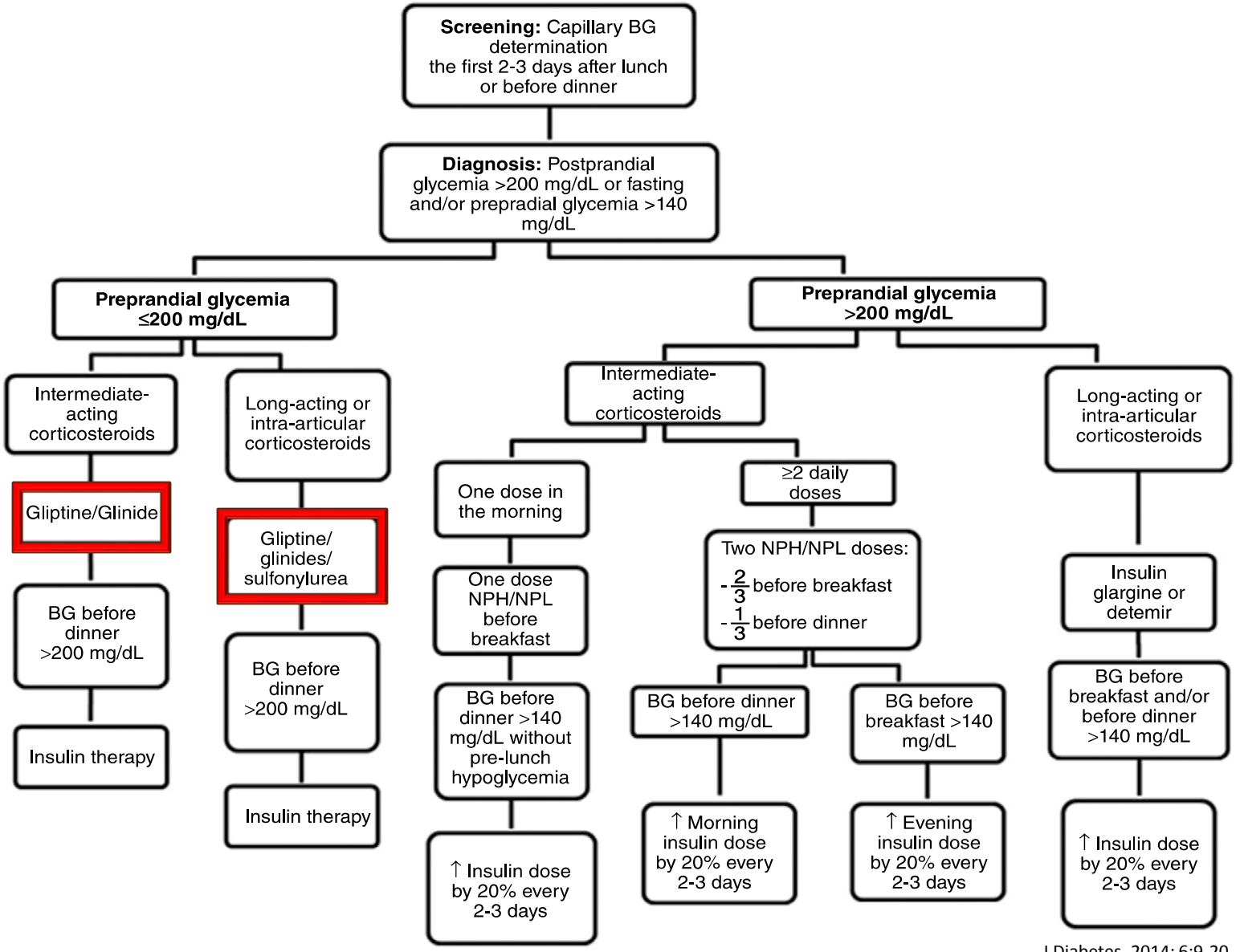
- Iperglicemia
- Osteoporosi
- Miopatia

Iperglicemia indotta da glucocorticoidi

- Possibili “predittori”: dose e durata del trattamento, età, razza, peso corporeo, storia di intolleranza glucidica o familiarità per diabete mellito
- I criteri utilizzati per la diagnosi di diabete mellito, in particolare FPG > 126 mg/dl o HbA1c > 6.5%, possono sottostimare l’iperglicemia da glucocorticoidi
- Mancanza di studi sull’argomento per la definizione di linee guida per il trattamento ed il monitoraggio
- Le modificazioni dello stile di vita risultano molto spesso improponibili
- Non sempre la sospensione dei glucocorticoidi porta alla normalizzazione del compenso glicemico



Modified from Trends Endocrinol Metab. 2011; 22:499-506.



J Diabetes. 2014; 6:9-20.

Farmaci antidiabetici orali

Table 3 Currently available non-insulin hypoglycemic drugs: advantages and disadvantages in terms of the hyperglycemia induced by transient treatment with glucocorticoids (modified from Saigi and Perez[88])

Drugs	Advantages	Disadvantages
Metformin	Mechanism of action (insulin sensitizer) No hypoglycemia High security	Slow onset of action Main effect on fasting glucose Need for progressive dose tritation to improve tolerance Unpredictable and unchanging hypoglycemic effect Contraindicated in renal failure and conditions associated with hypoxia
Sulfonylureas (e.g. glibemclamide, glimepiride, glipizide, glicazide)	Immediate onset of action	Prolonged effect (24 h) Main effect on fasting glucose Unpredictable and unchanging hypoglycemic effect Moderate–high risk of hypoglycemia
Glinides (e.g. repaglinide)	Immediate onset of action Main effect on postprandial glucose Short duration of action (4–6 h) Minimal dose tritation	Low risk of hypoglycemia Unpredictable effect
Glitazones (e.g. pioglitazone)	Mechanism of action (insulin sensitizer) No hypoglycemia	Onset of action (4–6 weeks) Main effect on fasting glycemia Unpredictable and unchanging hypoglycemic effect Risk of heart failure due to fluid retention
Gliptines (e.g. sitagliptine, vildagliptine, saxagliptine)	Immediate onset of action Main effect on postprandial glucose No hypoglycemia	Unpredictable and unchanging hypoglycemic effect Limited experience
GLP-1 analogues (e.g. exenatide, liraglutide)	Immediate onset of action Main effect on postprandial glucose No hypoglycemia	Unpredictable and unchanging hypoglycemic effect Limited experience Poor initial tolerance (nausea and votiming) Need for progressive dose tritation to improve tolerance Subcutaneous administration

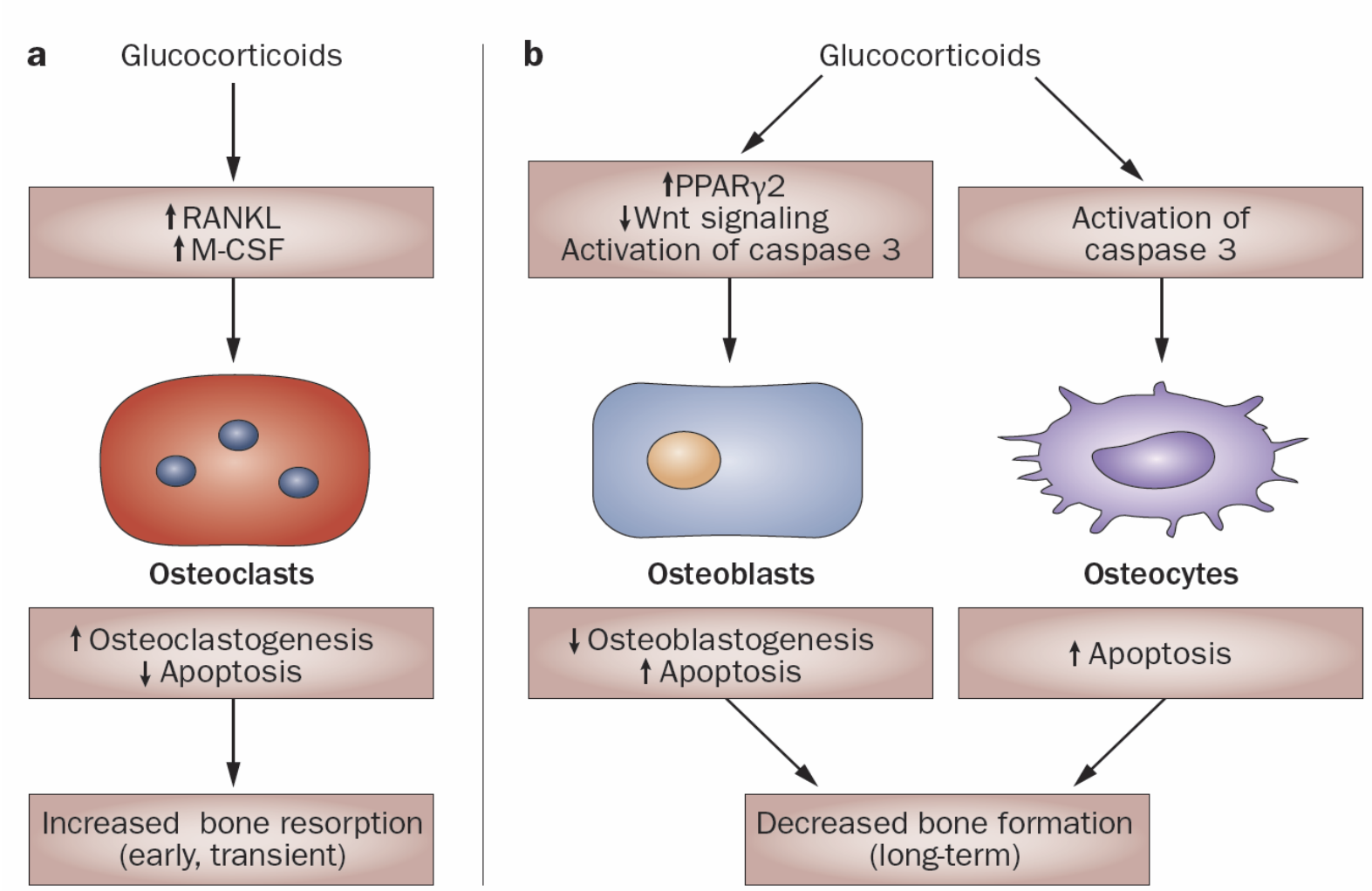
GLP-1, glucagon-like peptide-1.

J Diabetes. 2014; 6:9-20.

Osteoporosi indotta da glucocorticoidi

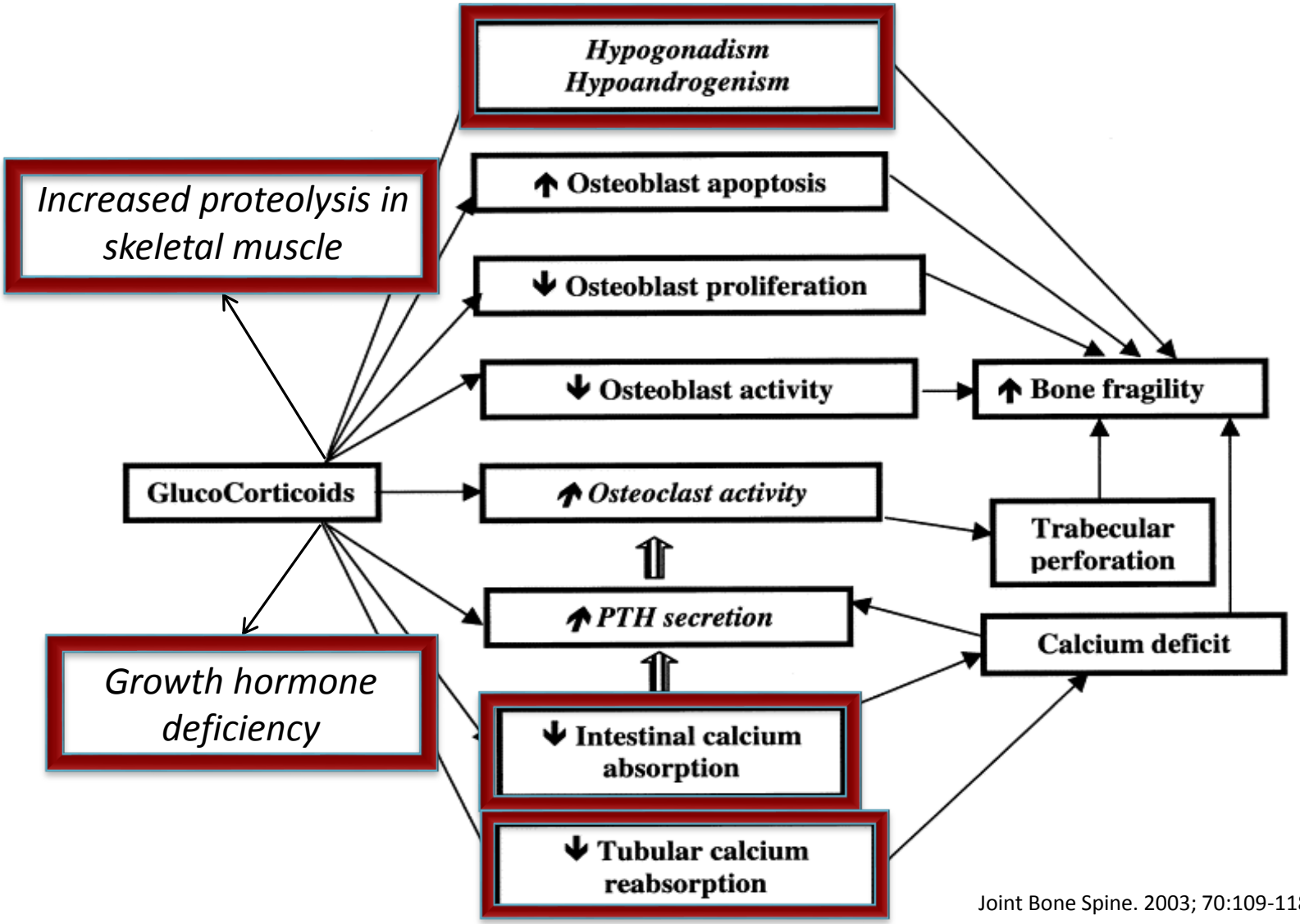
- Non vi è una dose o via di somministrazione “sicura”
- Il rischio di frattura è dose-dipendente e risulta incrementato a partire già dai primi 3-6 mesi di terapia
- E’ interessato principalmente l’osso trabecolare
- La qualità dell’osso è ridotta ed, a parità di BMD, il rischio di frattura è maggiore nei pazienti in terapia con glucocorticoidi vs non
- Il rischio di frattura diminuisce dopo la sospensione della terapia

Effetti diretti dei glucocorticoidi sull'osso



Nat Rev Rheumatol. 2010; 6:82-8.

Effetti indiretti dei glucocorticoidi sull'osso



Joint Bone Spine. 2003; 70:109-118.

Sulla base della fisiopatologia….

Aumentato riassorbimento osseo

- Bisfosfonati
- Denosumab?

Ridotta sintesi ossea

- Paratormone
- Ranelato di stronzio?

Ridotto assorbimento intestinale di calcio

- Calcio & Vitamina D3

Ridotto riassorbimento renale di calcio

- Tiazidici

Ipogonadismo

- Estrogeni, Testosterone, Raloxifene

Deficit di ormone della crescita

- Ormone della crescita?

Table 1. Guidelines for glucocorticoid-induced osteoporosis.

Organization	American College of Rheumatology (ACR) [ACR, 2001]	Royal College of Physicians, UK (RCP) [RCP, 2002]	Osteoporosis Society of Canada [Brown and Josse, 2002]	Japanese Society for Bone and Mineral Research (JSBMR) [Nawata *et al*. 2005]	National Health Service, UK (NHS) [Kanis *et al*. 2007]	European League Against Rheumatism (EULAR) [Hoes *et al*. 2007]
Publication date	2001	2002	2002	2004	2007	2007
Evidence	Expert committee review of the literature	Systematic review with evidence grading	Systematic review with evidence grading	Based on two studies by the subcommittee and evidence from the literature	Systematic review and cost-effectiveness analysis	Systematic review with evidence grading and expert consensus
BMD testing	If GC planned for >6 months. All patients on long-term GC	Not required for those starting on bisphosphonate, but everyone else should be tested	All patients on >2.5 mg/d prednisone for >3 months	If GC planned for ≥3 months and no prior fragility fractures	All patients <75 years and with no prior fragility fracture	Not specified
Vitamin D and calcium	All patients initiating therapy (≥5 mg/d prednisone equivalent for ≥3 months). All patients on long-term GC. Use 800 IU/d Vitamin D or active vitamin D	Adequate dietary calcium recommended. Use as adjunct with bisphosphonate therapy	All patients: 400 IU/d vitamin D if <50 years, 800 IU/d if >50 years. 1000 mg/d calcium for women <50 years or men, 1500 mg/d for women >50 years	Active vitamin D as second-line treatment agent. Active vitamin D with bisphosphonate in high-risk patients	Not specified	If on ≥7.5 mg/d prednisone equivalent for >3 months
Bisphosphonates: -patients warranting treatment	All patients at initiation of GC therapy (≥5 mg/d prednisone equivalent for ≥3 months), and patients on long-term GC if T-score <−1.0. Alendronate or risedronate as first-line agents. Use caution in premepausal women	At initiation of GC therapy if >65 years, with prior fragility fracture, or BMD≤−1.5	Patients on >7.5 mg/d prednisone-equivalent for >3 months, or 2.5 mg/d–7.5 mg/d for >3 months and BMD ≤1.5. Alendronate, risedronate or etidronate for prevention or treatment	All patients with prior fragility fracture. All patients on ≥5 mg/d of prednisone-equivalent for ≥3 months or BMD <80% young adult mean	Patients with prior fragility fracture. All patients >75 years. Patients with BMD ≤− 2.0. Less stringent BMD cut-off if on higher-than-average dose of GC	Based on risk factors: low BMD, female gender, older age, postmenopausal
Sex hormones	Replace if deficient or clinically indicated	Offer to hypogonadal patients	Not specified	Consider raloxifene in postmenopausal women if cannot tolerate bisphosphonate	Not specified	Not specified
Monitoring frequency	As often as every 6 months to follow if not on therapy. Annually if on therapy	No specific recommendation, may see effects of therapy in 1–2 years	1–2 years after starting treatment	BMD and spinal X-rays every 6–12 mo to follow if not on therapy	Not specified	Not specified
Duration of treatment	Continue as long as receiving GC	Not specified	Not specified	Not specified	Not specified	Not specified

BMD, bone mineral density; GC, glucocorticoid.

TABLE 1

Lifestyle modifications and assessment of patients starting glucocorticoids for 3 months or more

Recommendation	Level of evidence
Weight-bearing activities	C
Smoking cessation	C
Avoidance of excessive alcohol intake (> 2 drinks per day)	C
Nutritional counseling on calcium and vitamin D intake	C
Assessment of risk of falling	C
Baseline dual-energy x-ray absorptiometry (DXA)	C
Serum 25-hydroxyvitamin D level	C
Baseline height	C
Assessment of prevalent fragility fractures	C
Consider radiographic imaging of the spine or vertebral fracture assessment (by DXA) for those initiating or currently receiving prednisone ≥ 5 mg/day or its equivalent	C
Calcium intake (supplement plus oral intake) of 1,200–1,500 mg daily	A
Vitamin D supplementation*	A

*Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids rather than a duration of at least 3 months.

GROSSMAN JM, GORDON R, RANGANATH VK, ET AL. AMERICAN COLLEGE OF RHEUMATOLOGY 2010 RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS. ARTHRITIS CARE RES (HOBOKEN) 2010; 62:1515–1526.

Misure generali

Modificazione dello stile di vita e valutazione iniziale dei pazienti per cui è prevista terapia steroidea per 3 mesi o più

Quale trattamento farmacologico?

Table 6 Grading of evidence for pharmacological interventions used in the management of GIO

Intervention	Spine BMD	Hip BMD	Vertebral fracture	Non-vertebral fracture
Alendronate	A	A	B[c]	nae
Etidronate	A	A	A[c]	nae
Risedronate	A	A	A[c]	nae
Zoledronic acid	A[a]	A[a]	nae	nae
Teriparatide	A[a]	A[a]	A[a,c]	nae
Alfacalcidol	A	A[b]	nae	nae
Calcitriol	A	A[b]	nae	nae

nae not adequately evaluated

[a] Comparator study

[b] Data inconsistent

[c] Not a primary end point

Osteoporos Int. 2012; 23:2257-76.

Monitoraggio

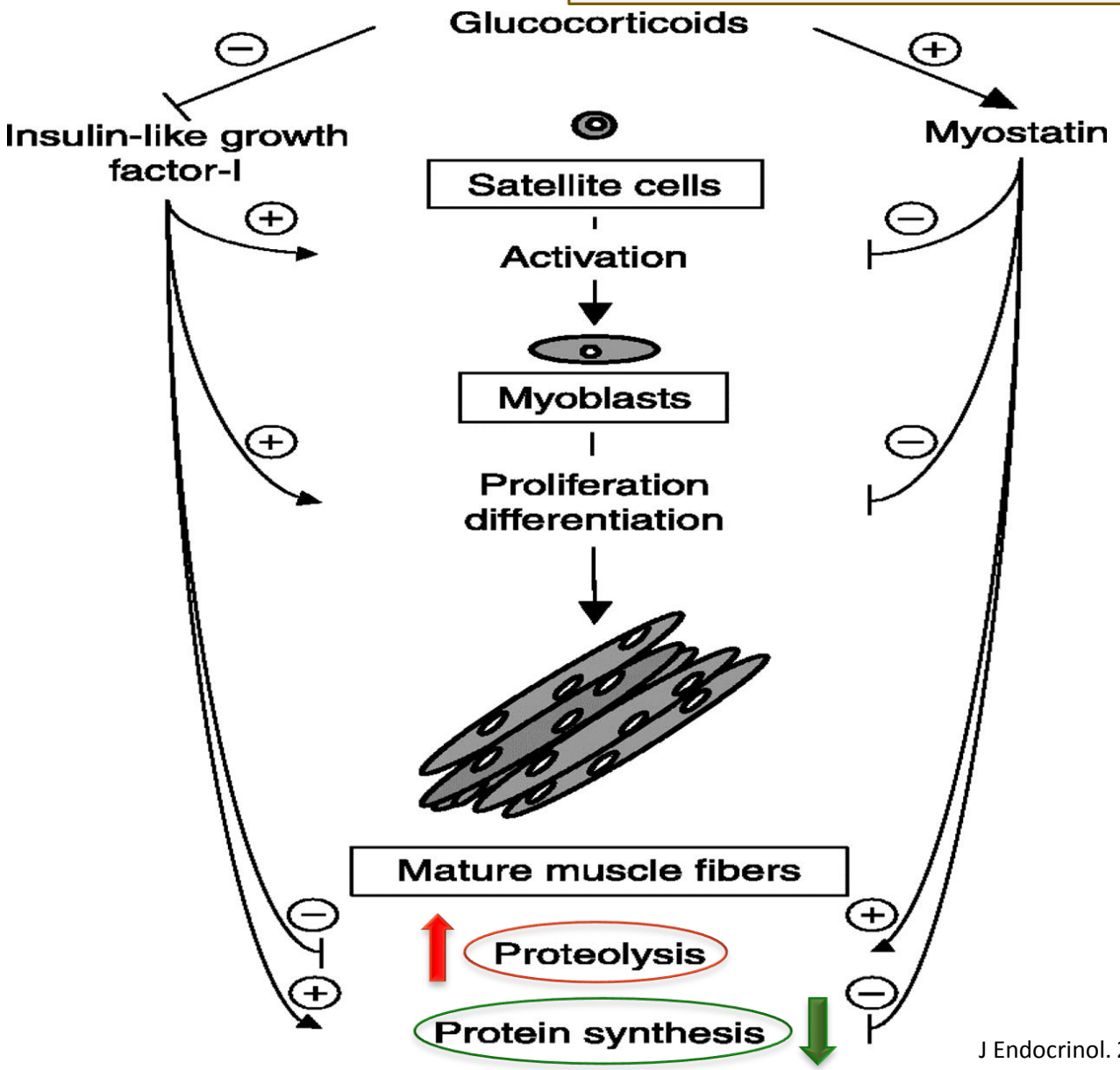
Recommendation	Grading of evidence
Assessment of ad… vitamin D, at eac…	C
Measurement of …	C
Annual height mea…	C
Vertebral fracture assessme… …XA if fracture is suspected	C
Measurement of serum PINP after 3 months of teriparatide therapy	C

Altri marcatori di turnover osseo?

Osteoporos Int. 2012; 23:2257-76.

Miopatia indotta da glucocorticoidi

- Non sembra esistere una relazione tra dose o durata del trattamento con glucocorticoidi e sviluppo di miopatia
- Sono colpite quasi esclusivamente le fibre muscolari a contrazione rapida di tipo IIb
- Esistono una forma acuta, caratterizzata da un'astenia generalizzata rapidamente progressiva, ed una forma cronica, che coinvolge principalmente i muscoli prossimali degli arti inferiori
- I glucocorticoidi fluorurati (desametasone>betametasone>triamcinolone) sembrano causare più frequentemente miopatia rispetto ai non fluorurati (ad es. idrocortisone o prednisone)
- Il sesso femminile sembrerebbe essere più colpito rispetto a quello maschile
- Oltre alla clinica, difficoltà nella diagnostica e nel monitoraggio di un eventuale trattamento (CK, aldolasi, DEXA, EMG?)

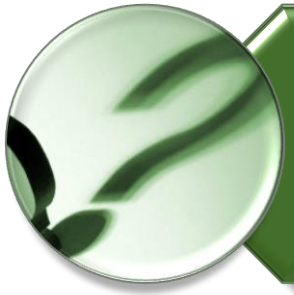


J Endocrinol. 2008; 197:1-10.

Strategie terapeutiche

Adeguato introito proteico giornaliero e, se possibile, attività fisica

Privilegiare l'utilizzo di glucocorticoidi non fluorurati



Altre terapie: IGF-1, androgeni, creatina, aminoacidi a catena ramificata, glutamina

Prospettive terapeutiche

Agonisti selettivi del recettore per i glucocorticoidi (SEGRA)

Inibitori della 11β-HSD di tipo 1