Iperglicemia in corso di terapia steroidea

Il punto di vista dell'immunoreumatologo

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U.O.C Medicina Interna
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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con nessun soggetto portatore di interessi commerciali in campo sanitario

Fifty Years of Experience with Cortisone Therapy in the Study and Treatment of Rheumatoid Arthritis

GUNTHER NEECK

Rostock Clinic South, Rostock, Germany

HISTORY AND INTRODUCTION

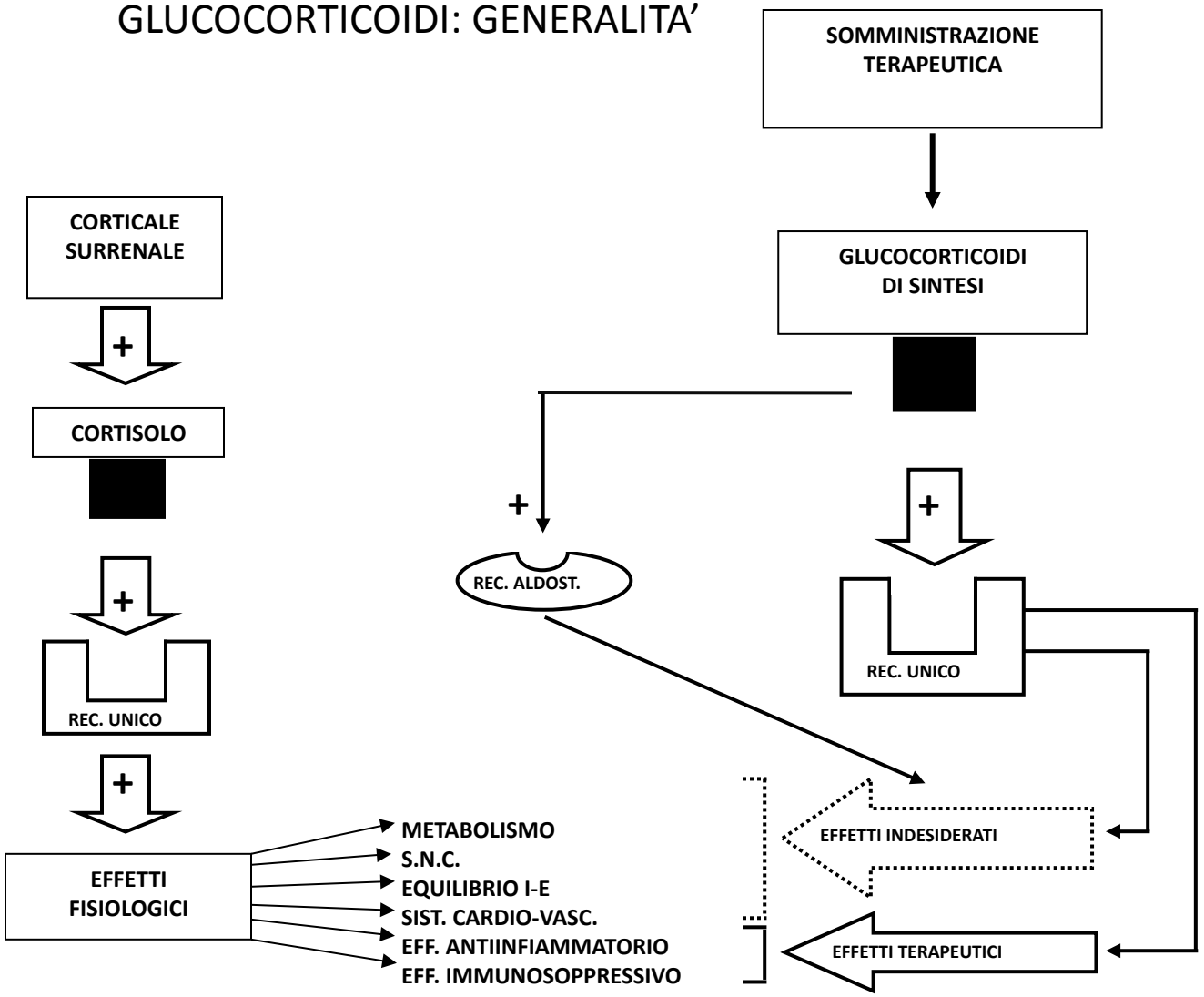
In 1948, the American rheumatologist Phillip S. Hench was the first to administer cortisone to a patient with rheumatoid arthritis (RA); consequently, Hench discovered the therapeutic effects of glucocorticoids (GCs). In 1949, he published his observations together with Kendall, Slocumb, and Polly. In 1950, together with the biochemists Reichstein and Kendall, Hench was awarded the Nobel Prize for medicine.

Ann. N.Y. Acad. Sci. **966: 28–38 (2002).**

Table 1 Examples of the Clinical Use of Glucocorticoids

Pulmonology	asthma, sarcoidosis
Rheumatology	rheumatoid arthritis, systemic lupus erythematosus, myositis, gout
Gastroenterology	ulcerative colitis, Crohn's disease
Immunology	allergic diseases
Endocrinology	replacement therapy in glucocorticoid deficiency
Nephrology	glomerulonephritis
Oncology	lymphoproliferative disorders
Dermatology	connective tissue and immunobullous diseases, vasculitis, dermatitis
Neurology	multiple sclerosis, myasthenia gravis
Ophthalmology	uveitis, iritis, scleritis

GLUCOCORTICOIDI: GENERALITA’



Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice

M C van der Goes,[1] J W G Jacobs,[1] M Boers,[2] T Andrews,[3] M A M Blom-Bakkers,[1] F Buttgereit,[4] N Caeyers,[5] M Cutolo,[6] J A P Da Silva,[7] L Guillevin,[8] J R Kirwan,[3] J Rovensky,[9] G Severijns,[10] S Webber,[3] R Westhovens,[10] J W J Bijlsma[1]

DISCUSSION

It is remarkable that after 60 years of GC use in clinical practice, there is no certainty about the actual incidence of AEs. Therefore, the EULAR Task Force on GCs set out to formulate recommendations for the monitoring of GC-related AEs, based on reports of GC-related AEs in literature.

van der Goes MC, Jacobs JWG, Boers M, *et al*. *Ann Rheum Dis* (2010). doi:10.1136/ard.2009.124958

Steroid-induced diabetes in rheumatologic patients

T.P. Angelopoulos[1], N.K. Tentolouris[2], G.K. Bertsias[3], D.T. Boumpas[1]

In summary, both the dose and duration of GC treatment are strong predictors for development of NOSID. Age and increase
identifie
Surprisi
tes has
increase
ethnicity

Studies on harm are often of low quality: observational designs with high risk of bias (especially confounding by indication), poor documentation of glucocorticoid exposure and differing models of risk attribution. Moreover, clinical trials of glucocorticoids have often been small, short and with limited assessment of adverse events. Consequently, results can be contradictory and their interpretation is sometimes biased

Prevalence

ertheless, most studies agree that the prevalence of NOSID is approximately 10–20%, depending mainly on dose and duration of steroid administration. In a

Clin Exp Rheumatol 2014; 32: 126-130.

Steroid-induced diabetes in rheumatologic patients

T.P. Angelopoulos[1], N.K. Tentolouris[2], G.K. Bertsias[3], D.T. Boumpas[1]

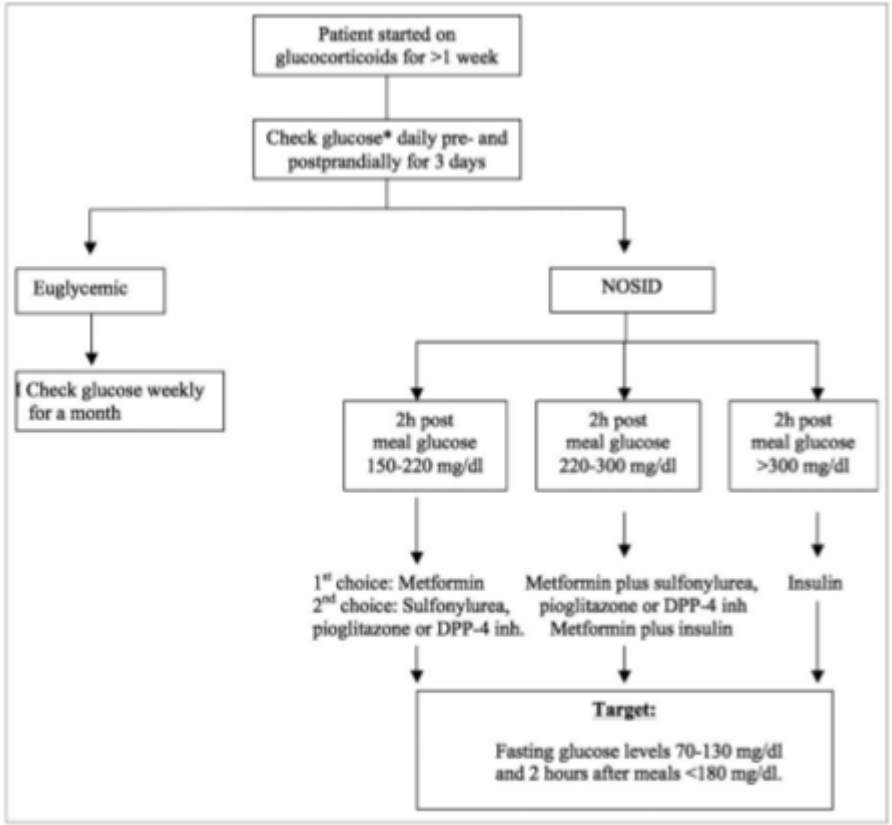


Fig. 2. Algorithm for new onset steroid-induced diabetes (NOSID) management.
*glucose levels measured by test strips and verified by serum levels if abnormal.

Clin Exp Rheumatol 2014; 32: 126-130.

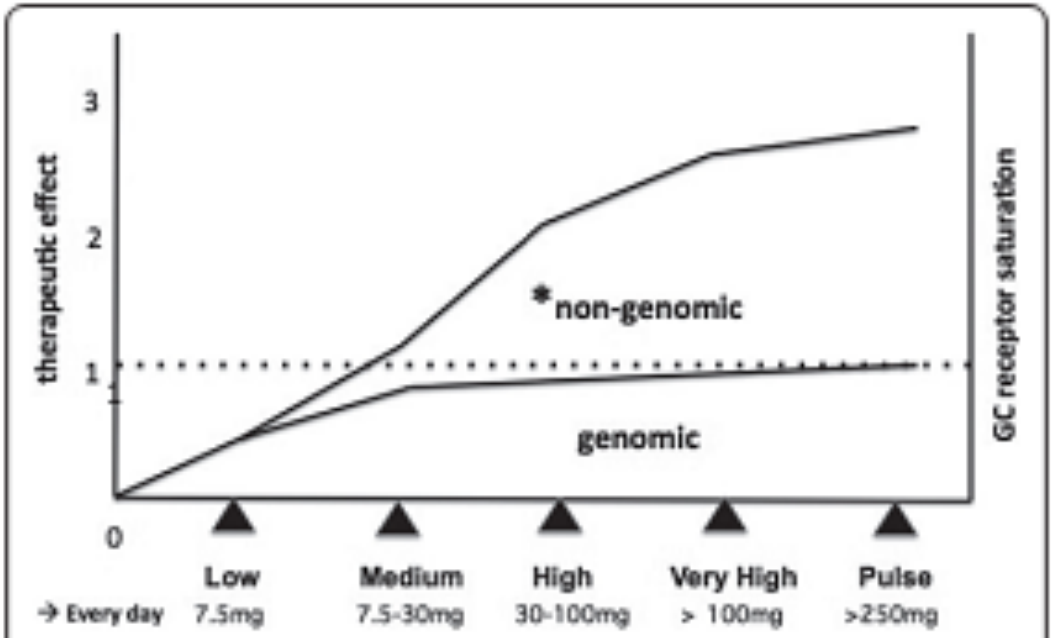


Figure 1. Relationship between different glucocorticoid doses (prednisone equivalent milligrams), intensity of the therapeutic effect (arbitrary units), and genomic/nongenomic mechanism of action. Low-dose therapy, <7.5 mg/day; medium-dose therapy, 7.5 up to 30 mg/day; high-dose therapy, 30 up to 100 mg/day; very high-dose therapy, >100 mg/day; pulse therapy, >250 mg/day for a few days [12]. *When administering 100 to 200 mg prednisone per day, all cytosolic glucocorticoid (GC) receptors are occupied (nongenomic action) [23].

Meccanismo d'azione dei glucocorticoidi

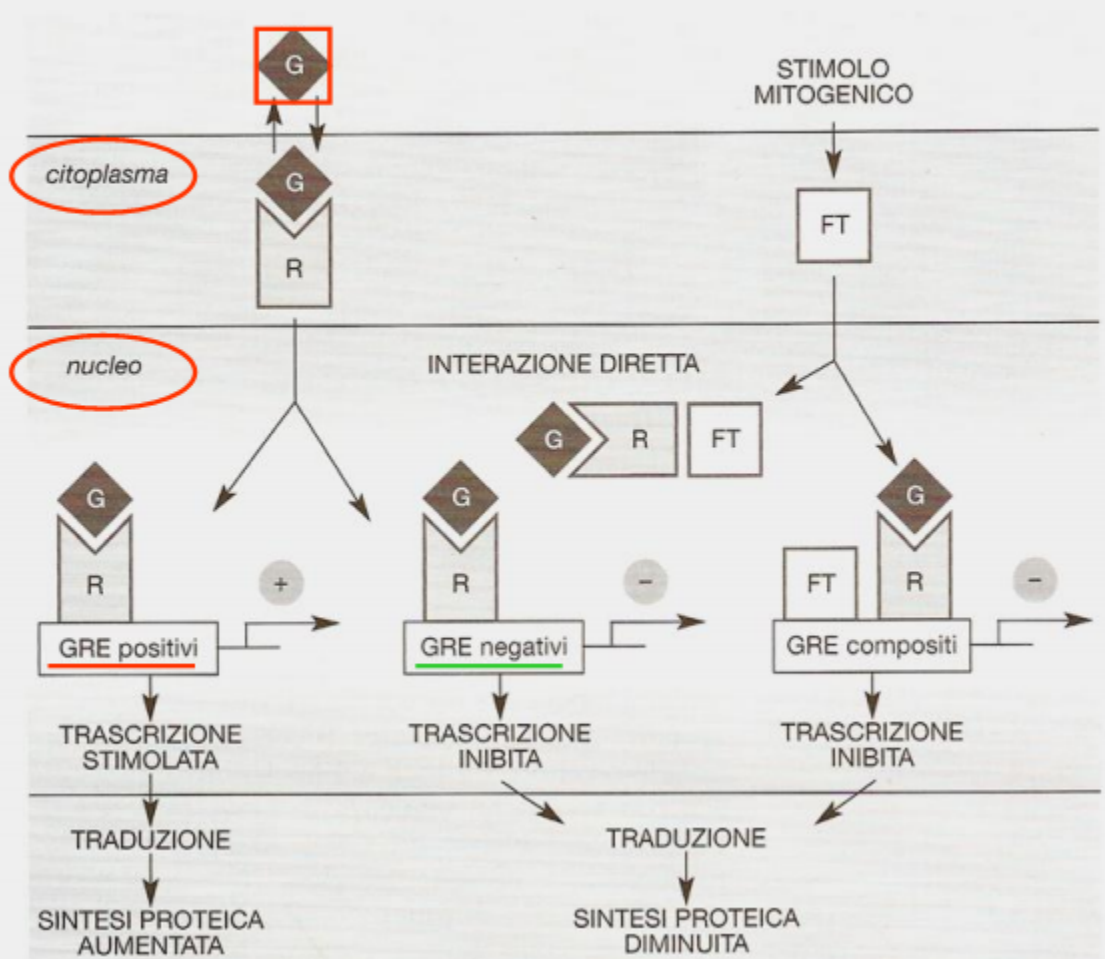


Fig. 5.2. Meccanismo d'azione dei glicocorticoidi. Dopo aver attraversato la membrana cellulare per diffusione passiva, il glicocorticoide (G) si lega a specifici recettori (R) citosolici. Il complesso glicocorticoide-recettore (G-R) trasloca nel nucleo dove il recettore attivato si lega a specifiche sequenze di DNA (*glucocorticoid responsive elements*, GRE) nel promotore di geni sensibili. Il legame del complesso G-R a GRE positivi stimola la trascrizione e la sintesi proteica, mentre il legame a GRE negativi inibisce la trascrizione. Inoltre il complesso G-R è in grado di inibire in vario modo gli effetti di fattori di trascrizione (FT) come AP-1 stimolati da mitogeni. Il complesso G-R può bloccare direttamente FT mediante interazione diretta proteina-proteina oppure può interferire con l'attivazione trascrizionale di FT a livello dei GRE compositi (vedi testo).

Cutolo *et al. Arthritis Research & Therapy* 2014, 16(Suppl 2):S1

Inibizione della sintesi di proteine proinfiammatorie ed immunostimolanti	Induzione della sintesi di proteine antiinfiammatorie ed immunodepressive
Citochine e recettori IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, TNF-α, IFN-γ Recettori per IL-2	Lipocortina-1 Recettore di tipo II per IL-1
Chemiochine IL-8 MCP-1	Endonucleasi Iκ-Bα Annessina 1
Fattori di crescita GM-CSF G-CSF	
Molecole di adesione ELAM-1 ICAM-1	
Enzimi Fosfolipasi A_2 Cicloossigenasi inducibile Nitrossidosintasi inducibile Collagenasi	

(-)

IL = interleuchina, TNF-α = *tumor necrosis factor-α*, IFN-γ = interferone-γ, MCP-1 = *monocyte chemotactic protein-1*, GM-CSF = *granulocyte-macrophage colony stimulating factor*, G-CSF = *granulocyte colony stimulating factor*, ELAM-1 = *endothelial-leukocyte adhesion molecule-1*, ICAM-1 = *intercellular adhesion molecule-1*.

Meccanismo antinfiammatorio/ immunodepressivo dei glucocorticoidi

attivano sistema immunitario

risposta infiammatoria, attivano sistema immunitario

Cutolo *et al. Arthritis Research & Therapy* 2014, 16(Suppl 2):S1

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update

Table 1 2013 Update of the EULAR recommendations (the table of 2010 recommendations can be seen in the online supplement or the original publication)

	Overarching principles
A.	Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B.	Rheumatologists are the specialists who should primarily care for RA patients

7.Low dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more DMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible

Livello più basso di concordanza tra esperti=73% LoE 1a

10.	If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with another mode of action
11.	Tofacitinib may be considered after biological treatment has failed
12.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering‡ bDMARDs§, especially if this treatment is combined with a csDMARD
13.	In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician
14.	When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account

Smolen JS, *et al. Ann Rheum Dis* 2014;**73**:492–509. doi:10.1136/annrheumdis-2013-204573

When and for how long should glucocorticoids be used in rheumatoid arthritis? International guidelines and recommendations

Cécile Gaujoux-Viala[1] and Laure Gossec[2]

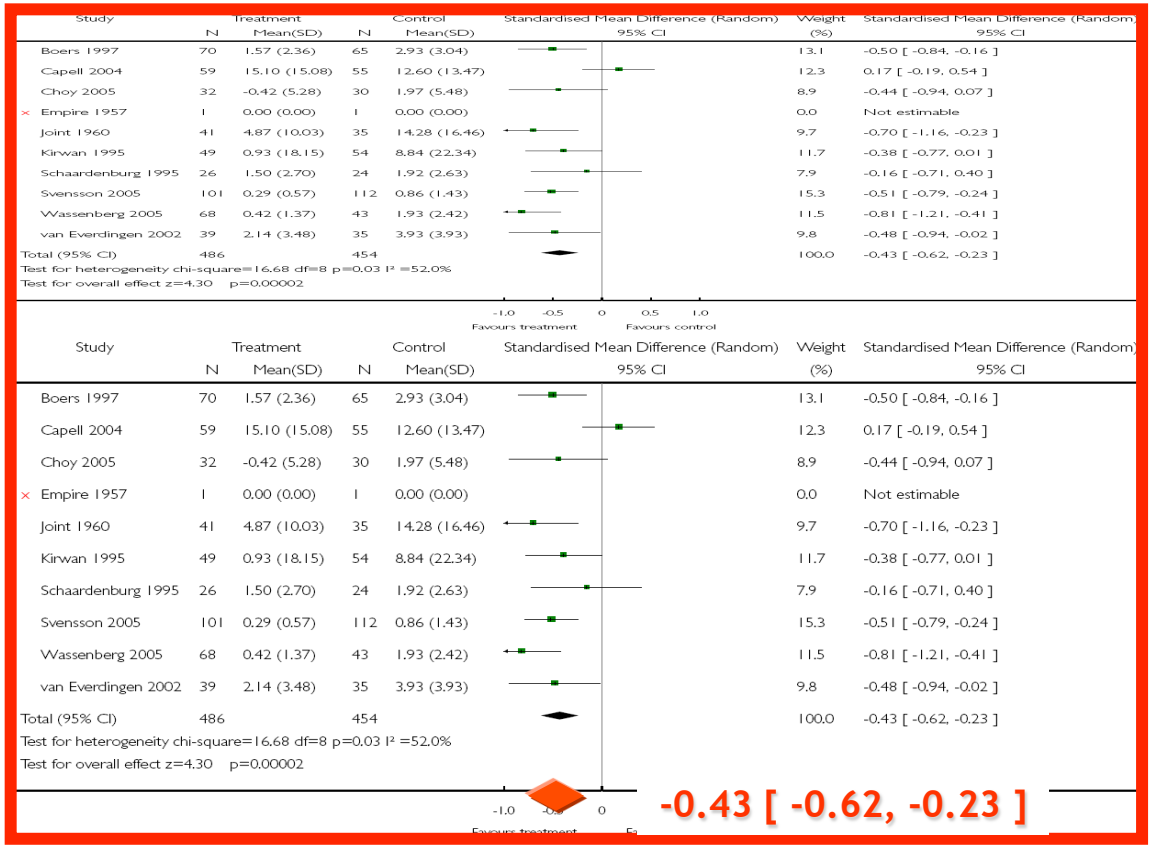
It should be noted that this recommendation was driven by clinical data. Structural data comparing 6 months of GCs and, for example, 1 or two years of GCs are missing. Thus, here also, the recommendation may be seen as controversial

Ann. N.Y. Acad. Sci. 1318 (2014) 32–40

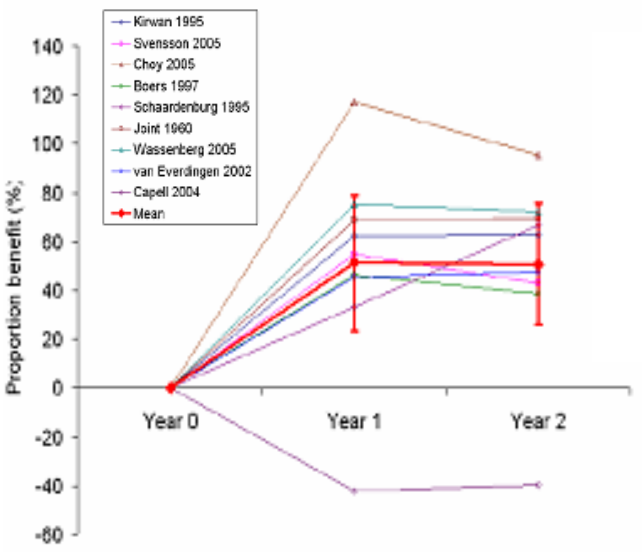
Significant reduction in joint damage progression when GC added to antirheumatic Tx

THE COCHRANE COLLABORATION®

Erosions at 2 years
Low dose GC+DMARD vs DMARD



1 & 2-year benefit, %



Kirwan JR, Bijlsma JWJ, Boers M, Shea BJ, The Cochrane Library 2007

Rheumatoid factor and anti-CCP do not predict progressive joint damage in patients with early rheumatoid arthritis treated with prednisolone: a randomised study

Studio prospettico
2 anni

Ingiäld Hafström,[1] Inga-Lill Engvall,[1] Johan Rönnelid,[2] Annelies Boonen,[3]
Désirée van der Heijde,[4] Björn Svensson,[5] on behalf of the BARFOT study group

Conclusions: The presence of RF and anti-CCP predicted radiographic progression in patients not treated with prednisolone but failed to predict progression in patients treated with this drug. The data suggest that early treatment with prednisolone may modulate not only inflammation but also autoimmunity-associated pathogenetic mechanisms.

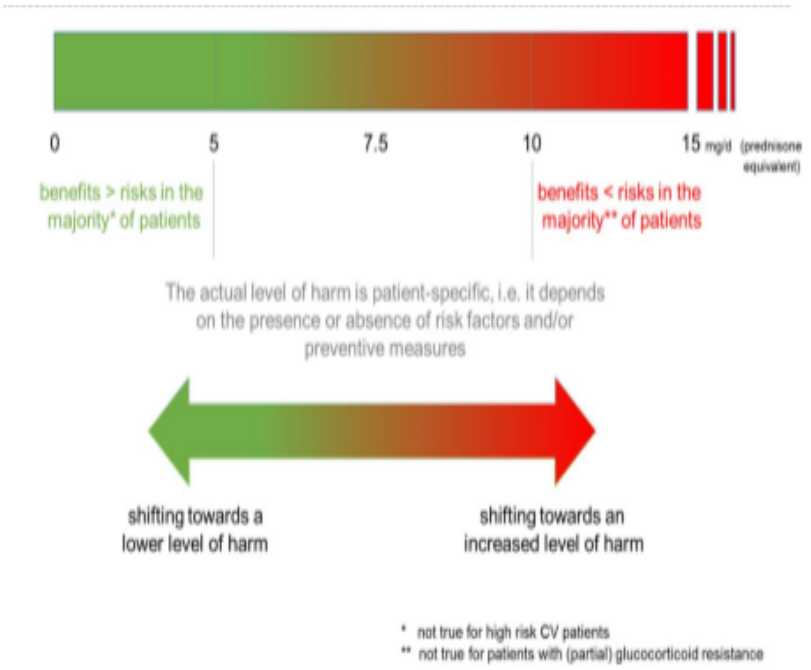
Hafström I, *et al. BMJ Open* 2014;**4**:e005246. doi:10.1136/bmjopen-2014-005246

Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force

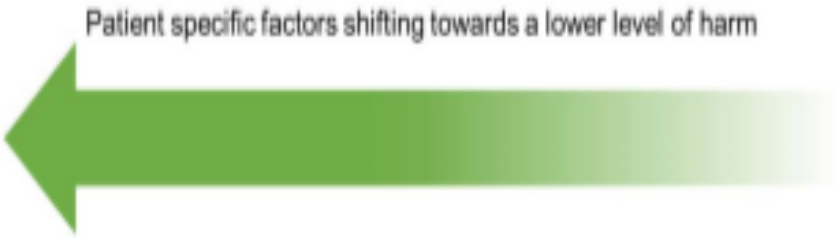
Risks of long-term glucocorticoid therapy are defined by both drug-specific (dose, duration) and patient-specific characteristics

Strehl C, *et al. Ann Rheum Dis* 2016;**75**:952–957. doi:10.1136/annrheumdis-2015-208916

- ▸ At ≤5 mg/day, there is an acceptably low level of harm for the specified outcomes (with the exception of patients at high risk for CVD who may require preventive measures).
- ▸ At >10 mg/day, the risk of harm is elevated.
- ▸ At dosages between >5 and ≤10 mg/day, uncertainty still exists and, consequently, patient-specific characteristics need particular consideration to interpret and estimate the individual risk of harm.



Strehl C, *et al. Ann Rheum Dis* 2016;**75**:952–957. doi:10.1136/annrheumdis-2015-208916



	Factors	References
General	early diagnosis, low disease activity, low cumulative glucocorticoid dosage, healthy life style (especially cessation of smoking, low alcohol consumption), monitoring and treatment of risk factors and co-morbidities	[1] [21] [37]
Glucocorticoid-induced osteoporosis	sufficient vitamin D & calcium intake, exercise, muscle strengthening, prescription on indication: bisphosphonates, osteoanabolic drugs, selective oestrogen receptor modulators	[36] [39] [40] [41] [42]
Infections	screening for infections, vaccination, usage of risk scores before therapy, follow rules of conduct (avoiding infected persons, appropriate wound care,	[44] [50] [52]

Carbohydrate metabolism: healthy diet, appropriate exercise, weight loss for obese pts, prescription on indication hydroxychloroquine

Cardiovascular	diet in low saturated fat & calories, physical activity, weight normalization, sodium restriction, follow the EULAR-recommendations for cardiovascular risk management (including medications like statins or angiotensin-converting enzyme inhibitors on indication)	[2] [60] [70] [75] [76] [77]

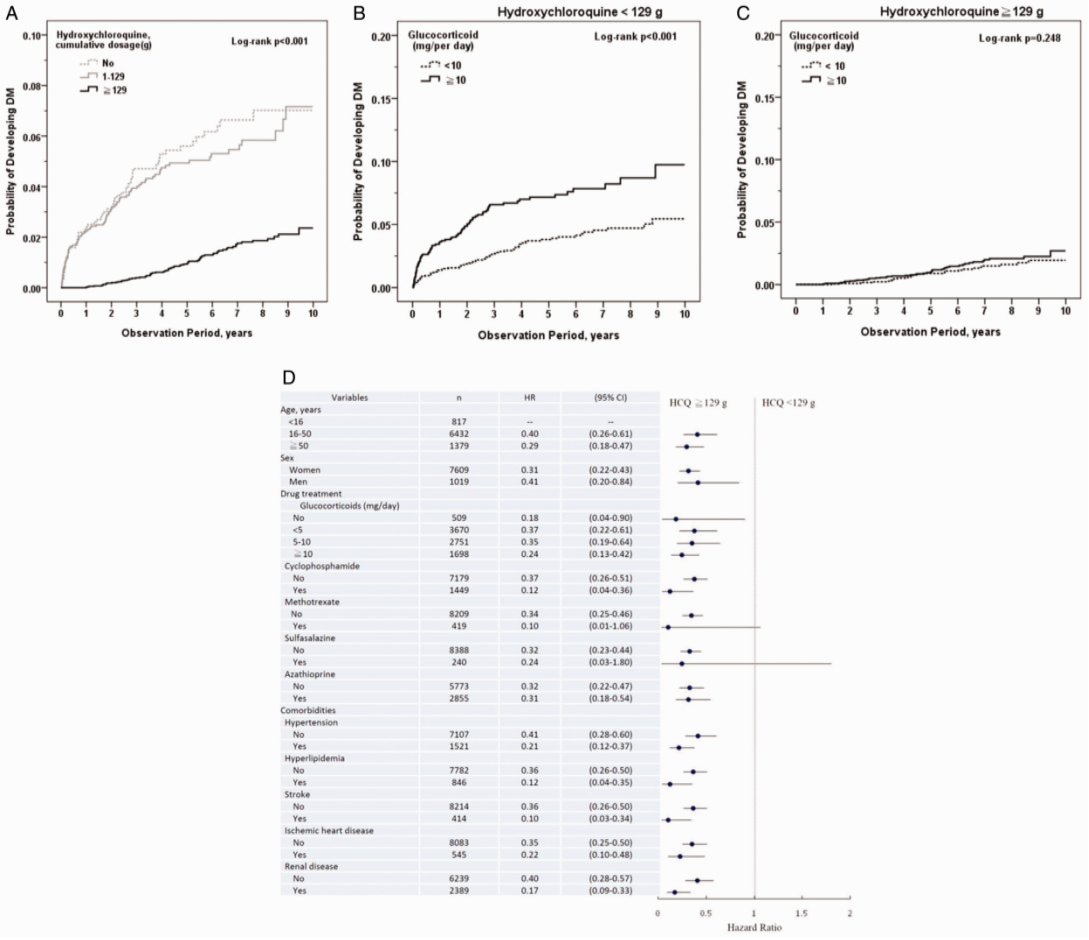
Bili A, Sartorius JA, Kirchner HL, et al. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. J Clin Rheumatol 2011;17:115–20.
Ito S, Ogishima H, Kondo Y, et al. Early diagnosis and treatment of steroid-induced diabetes mellitus in patients with rheumatoid arthritis and other connective tissue diseases. Mod Rheumatol 2014;24:52–9.

RHEUMATOLOGY

Rheumatology 2015;54:1244–1249
doi:10.1093/rheumatology/keu451
Advance Access publication 12 January 2015

Concise report

Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study



From: Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study

Rheumatology (Oxford). 2015;54(7):1244-1249. doi:10.1093/rheumatology/keu451

Association between use of disease-modifying antirheumatic drugs and diabetes in patients with ankylosing spondylitis, rheumatoid arthritis, or psoriasis/psoriatic arthritis: a nationwide, population-based cohort study of 84,989 patients

The mechanism of action of HCQ in the prevention of insulin resistance and DM is not completely resolved, but may involve blocking of toll-like receptors 7 and 9 and inhibition of the production of interferon-α.

Conclusion: The aHR for DM was lowest for patients with RA and PS/PSA who initiated treatment with an anti-TNF agent with concomitant HCQ, followed by HCQ users. Those who used anti-TNF agents without HCQ and other nonbiologic DMARDs had a similar risk of DM.

Therapeutics and Clinical Risk Management 2017:13 583–592

	Factors	References
General	high disease activity, high cumulative glucocorticoid dosage, lifestyle (especially bad nutrition, smoking, high alcohol consumption)	[17] [28] [66]
Glucocorticoid-induced osteoporosis	age > 60 years, female sex, low body weight, low bone mineral density, family history of osteoporosis, prevalent fractures, low calcium intake	[23] [35] [36] [37] [38]
Infections	age > 60, male sex, comorbidities (e.g. chronic lung disease, coronary heart disease, heart failure, peripheral vascular diseases, diabetes mellitus, hepatitis C, chronic renal diseases, leukopenia, neurological disease) high	[28] [43] [46] [47] [48] [49] [50] [51]

Carbohydrate metabolism: higher age, high body mass index, genetic predisposition, long disease duration

Cardiovascular	higher age, male sex, severe extra-articular disease manifestation, RF positivity, ACPA positivity, comorbidities (e.g. hypertension, diabetes, dyslipidaemia, obesity, Cushing's syndrome)	[29] [47] [65] [67] [72] [73] [74]

Raul Ariza-Andraca C, Barile-Fabris LA, Frati-Munari AC, et al. Risk factors for steroid diabetes in rheumatic patients. Arch Med Res 1998;29:259–62.
Su CC, Chen IeC, Young FN, et al. Risk of diabetes in patients with rheumatoid arthritis: a 12-year retrospective cohort study. J Rheumatol 2013;40:1513–18.

ciclosporina

Disturbi del metabolismo e della nutrizione	
Molto comune	Iperlipidemia
Comune	Iperglicemia, anoressia, iperuricemia, iperkaliemia, ipomagnesemia

tacrolimus

Disturbi del metabolismo e della nutrizione

molto comune: diabete mellito, iperglicemia, iperkaliemia

comune: acidosi metabolica, altre alterazioni degli elettroliti, iponatriemia, sovraccarico di liquidi, iperuricemia, ipomagnesemia, ipokaliemia, ipocalcemia, diminuzione dell'appetito, ipercolesterolemia, iperlipidemia, ipertrigliceridemia, ipofosfatemia

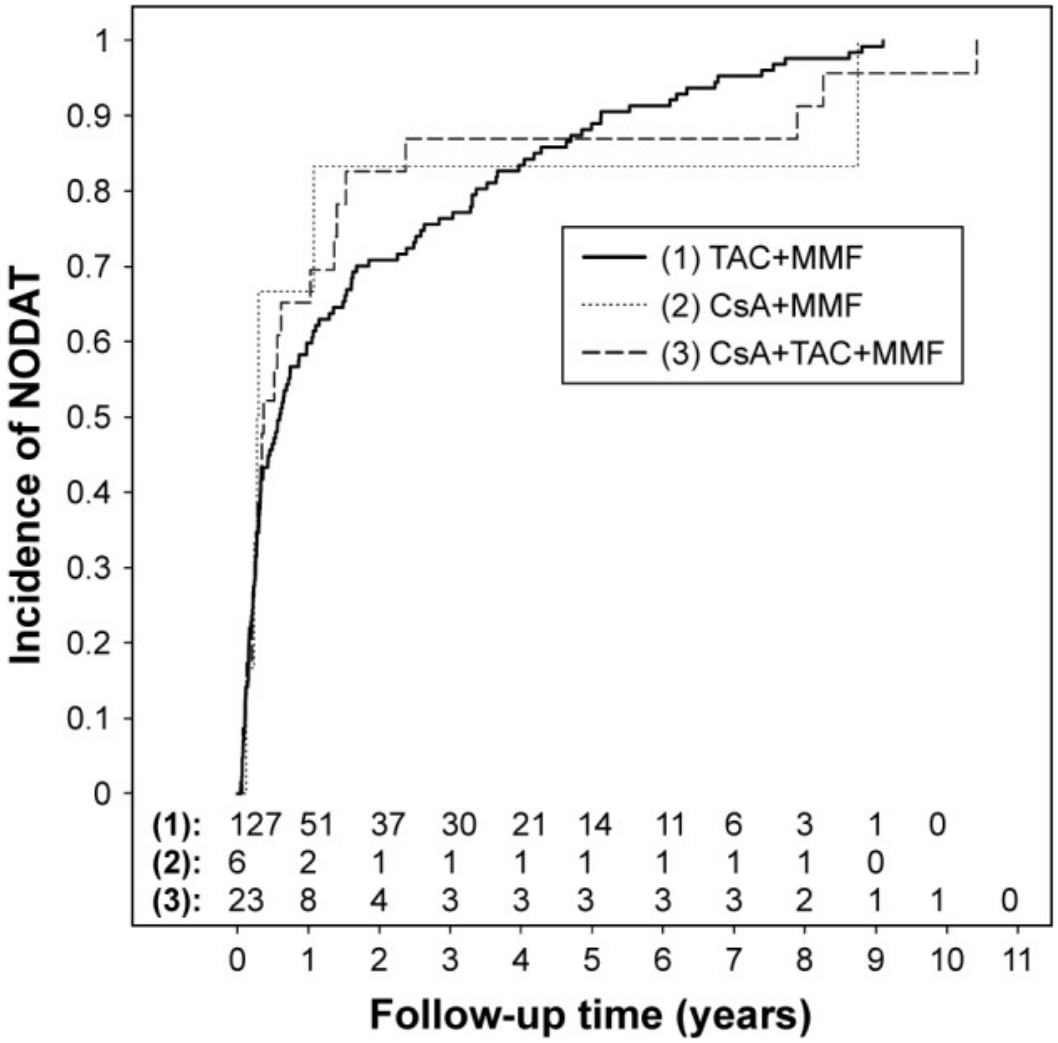
non comune: disidratazione, ipoglicemia, ipoproteinemia, iperfosfatemia

micofenolato

Disturbi del metabolismo e della nutrizione	Molto comune	-
	Comune	Acidosi, iperpotassiemia, ipopotassiemia, iperglicemia, ipomagnesemia, ipocalcemia, ipercolesterolemia, iperlipemia, ipofosfatemia, iperuricemia, gotta, anoressia

Impact of immunosuppressant therapy on new-onset diabetes in liver transplant recipients

Ther Clin Risk Manag. 2017; 13: 1043–1051.



Immunosuppressive regimens and development of NODAT.

Notes: NODAT was defined as new-onset diabetes if it occurred 90 days after liver transplantation. The median time of developing NODAT was 0.5996 years with TAC+MMF, 0.2888 years with CsA+MMF, and 0.3696 years with CsA+TAC+MMF regimens.

Abbreviations: NODAT, new-onset diabetes after transplantation; TAC, tacrolimus; MMF, mycophenolate mofetil; CsA, cyclosporine.

Metabolic Effects of High-Dose Prednisolone Treatment in Early Rheumatoid Arthritis

Balance Between Diabetogenic Effects and Inflammation Reduction

Table 2. Parameters of beta cell function and insulin sensitivity during the oral glucose tolerance test, before and after 7 days of prednisone treatment*

	Prednisone 60 mg/day (n = 21)			Prednisone 30 mg/day (n = 20)		
	Pretreatment	After treatment	P†	Pretreatment	After treatment	P†
Fasting glucose, mean ± SD mmoles/liter	5.5 ± 0.7	5.3 ± 0.9	NS	5.6 ± 0.5	5.3 ± 0.6	NS
Fasting insulin, pmoles/liter	43 (34–69)	53 (37–77)	NS	36 (30–113)	68 (44–129)	0.004
Fasting C-peptide, nmoles/liter	0.5 (0.4–0.7)	0.8 (0.7–1.0)	0.000	0.5 (0.4–0.9)	0.9 (0.6–1.1)	0.000
AUC_G (4 hour), mean ± SD mmoles/liter	1,051 ± 237	1,077 ± 341	NS	1,050 ± 172	1,031 ± 260	NS
AUC_I (4 hour), pmoles/liter	48 (35–74)	46 (32–83)	NS	50 (28–95)	63 (33–90)	NS
AUC_{CP} (4 hour), mean ± SD nmoles/liter	304 ± 92	355 ± 141	NS	339 ± 172	389 ± 180	NS
IGI	73 (46–161)	95 (37–284)	0.02	95 (58–148)	127 (65–236)	0.04
AUC_{CP}:AUC_G	0.3 (0.2–0.4)	0.3 (0.2–0.5)	NS	0.3 (0.2–0.4)	0.4 (0.2–0.5)	0.02
OGIS, mean ± SD	366 ± 64.2	365 ± 71.4	NS	358 ± 68	363 ± 68	NS
HOMA-IR	1.0 (0.7–1.5)	1.1 (0.8–1.6)	NS	0.8 (0.7–2.5)	1.5 (1.0–2.8)	0.005
HOMA-B	84 (60–113)	104 (76–124)	NS	75 (61–122)	119 (77–169)	0.001

* Except where indicated otherwise, values are the median (interquartile range). There were no statistically significant differences between the 2 treatment groups in the degree of change, as assessed by independent *t*-test or Mann-Whitney U test. NS = not significant; AUC_G = glucose area under the curve; AUC_I = insulin AUC; AUC_{CP} = C-peptide AUC; IGI = insulinogenic index; OGIS = oral glucose insulin sensitivity index; HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-B = HOMA of beta cell function.

† By paired-samples *t*-test or Wilcoxon's signed rank test.

ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 639–646

Metabolic Effects of High-Dose Prednisolone Treatment in Early Rheumatoid Arthritis

Balance Between Diabetogenic Effects and Inflammation Reduction

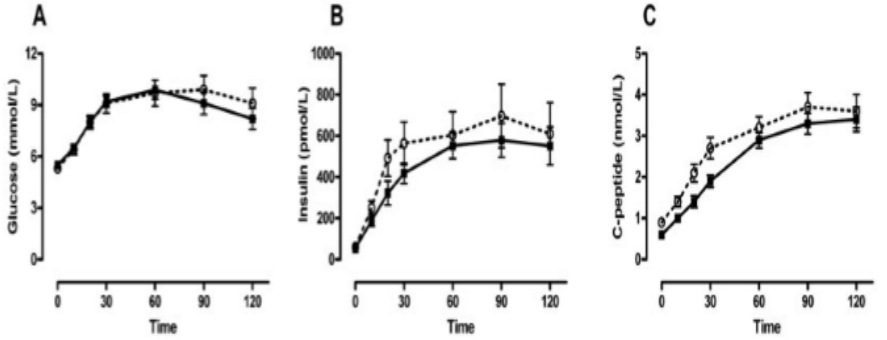


Figure 1. Oral glucose tolerance test results before treatment (squares connected by solid lines) and on day 7 of treatment with prednisolone 60 mg/day (circles connected by dashed lines). **A,** Glucose concentrations. **B,** Insulin concentrations. **C,** C-peptide concentrations. No significant changes were induced by treatment with prednisolone 60 mg/day. Values are the mean ± SD.

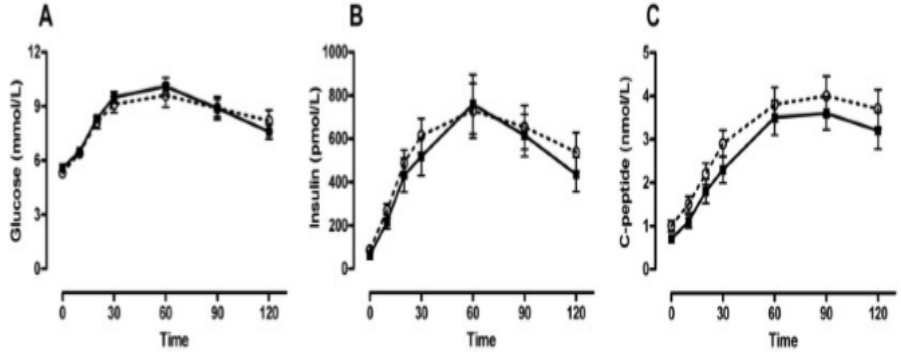
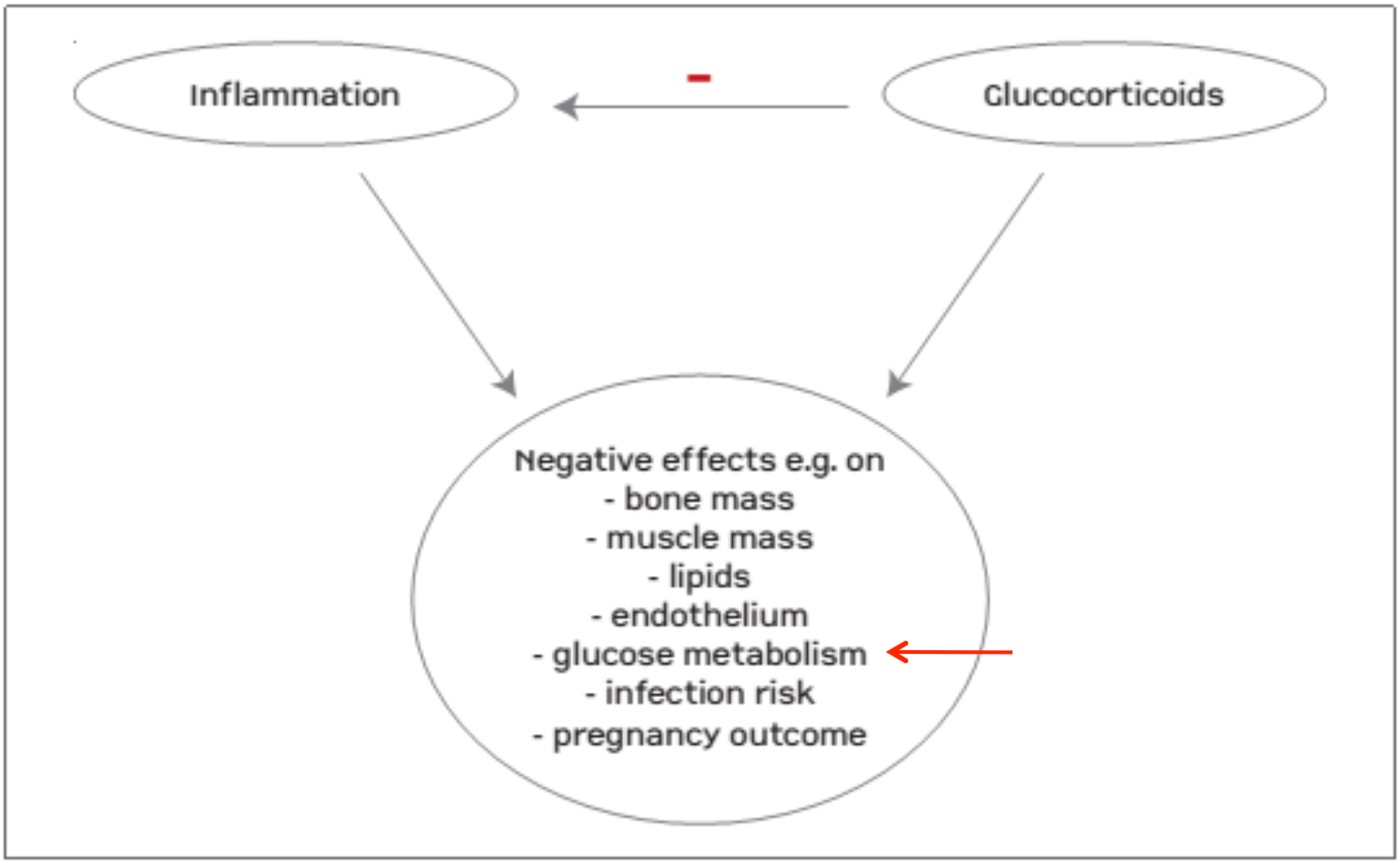


Figure 2. Oral glucose tolerance test results before treatment (squares connected by solid lines) and on day 7 of treatment with prednisolone 30 mg/day (circles connected by dashed lines). **A,** Glucose concentrations. **B,** Insulin concentrations. **C,** C-peptide concentrations. No significant changes were induced by treatment with prednisolone 30 mg/day. Values are the mean ± SD.

ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 639–646

Magic triangle



ACTA REUMATOL PORT. 2015;40:10-22

Risk of Diabetes Mellitus among Patients Diagnosed with Giant Cell Arteritis or Granulomatosis with Polyangiitis: Comparison with the General Population

Mikkel Faurschou, Magnus G. Ahlström, Jesper Lindhardsen, Niels Obel, and Bo Baslund

Patients diagnosed with GCA or GPA have a substantially increased risk of developing DM during early followup periods. Implementation of a screening program for DM should be considered in these patient groups.

J Rheumatol 2017;44;78-83

The Risk of Developing Diabetes Mellitus in Patients with Psoriatic Arthritis: A Cohort Study

Lihi Eder, Vinod Chandran, Richard Cook, and Dafna D. Gladman

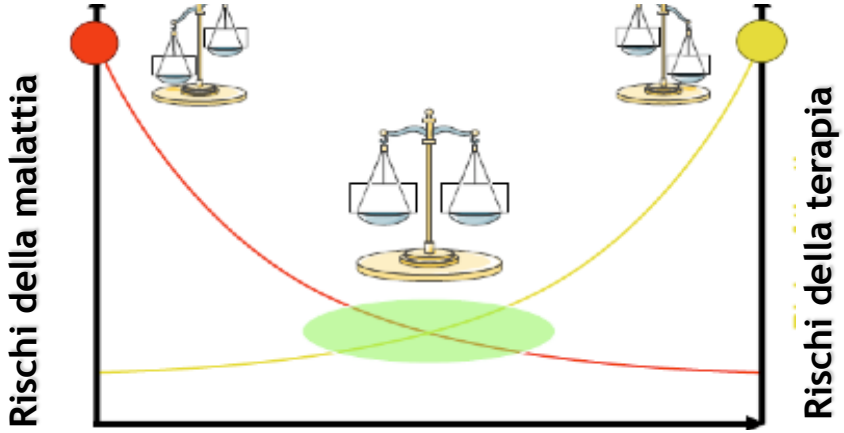
We found that the prevalence of DM was 43% higher in patients with PsA than in the general population of Ontario, Canada. Additionally, we found an independent association between higher levels of inflammation and measures of disease activity over time and DM risk. Patients with higher TJC and those with higher ESR levels were at higher risk of developing the disease independently of other known risk factors.

; J Rheumatol 2017;44:286–91;

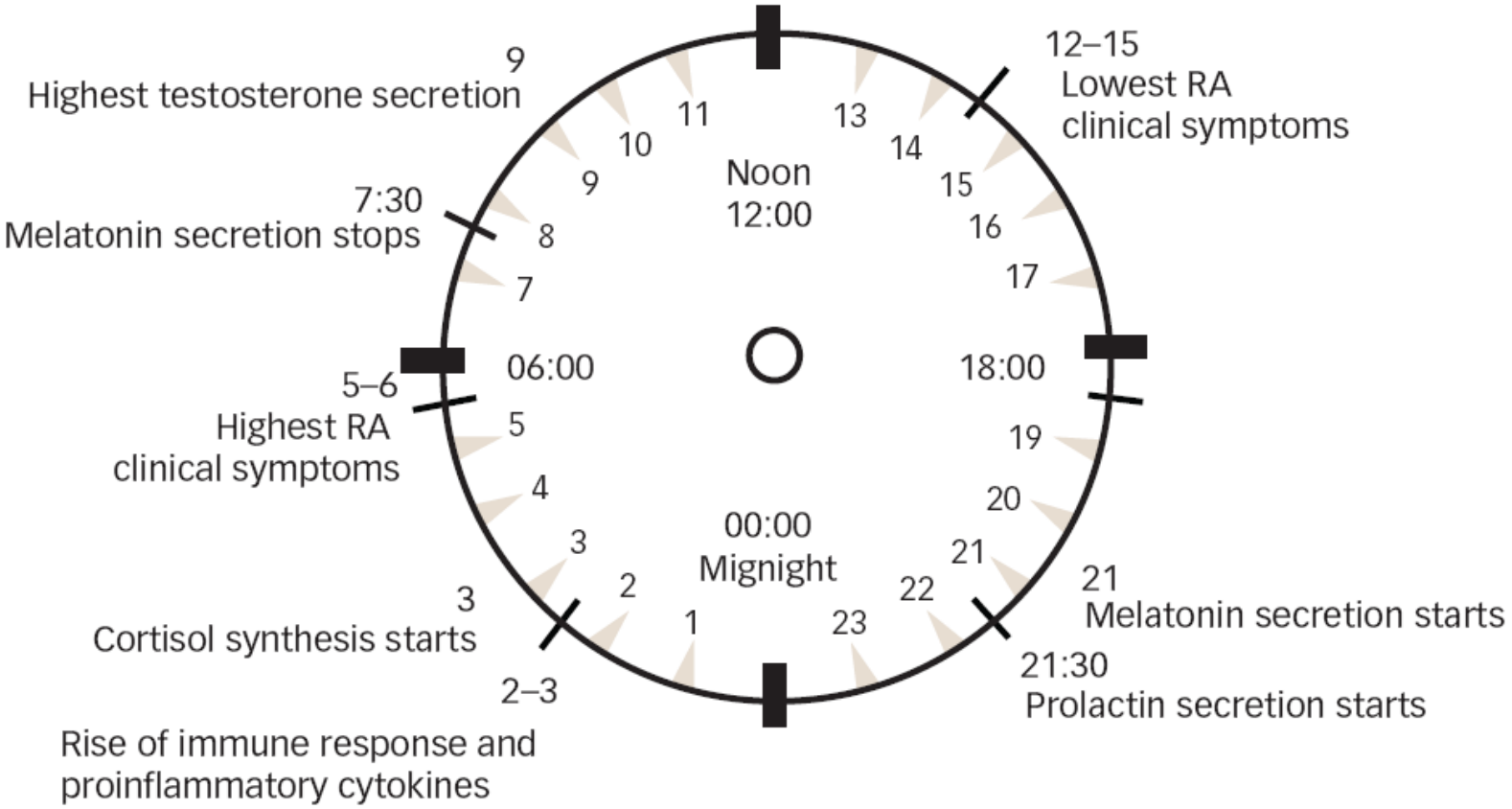
Benefici **Rischi**

Azione anti-infiammatoria

Effetti collaterali



Nocturnal hormonal rhythms in RA



Cutolo M, Eur Muscoloskel Review 2012

Drug Design, Development and Therapy

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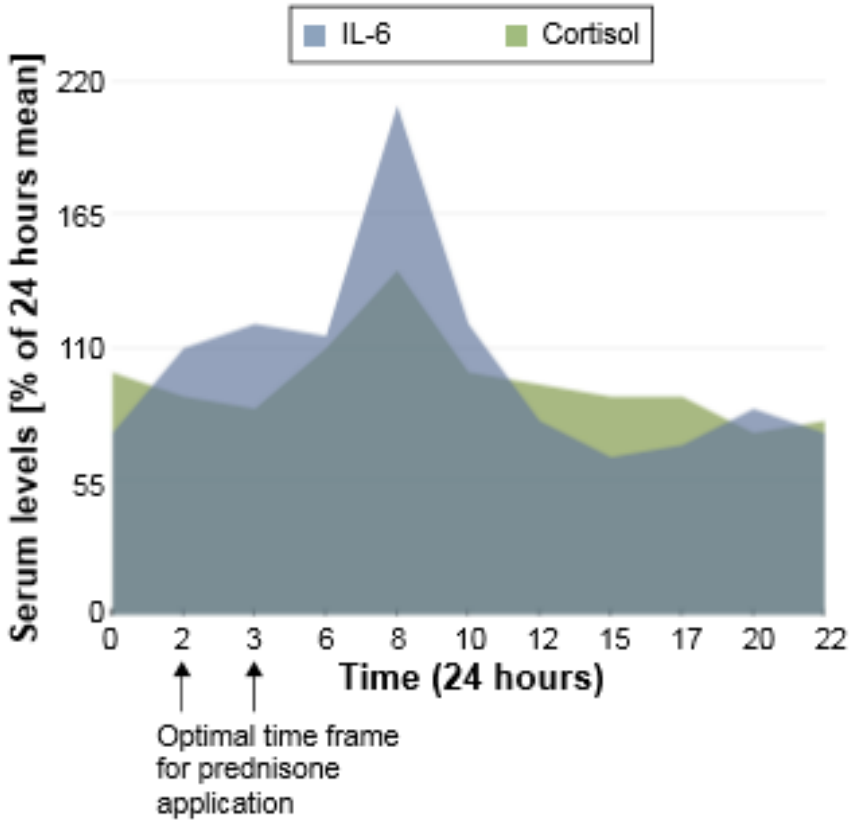
REVIEW

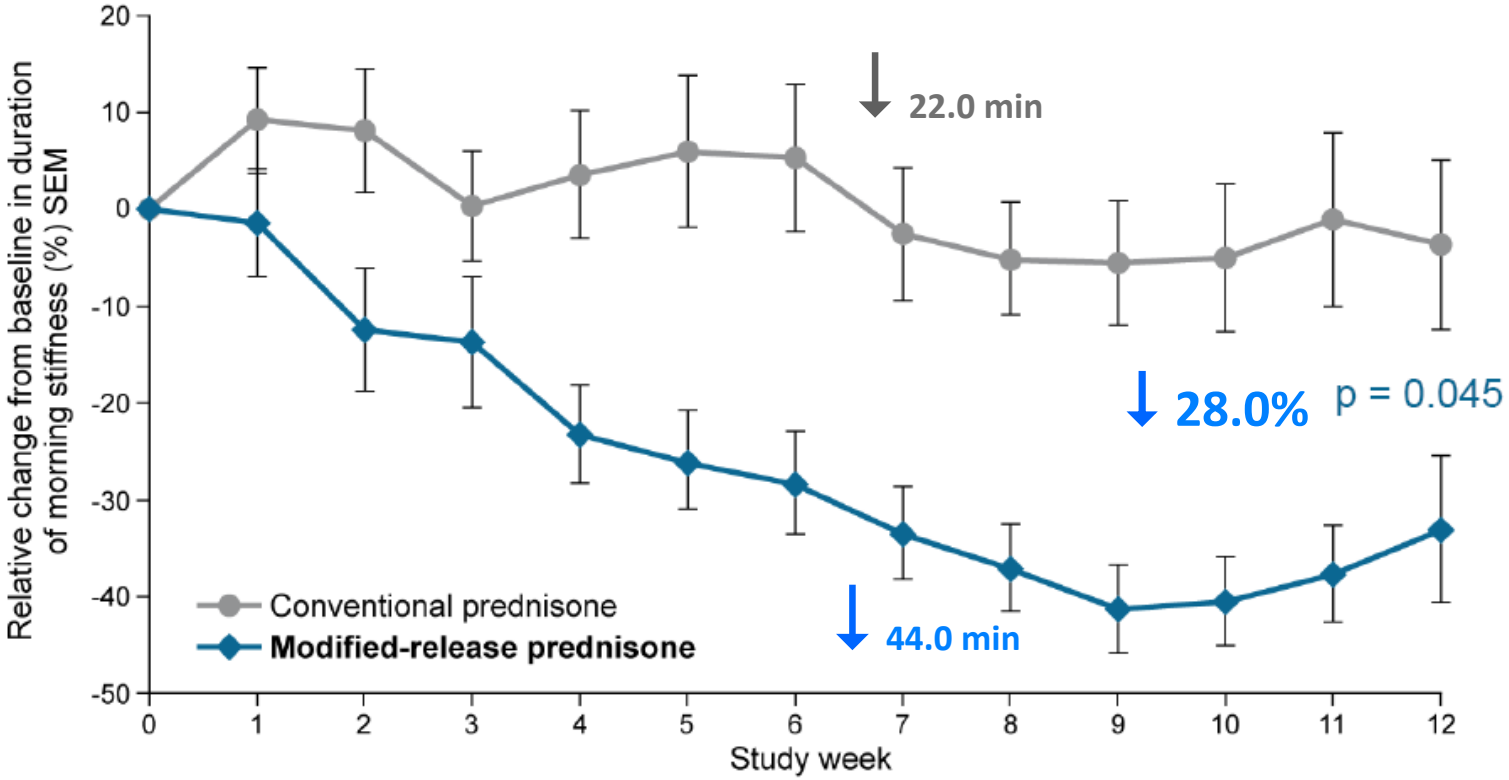
Efficacy and safety of modified-release prednisone in patients with rheumatoid arthritis



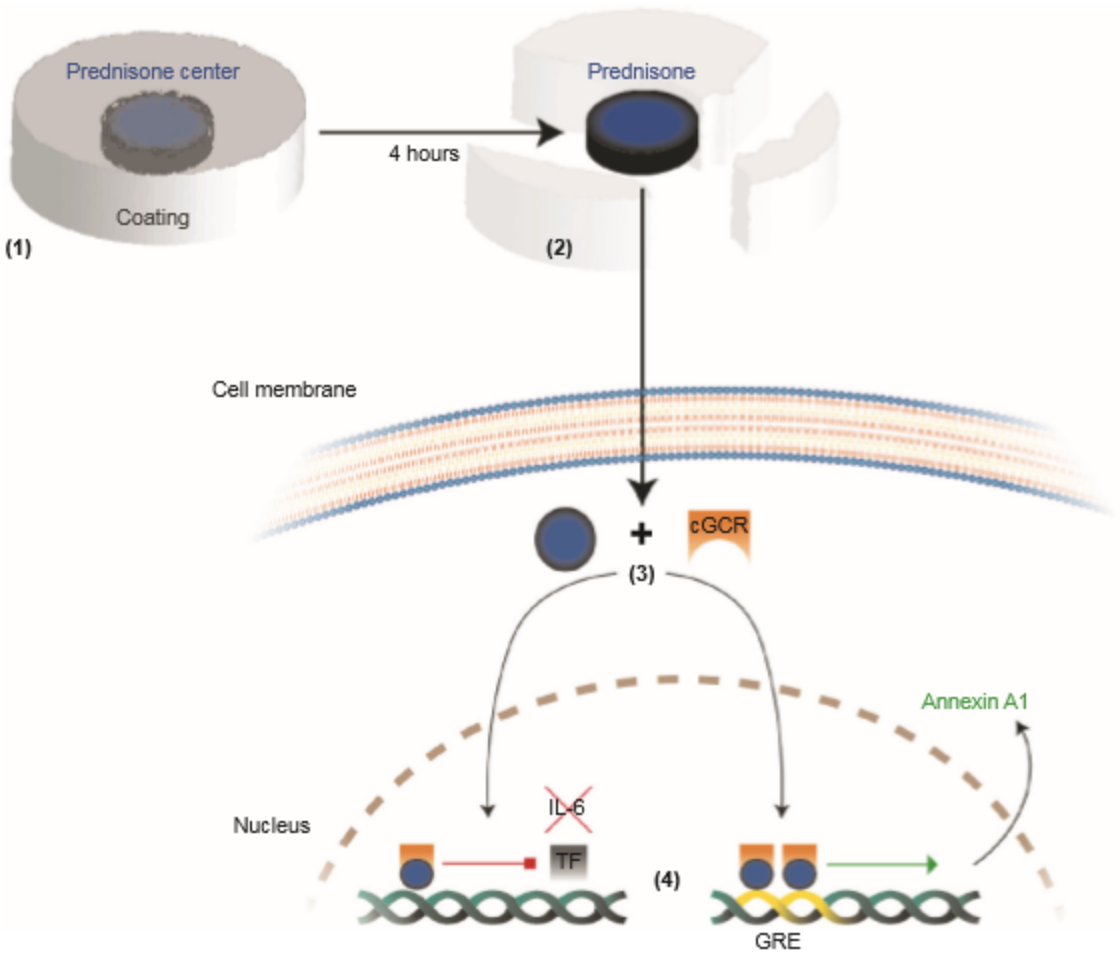
Drug Design, Development and Therapy 2016:10 1047–1058

Studio CAPRA-1

Durata Rigidità Articolare Mattutina nelle 12 settimane



Buttgereit et al, Lancet 2008;371:205-14



Drug Design, Development and Therapy 2016:10 1047–1058

Efficacy and safety of modified-release prednisone in patients with rheumatoid arthritis

Table 2 AEs reported in the clinical trials comparing MR prednisone with IR prednisone and placebo, respectively[36,38,39]

AE	MR (%)	IR (%)*	Placebo (%)‡
Arthralgia	1*–10.4‡	2	20.2
RA flare	6.5‡–8*	9	9.2
Abdominal pain	4*	6	–
Nasopharyngitis	3*–4.8‡	6	3.4
Headache	3.9‡–4*	3	4.2
Flush	3*	4	–
Weight increase	2.4•	–	–
Hypertension	2*–2.2‡	2	0.8
Chest pain	2*	2	–
Nausea/vomiting	1.3‡–4*	3	0.8
Diarrhea	1.7‡	–	0.8
Rash	1.7‡	–	0.8
Gastritis	1.6•	–	–
Back pain	1.3‡	–	0.8
Bronchitis	1*–1.3‡	4	4.2
Vertigo	1*	3	–
Dyspepsia	1*	2	–
Upper respiratory tract infection	1*	2	–
Peripheral edema	0.9‡	–	1.7
Hematuria	0.4‡	–	2.5

Review

More Night Than Day — Circadian Rhythms in Polymyalgia Rheumatica and Ankylosing Spondylitis

CORNELIA M. SPIES, MAURIZIO CUTOLO, RAINER H. STRAUB, GERD-RÜDIGER BURMESTER, and FRANK BUTTGEREIT

ABSTRACT. The circadian rhythm of symptoms in patients with chronic inflammatory diseases is well known. Circadian rhythms could be used to identify targets for time-adapted antiinflammatory therapies, which are administered prior to the flare of cytokine synthesis and inflammatory activity. In recent years, the diurnal variations in rheumatoid arthritis have been described precisely for pain, stiffness, and functional disability, as well as the underlying cyclic variations in hormone levels and cytokine concentrations. This review summarizes the current knowledge on circadian rhythms in other rheumatic diseases, focusing on polymyalgia rheumatica and ankylosing spondylitis. (First Release April 1 2010; J Rheumatol 2010;37:894–9; doi:10.3899/jrheum.091283)

Corticosteroidi in Reumatologia

- Dosi
- Durata
- Infiammazione sistemica
- Caratteristiche del paziente
- Polifarmacoterapia

Grazie per l’attenzione