Glucocorticoid-Induced Osteoporosis

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OUTLINE OF SESSION

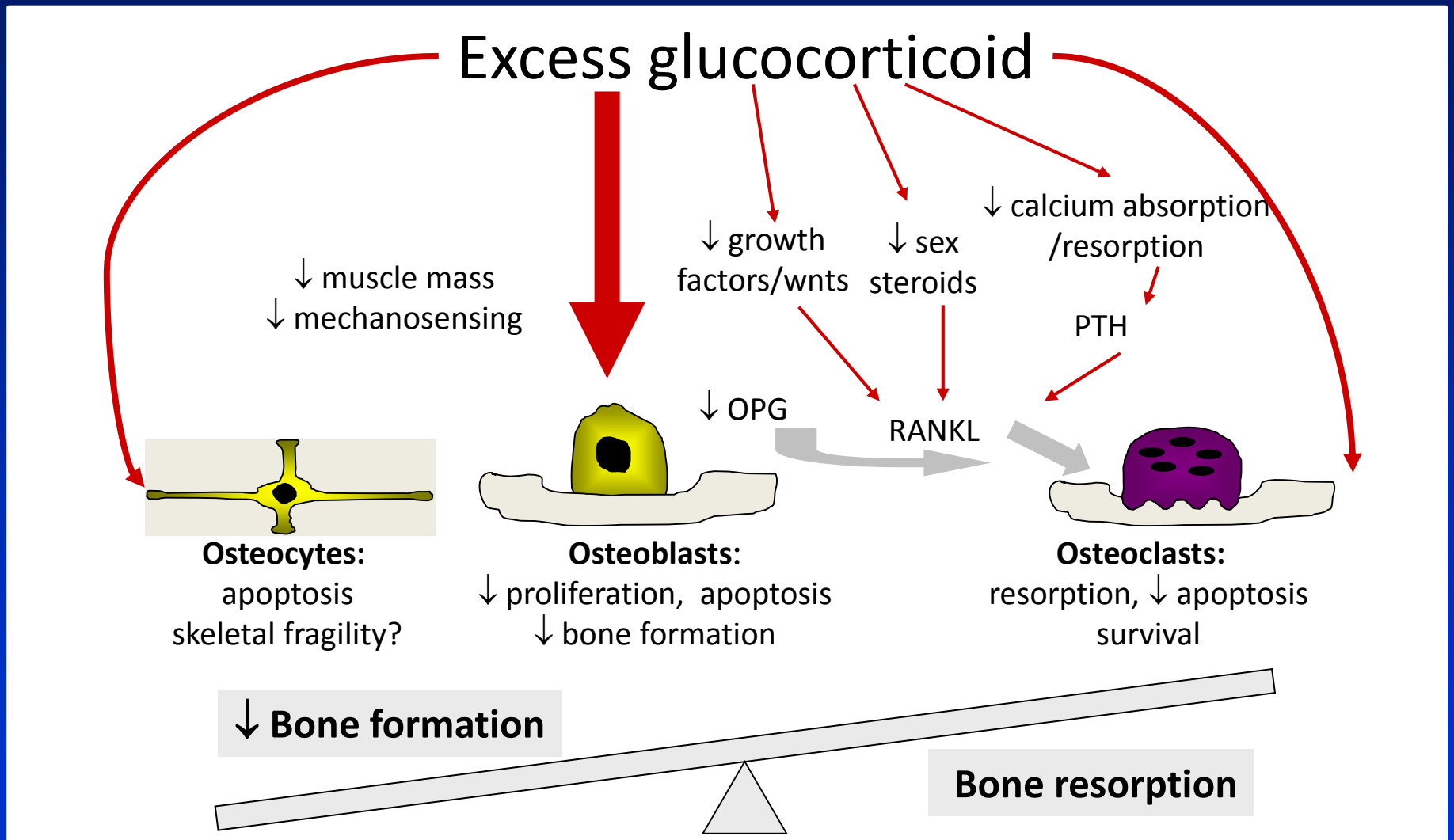
Reminder about the epidemiology and pathology of glucocorticoid associated bone damage

Current treatments, when to use them, and likely developments in the near future

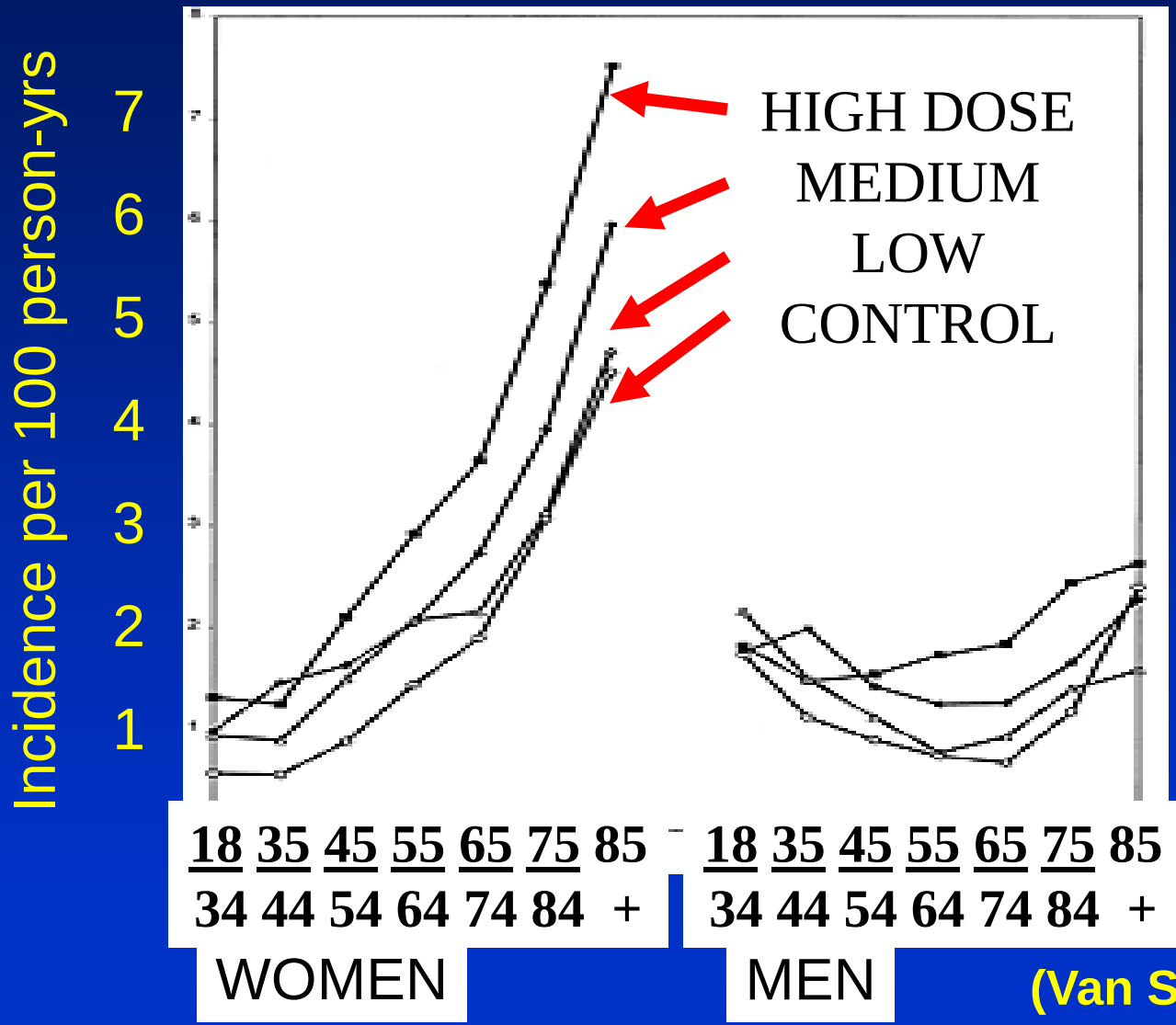
Limitations of current therapies and unresolved issues

Basis for sensitivity to effects of glucocorticoids and clinical implications

PATHOPHYSIOLOGY OF GIOP



Fracture Risk in Relation to Dose and Age



Incidence of non-vertebral # by dose, age and gender

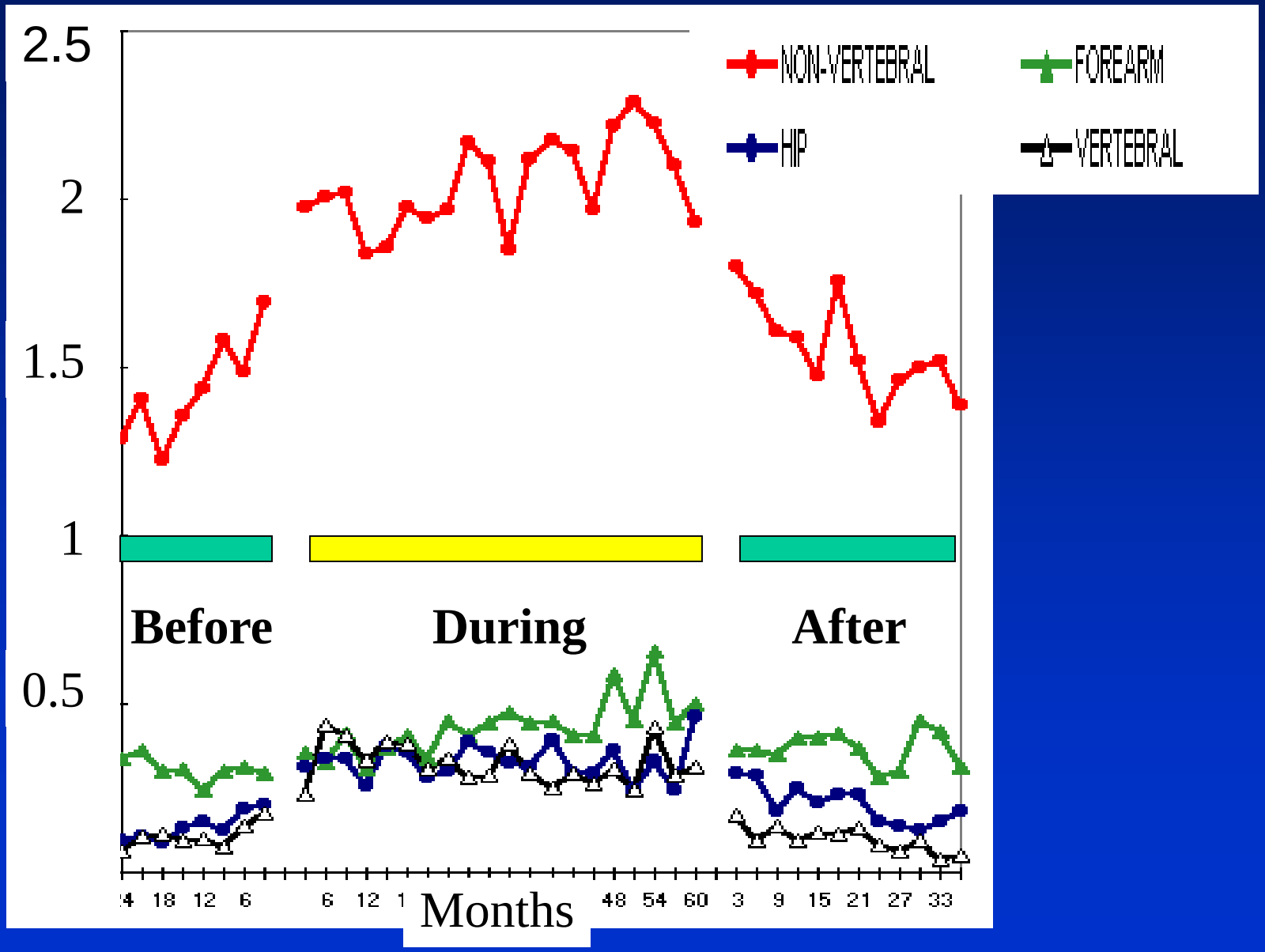
(Van Staa et al., 2000)

Fracture Risk at Spine and Hip

Pred dose (per day)	Rel Risk Vertebral #	Rel Risk Hip #
2.5-7.5 mg	2.59 (2.16-3.10)	1.77 (1.55-2.02)
>7.5 mg	5.18 (4.25-6.31)	2.27 (1.94-2.66)

(Van Staa et al., 2000)

Fracture Risk Rapidly With Glucocorticoids



FRAX® WHO Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: Meetthe Professor About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 77 Date of Birth: Y: M: D:
2. Sex ○ Male ◉ Female
3. Weight (kg) 65
4. Height (cm) 165
5. Previous Fracture ◉ No ○ Yes
6. Parent Fractured Hip ◉ No ○ Yes
7. Current Smoking ◉ No ○ Yes
8. Glucocorticoids ○ No ◉ Yes
9. Rheumatoid arthritis ◉ No ○ Yes
10. Secondary osteoporosis ◉ No ○ Yes
11. Alcohol 3 or more units/day ◉ No ○ Yes
12. Femoral neck BMD (g/cm^2) Select BMD

Clear Calculate

BMI: 23.9
The ten year probability of fracture (%)

without BMD

Major osteoporotic	27
Hip Fracture	12

Weight Conversion

Pounds → kg

Convert

Height Conversion

Inches → cm

Convert

03491915
Individuals with fracture risk assessed since 1st June 2011

Suggested adjustments to FRAX™ # risk score based on level of glucocorticoid exposure

Dose	Prednisolone equivalent (mg/d)	Average adjustment over all ages
Hip fracture		
Low	<2.5	0.65
Medium	2.5–7.5	No adjustment
High	≥7.5	1.20
Major osteoporotic fracture		
Low	<2.5	0.8
Medium	2.5–7.5	No adjustment
High	≥7.5	1.15

Osteoporos Int (2012) 23:2257–2276

Reduction and NNT to Prevent One Vertebral # in Postmenopausal Women in Bisphosphonate Trials

Intervention	# rate control	# rate treatment	NNT
Etidronate	21.9%	3.2%	5
Alendronate	13%	4.4%	26
Risedronate	20.8%	8.3%	8

Differences in NNT probably relate to differences in absolute risk.
** Zoledronic acid has been shown to be non-inferior to Risedronate

(Sambrook, 2000)

Teriparatide or Alendronate in Glucocorticoid-Induced Osteoporosis

Kenneth G. Saag, M.D., Elizabeth Shane, M.D., Steven Boonen, M.D., Ph.D., Fernando Marín, M.D., David W. Donley, Ph.D., Kathleen A. Taylor, Ph.D., Gail P. Dalsky, Ph.D., and Robert Marcus, M.D.

RESULTS

At the last measurement, the mean (±SE) bone mineral density at the lumbar spine had increased more in the teriparatide group than in the alendronate group (7.2±0.7% vs. 3.4±0.7%, P<0.001). A significant difference between the groups was reached by 6 months (P<0.001). At 12 months, bone mineral density at the total hip had increased more in the teriparatide group. Fewer new vertebral fractures occurred in the teriparatide group than in the alendronate group (0.6% vs. 6.1%, P=0.004); the incidence of nonvertebral fractures was similar in the two groups (5.6% vs. 3.7%, P=0.36).

N Engl J Med 2007;357:2028-39.

DENOSUMAB IN GIOP

- Currently being evaluated in a 2 year non-inferiority RCT comparing DMab vs Risedronate
- 12 month data based on 795 patients published in abstract form
- BMD increased more with DMab than RIS
- Spine BMD increased 4.4% with DMab vs 2.3%
- Similar results in those starting steroids and those already on steroids long term
- No obvious safety signals and well tolerated

OTHER CLINICAL POINTERS

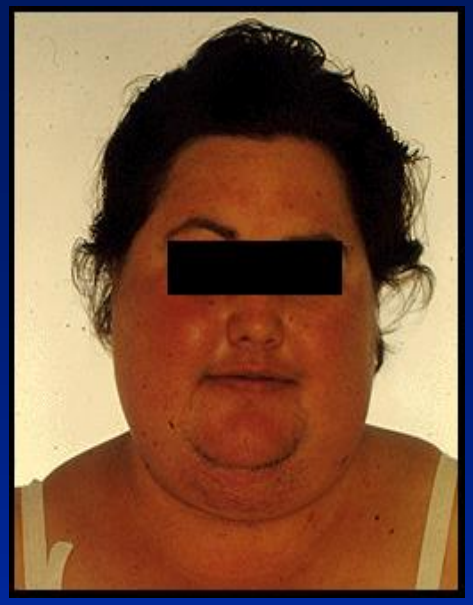
In placebo arms of RCTs fractures were very rare in premenopausal women and men under 50

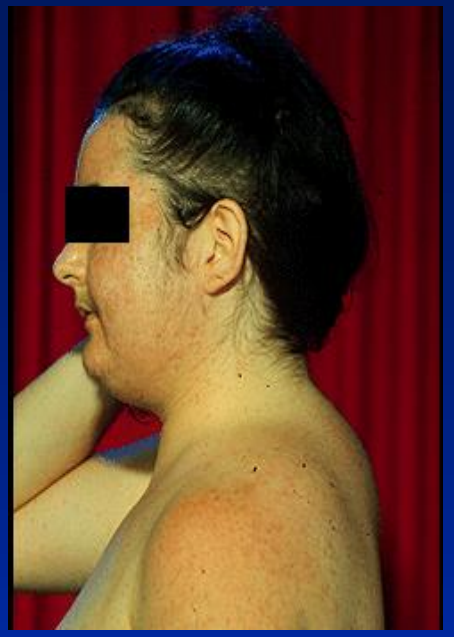
Where fractures occurred in young people their BMD T-score was <1.5

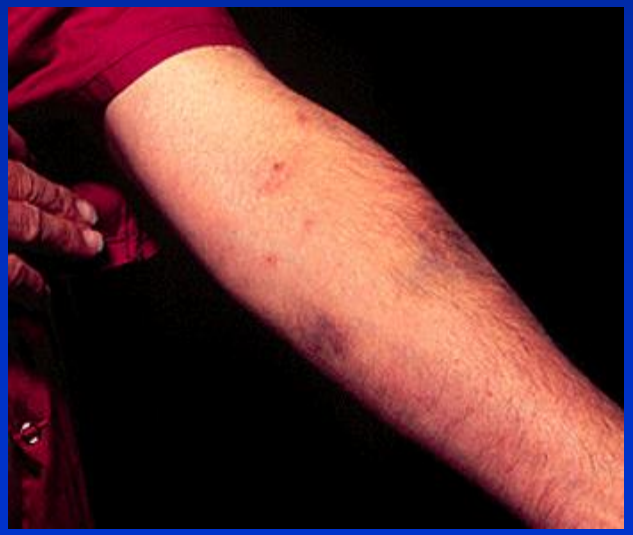
Intermittent oral steroid users had minimal increase in longterm fracture risk if cumulative pred exposure <1000 mg

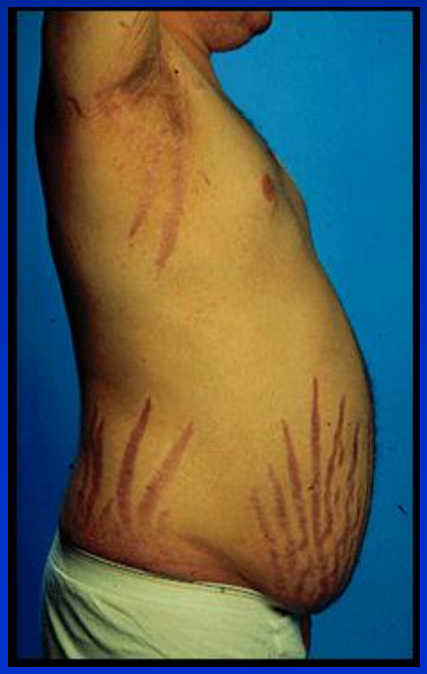
Inhaled steroid users have increased fracture risk but much of this is driven by underlying disease. Consider doing Synacthen Test?

Clinical features of glucocorticoid excess









Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study

Akbar K Waljee,[1,2,3,4] Mary A M Rogers,[2,4,5] Paul Lin,[2] Amit G Singal,[6] Joshua D Stein,[2,7,8] Rory M Marks,[9] John Z Ayanian,[2,5,8] Brahmajee K Nallamothu[1,2,4,10]

Table 4 | Incidence rate ratios for adverse events associated with short term use of oral steroids, by reason for medical visit

Adverse event	5-30 days* Incidence rate ratio† (95% CI)	P value	31-90 days* Incidence rate ratio† (95% CI)	P value
Sepsis:				
Respiratory conditions‡	3.77 (1.94 to 7.35)	<0.001	2.53 (1.25 to 5.10)	0.01
Musculoskeletal conditions§	12.91 (5.49 to 30.34)	<0.001	4.32 (1.87 to 9.97)	0.001
Venous thromboembolism:				
Respiratory conditions‡	3.11 (2.20 to 4.40)	<0.001	1.27 (0.88 to 1.82)	0.20
Musculoskeletal conditions§	4.70 (3.08 to 7.17)	<0.001	2.02 (1.31 to 3.11)	0.001
Fracture:				
Respiratory conditions‡	1.96 (1.63 to 2.37)	<0.001	1.33 (1.13 to 1.56)	<0.001
Musculoskeletal conditions§	2.46 (2.02 to 3.00)	<0.001	1.65 (1.37 to 1.99)	<0.001

BMJ 2017;357:j1415

LIMITATIONS OF CURRENT TREATMENTS FOR GLUCOCORTICOID ADVERSE EFFECTS

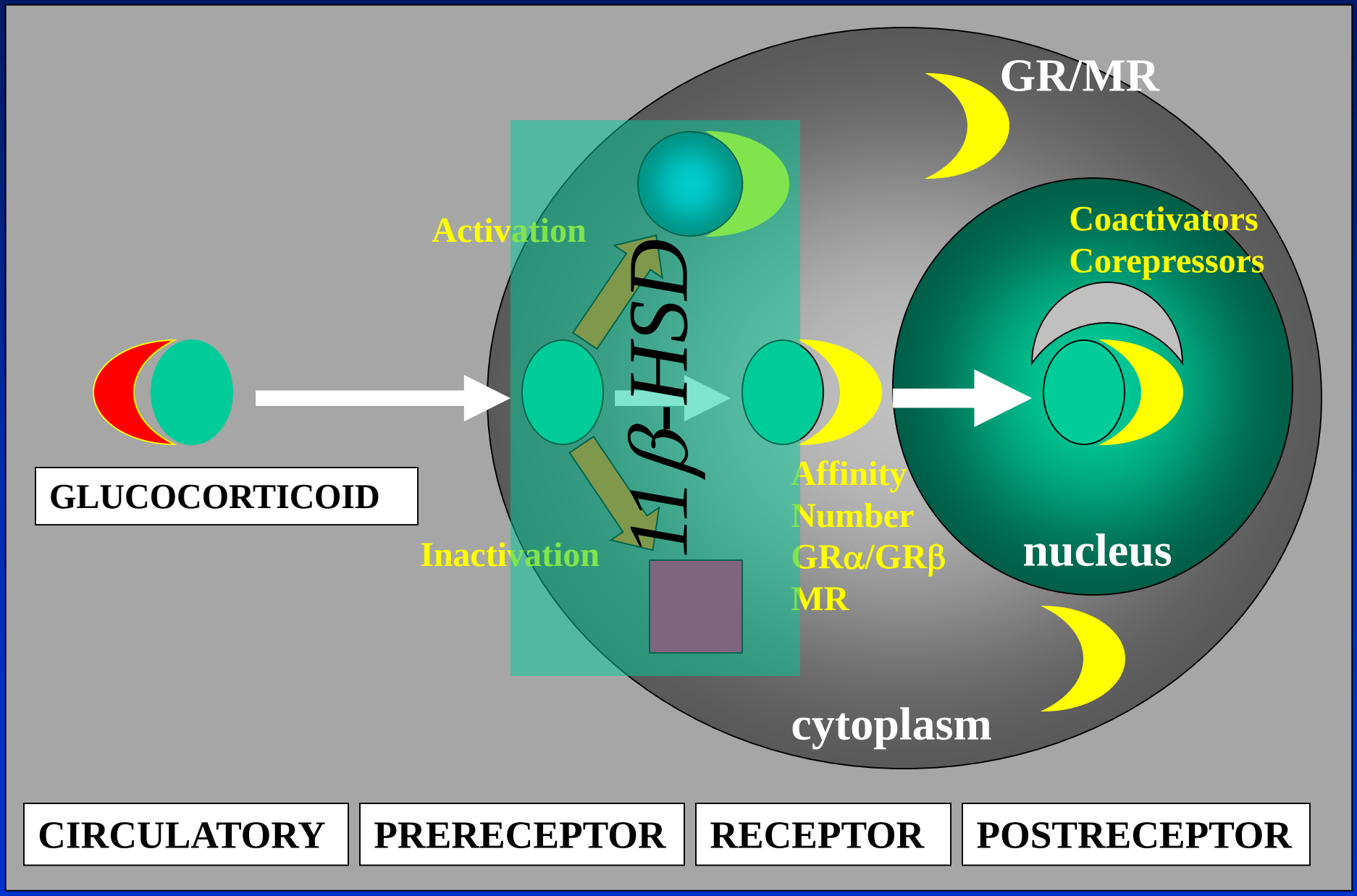
Only address issues with bone

Bone is only one negative consequence of glucocorticoid exposure

Glucocorticoids act on bone through similar molecular mechanisms to their beneficial effects on inflammatory disease – can you have one without the other???

Effects of glucocorticoids are difficult to predict at an individual level

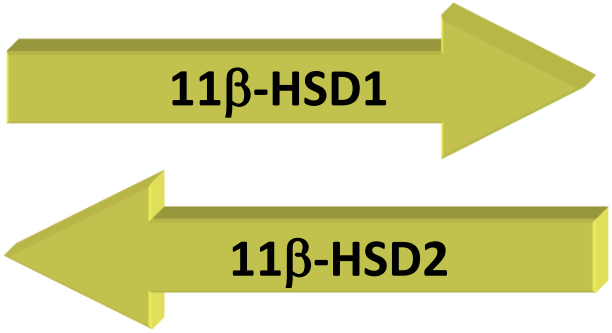
Levels Contributing to Glucocorticoid Action



11β-Hydroxysteroid dehydrogenases

Liver
Adipose
Muscle
Bone
Macrophages, lymphocytes

Cortisone
Prednisone
Dehydrocortico-sterone (DHC)

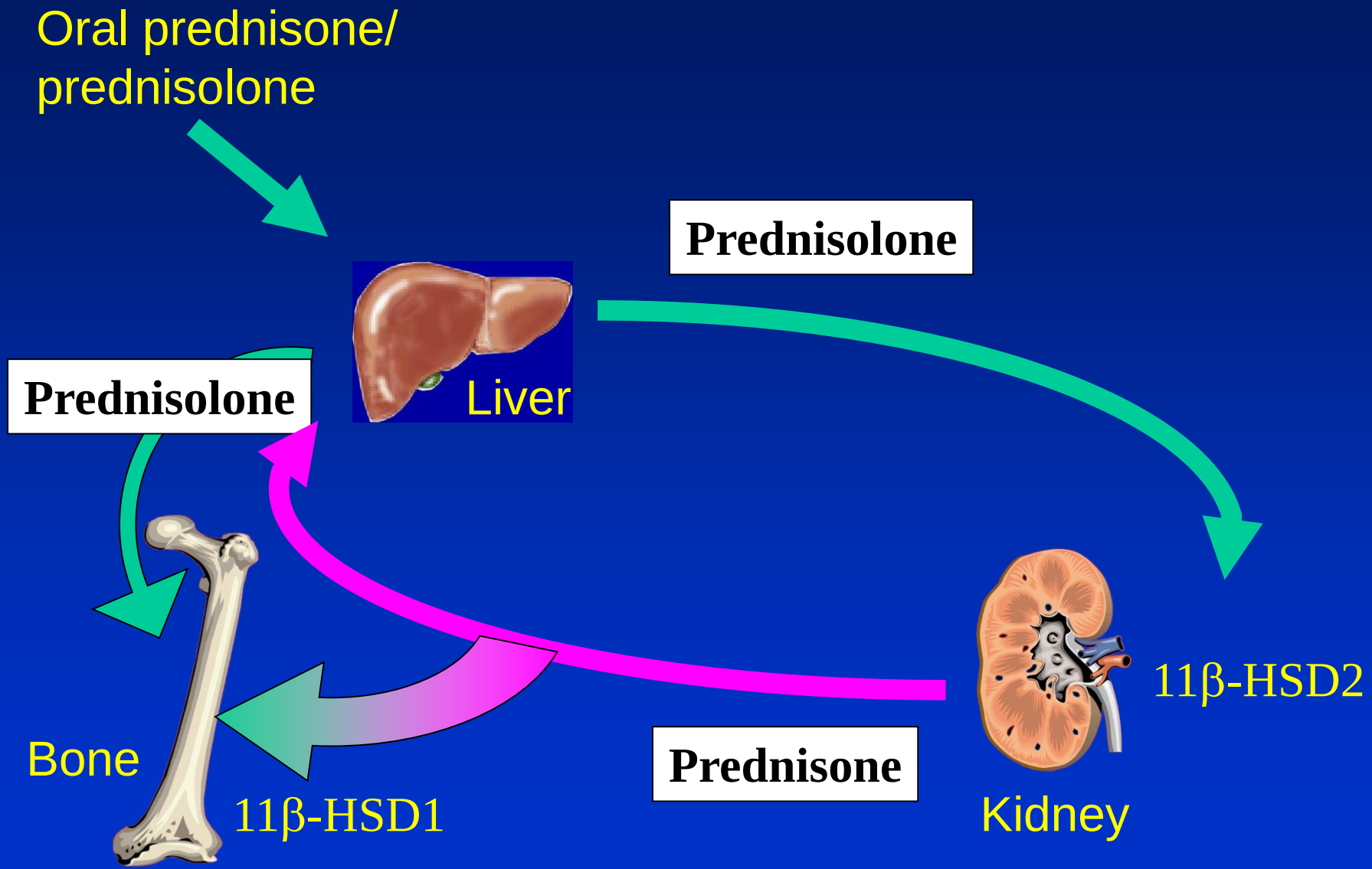


Cortisol
Prednisolone
Corticosterone

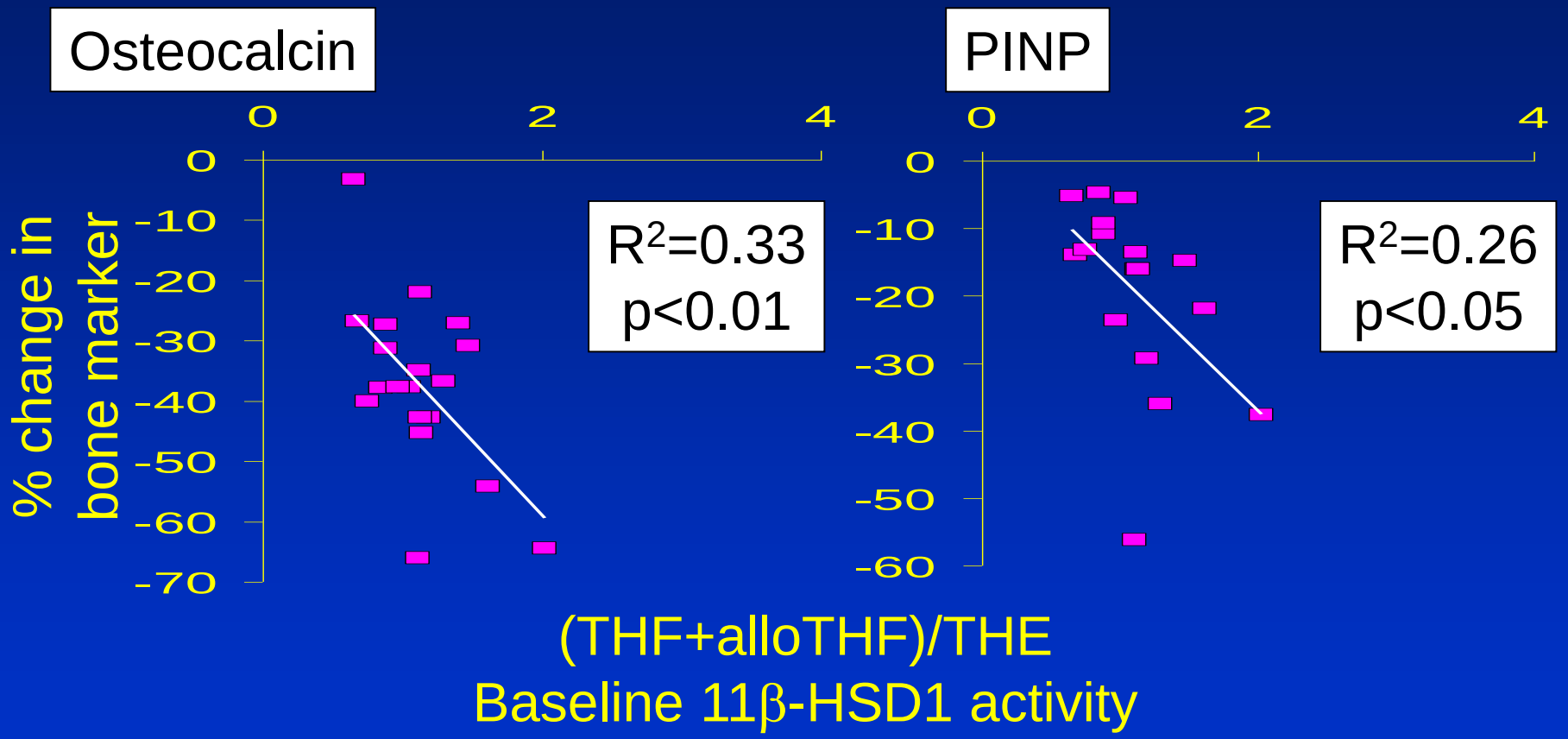
Kidney

Inactive

Active


Oral prednisone/
prednisolone
Prednisolone
Liver
Prednisolone
11β-HSD2
Bone
Prednisone
11β-HSD1
Kidney

11β-HSD1 activity predicts change in bone formation markers in healthy men: prednisolone 10mg/d for 1 week



Cooper et al., JCEM 2003

SUMMARY AND FUTURE PROSPECTS

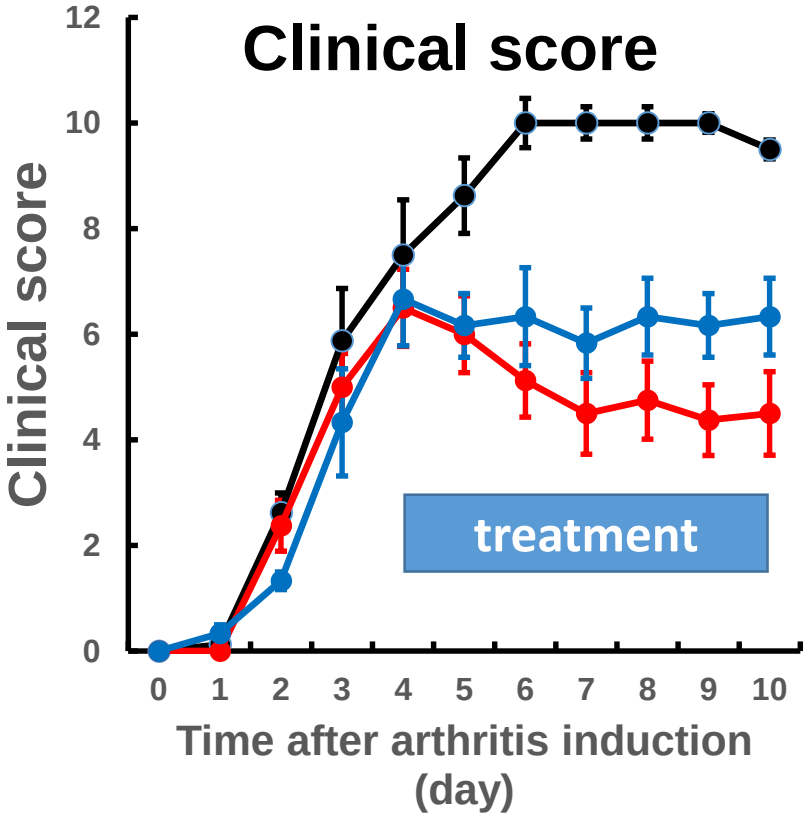
GIOP remains a common and important problem

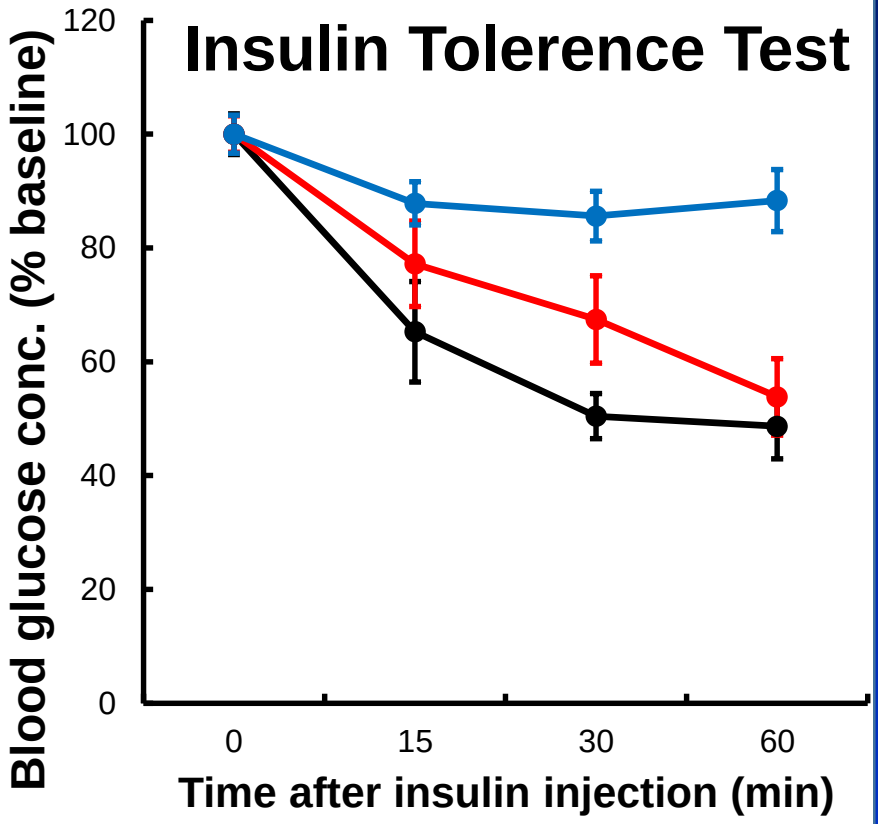
Treatments are effective (despite not really being mechanism based) but do not address non-bone risks of glucocorticoids

There is no realistic prospect of developing glucocorticoids intrinsically bone sparing

Future developments more likely based on selective targeting of glucocorticoids to specific tissues

Liposomal DHC (inactive) as a treatment for arthritis (WT mice with induced arthritis)





Emply Liposomes Liposomal DHC Non-liposomal CS

Acknowledgments

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N H M R C