Altogether to Beat Cushing's Syndrome

ABC 2017

PROGRAMMA

10:30-11:30	**SIMPOSIO 4** **LA GUARIGIONE DALLA SINDROME DI CUSHING: EFFETTO SU COMPOSIZIONE CORPOREA E METABOLISMO** Moderatori: Renato Pasquali, Carla Giordano
10:30-10:45	OBESITA' VISCERALE E COMPOSIZIONE CORPOREA Nora Albiger
10:45-11:00	IL METABOLISMO GLICIDICO E LIPIDICO Roberta Giordano
11:00-11:15	IL METABOLISMO PROTEICO, IL MUSCOLO E L'OSSO Iacopo Chiodini
11:15-11:30	Discussione

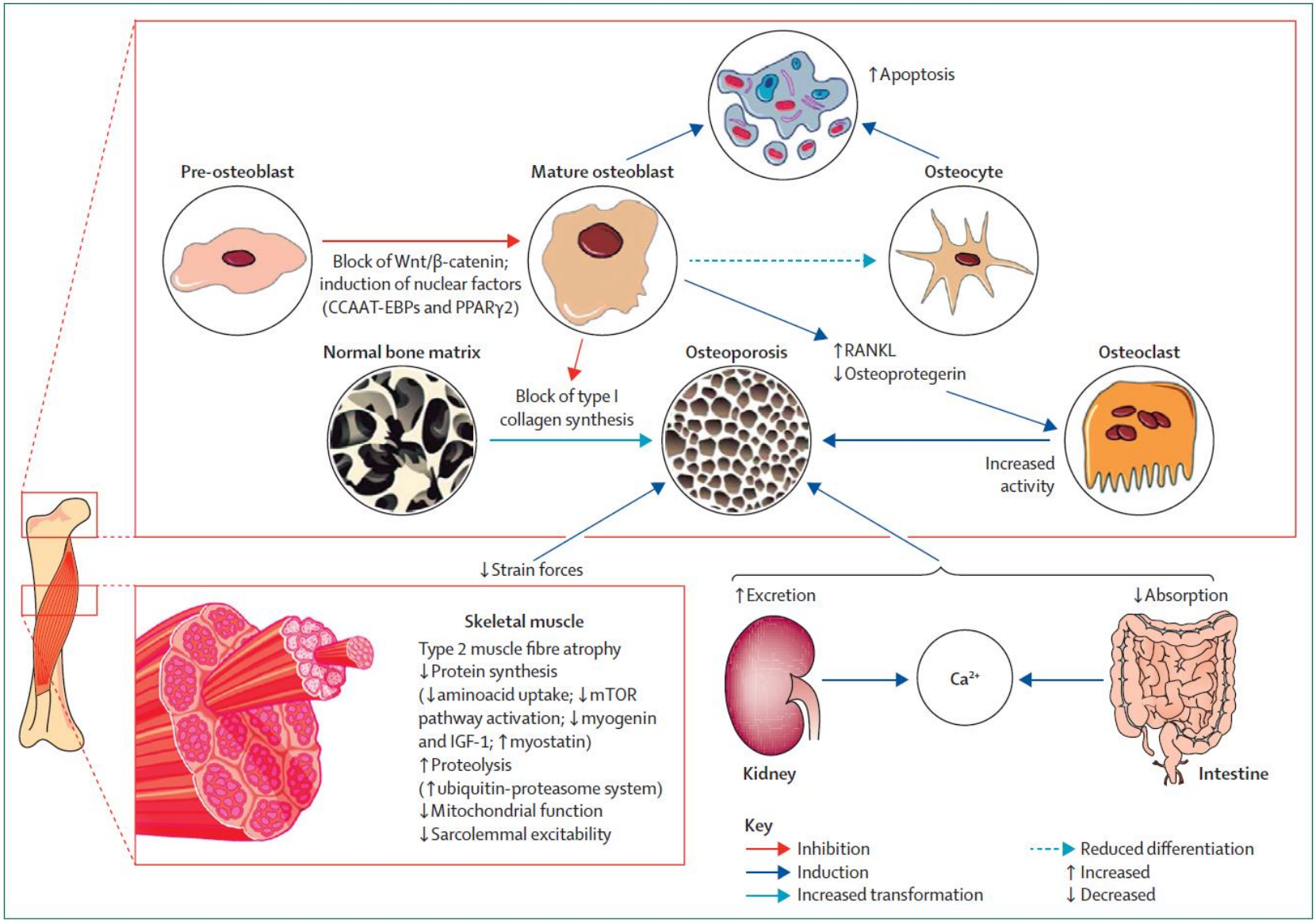
DISCLOSURES

Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abiogen
- Italfarmaco
- Kyowa Kyrin

- **Muscolo**
- **Osso**

PATHOPHYSIOLOGY OF BONE DAMAGE IN CUSHING SYNDROME



Pivonello R et al, Lancet Diabetes Endocrinol 2016

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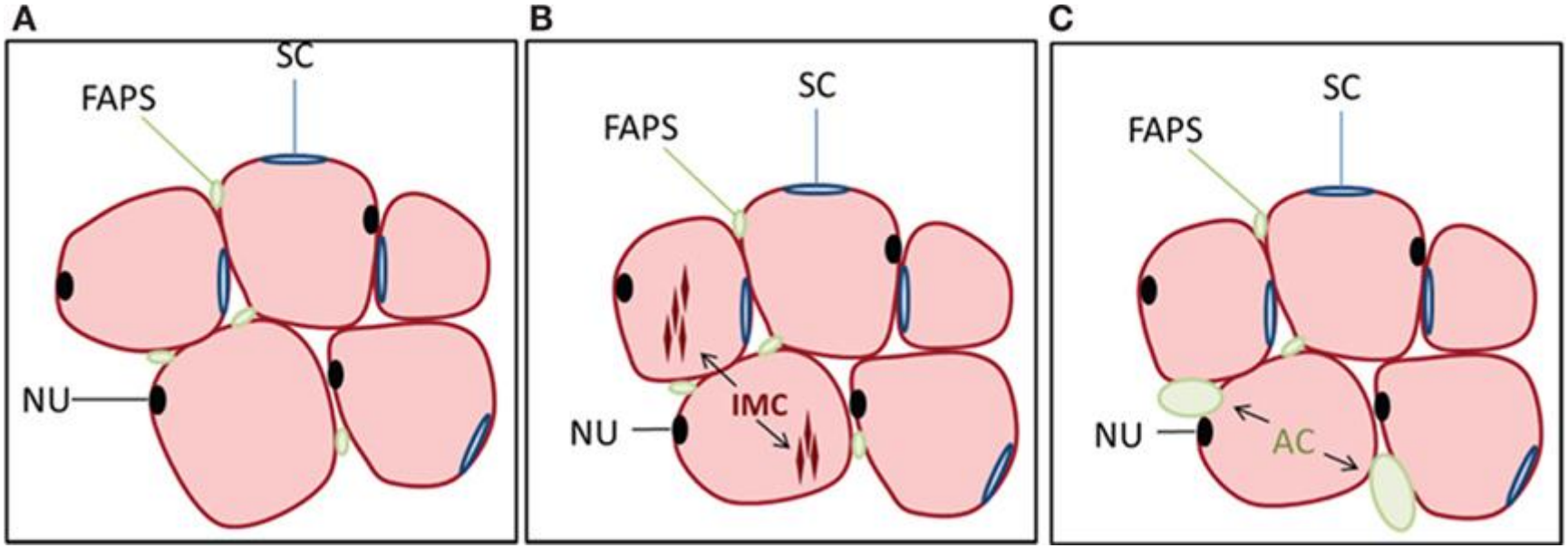
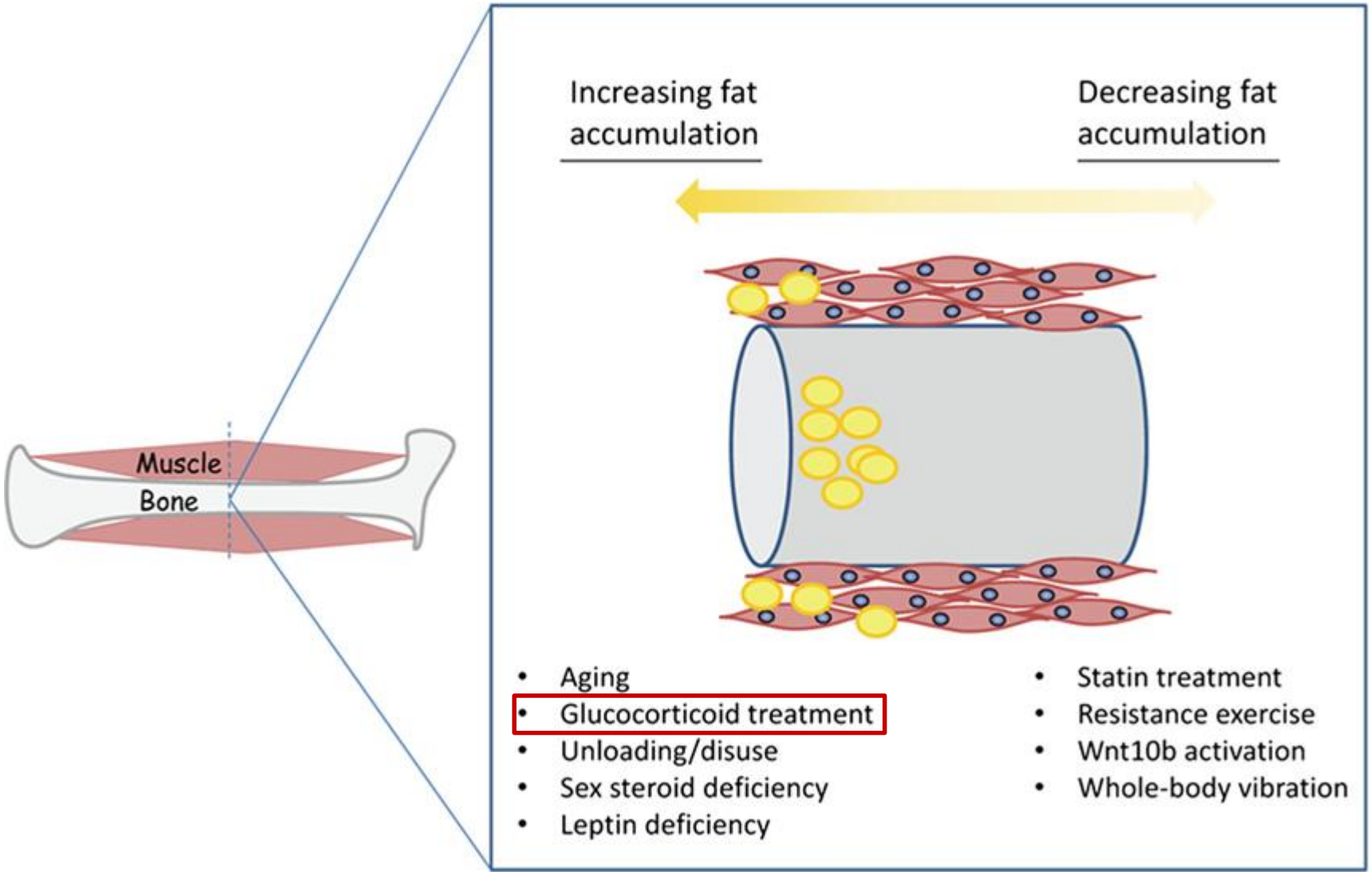
CELL POPULATIONS IN MUSCLE AND THEIR RELATIONSHIP TO LIPID ACCUMULATION



Hamrick MW et a l, Front Endocrinol 2016,

Myofibers: pink are surrounded
SCs (blue): satellite cells
FAPS (green): fibro-adipogenic progenitors (multipotential cells of mesenchymal origin)

GLUCOCORTICOIDS AND MYOSTEATOSIS



Hamrick MW et a l, Front Endocrinol 2016,

SCIENTIFIC REPORTS

OPEN

Glucocorticoid receptor positively regulates transcription of *FNDC5* in the liver

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Hyoung Kyu Kim[1,2,*], Yu Jeong Jeong[1,*], In-Sung Song[1,3], Yeon Hee Noh[1], Kyo Won Seo[1], Min Kim[1] & Jin Han[1]

Irisin is secreted by skeletal muscle during exercise and influences energy and metabolic homeostasis. This hormone is a cleaved and secreted fragment of fibronectin type III domain-containing 5 (FNDC5). Elucidation of the *FNDC5* gene regulation mechanism is necessary to clarify the function of irisin as a potential therapeutic target in human metabolic diseases. Thus, we investigated the genetic and epigenetic mechanisms that regulate expression of the *FNDC5* gene. *FNDC5* mRNA was strong expressed in major energy-dependent human tissues, including heart, brain, liver, and skeletal muscle. Promoter analysis of the *FNDC5* gene revealed that the core promoter region of the *FNDC5* gene contained one CpG island that was located just upstream of the transcriptional start site for variants 2 and 3. Treatment with the histone deacetylase inhibitor sodium butyrate and the demethylating agent 5-azacytidine increased mRNA expression of *FNDC5* in Huh7 cells. Prediction of transcription factor binding sites suggested that the glucocorticoid receptor was involved in the regulation of *FNDC5* expression, and indeed, cortisol treatment increased mRNA expression of *FNDC5* in Huh7 cells. Collectively, these findings offer insight into the genetic and epigenetic regulation of *FNDC5*, providing the initial steps required for understanding the role of irisin in the metabolic homeostasis.

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LEAN TISSUE MASS AND DISTRIBUTION IN CUSHING DISEASE

	Lean tissue							
	Total		Trunk		Legs		Arms	
	kg	% BW	kg	% BW[b]	kg	% BW[b]	kg	% BW[b]
Cushing Disease n=8	38.9 ± 5.3	51.5 ± 4.7	19.8 ± 3.3	50.6 ± 1.9	12.3 ± 1.3	31.7 ± 2.0	4.8 ± 0.91	12.3 ± 1.1
Obese Controls n=10	43.9 ± 4.6	53.9 ± 5.6	21.5 ± 3.0	48.8 ± 2.6	13.9 ± 1.2	31.8 ± 1.8	6.6 ± 1.1	15.0 ± 1.6
Healthy Controls n=8	36.5 ± 3.9	63.5 ± 4.3	17.1 ± 2.1	46.8 ± 1.9	12.4 ± 1.6	34.1 ± 2.1	4.4 ± 0.6	12.0 ± 1.3
P value								
a *vs.* b	0.047	NS	NS	NS	0.012	NS	0.002	0.001
a *vs.* c	NS	<0.001	NS	0.003	NS	NS	NS	NS
b *vs.* c	0.005	0.003	0.008	NS	NS	0.033	<0.001	0.002

Wajchenberg BL et al, J Clin Endocrinol Metab 1995

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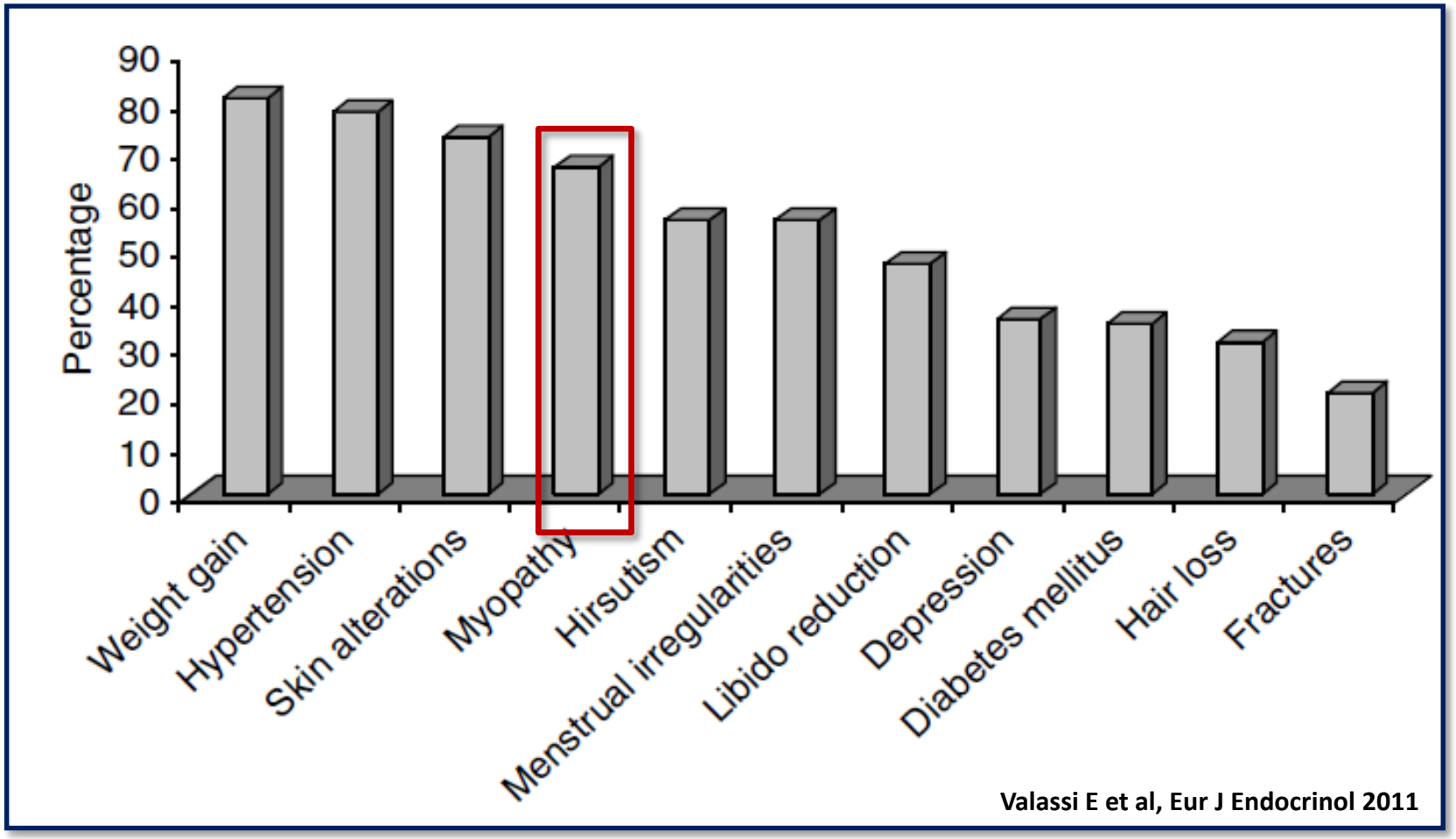
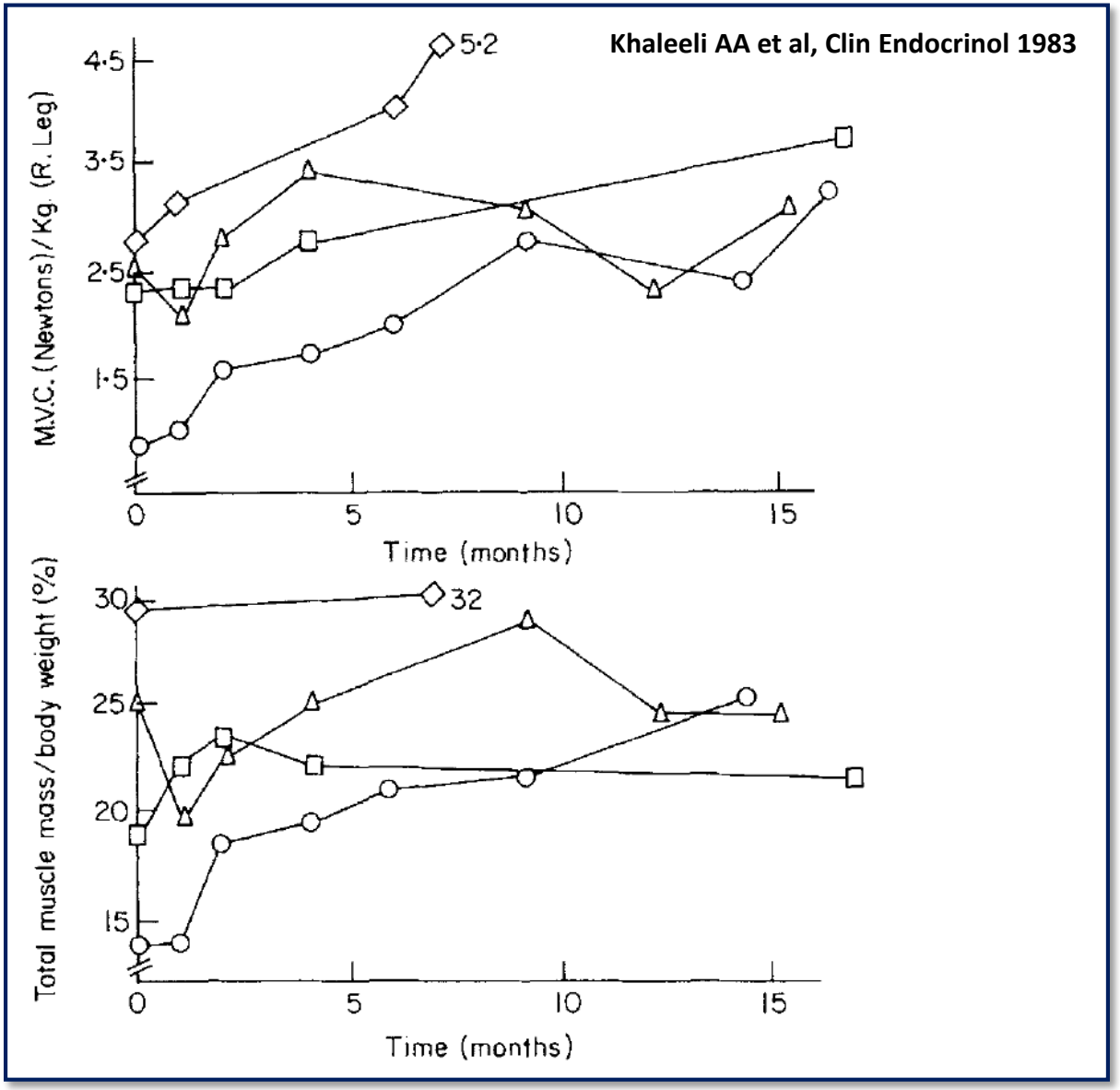
MUSCLE DAMAGE IN CUSHING'S SYNDROME



Valassi E et al, Eur J Endocrinol 2011

EFFECT OF TREATMENT OF CUSHING'S SYNDROME ON SKELETAL MUSCLE STRUCTURE AND FUNCTION



MRI ASSESSMENT OF LEAN AND ADIPOSE TISSUE DISTRIBUTION AFTER RECOVERY FROM CUSHING'S DISEASE

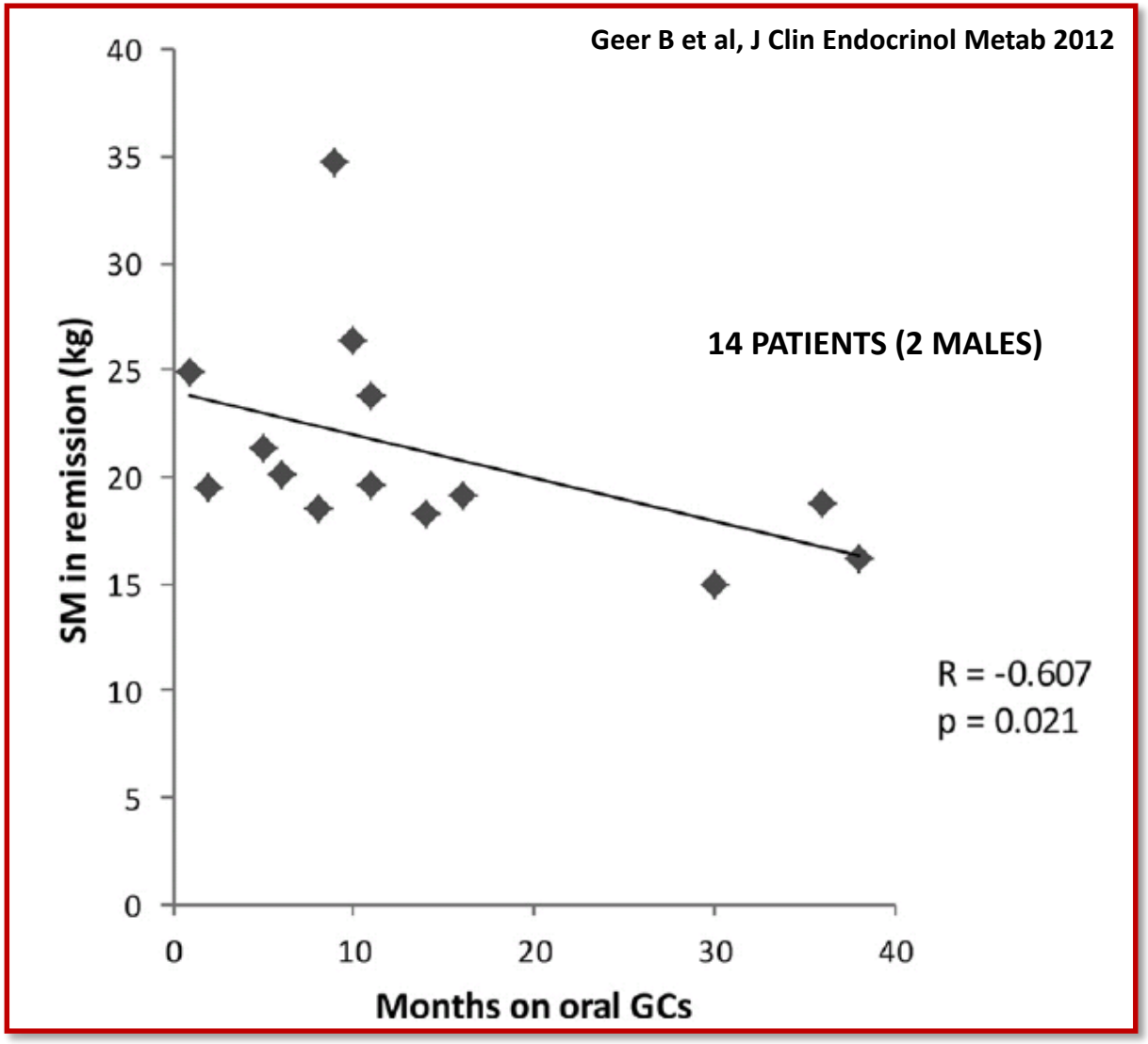
TABLE 2. Body composition measurements **14 PATIENTS (2 MALES)**

Measure (kg)	Active CD	Remission	Difference	Change (%)	Value decreased (no. of patients)	*P* value[a]
VAT	4.59 ± 2.68	3.21 ± 2.05	−1.38	−29.3	12	0.004
Pelvic BMAT[b]	0.26 ± 0.11	0.19 ± 0.09	−0.07	−20.5	11	0.012
TrSAT	19.54 ± 7.35	15.72 ± 7.92	−3.82	−21.9	12	0.0005
Limb SAT	13.82 ± 7.33	12.01 ± 7.29	−1.81	−14.8	13	0.001
Total SAT	33.36 ± 14.10	27.69 ± 14.33	−5.67	−19.1	13	0.0001
TAT	39.21 ± 14.15	32.00 ± 15.43	−7.21	−20.5	12	0.0002
IMAT	1.18 ± 0.46	1.10 ± 0.57	−0.08	−4.8	9	0.512
SM	21.18 (19.4–22.9)	19.58 (18.6–23.2)	−1.60	−4.5	10	0.02
Limb SM	11.04 (9.92–12.66)	10.86 (9.84–11.67)	−0.18	−2.9	10	0.12
VAT/SM	0.20 ± 0.09	0.14 ± 0.07	−0.06	−26.1	12	0.006
VAT/TAT	0.13 ± 0.09	0.11 ± 0.08	−0.02	−13.9	13	0.04

Data are presented as mean ± SD or median (interquartile range). *P* values are from Ln (natural logarithm) values.

Geer B et al, J Clin Endocrinol Metab 2012

MRI ASSESSMENT OF LEAN AND ADIPOSE TISSUE DISTRIBUTION AFTER RECOVERY FROM CUSHING'S DISEASE



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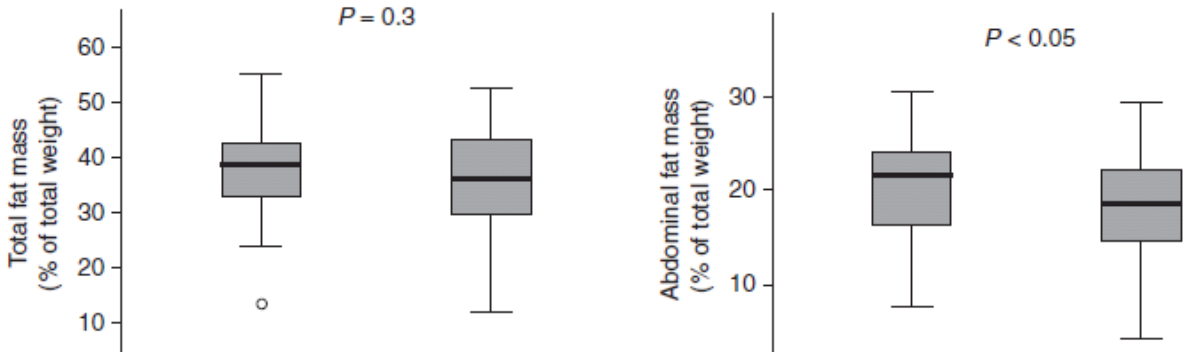
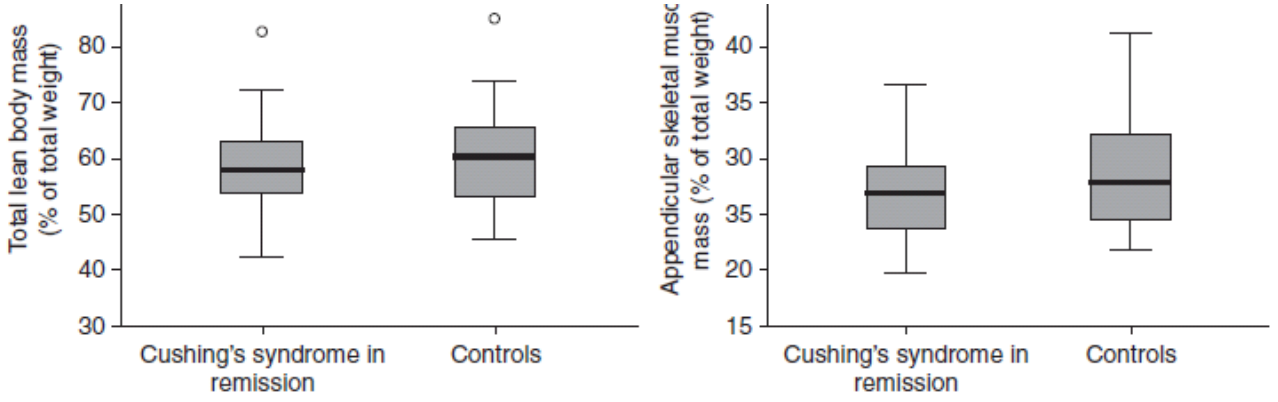
BODY COMPOSITION IN WOMEN WITH CUSHING'S SYNDROME IN REMISSION: ASSOCIATION WITH GLUCOCORTICOID SENSITIVITY

50 women treated for CS 50 controls

Median (interquartile range) remission time: 13 (5–19) years



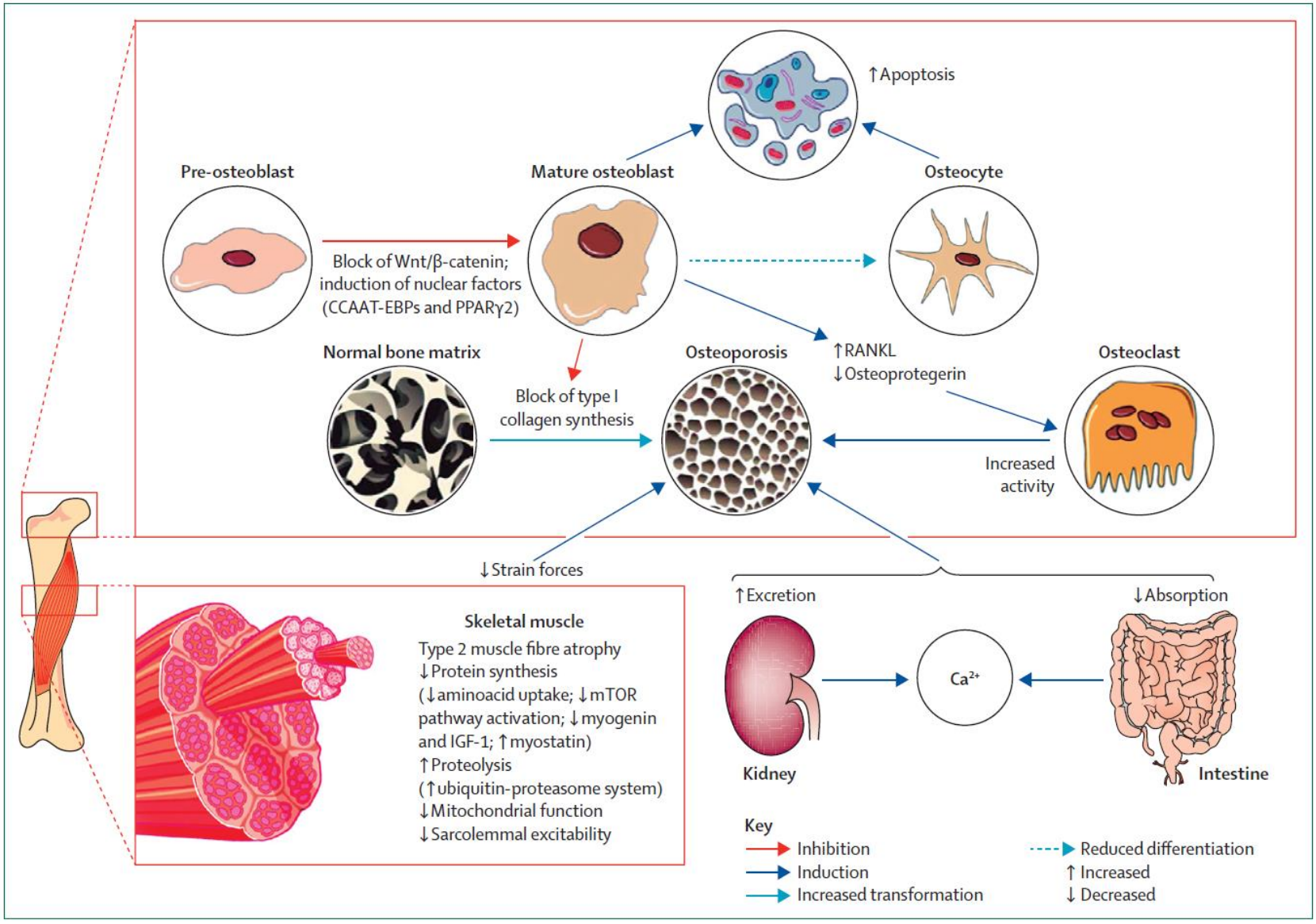
The patients carrying theTC/CCalleles of the ABCB1 rs1045642 polymorphism had increased abdominal fat mass and decreased appendicular skeletal muscle mass



Ragnarsson et al, EJE 2015

- **Muscolo**
- **Osso**

PATHOPHYSIOLOGY OF BONE DAMAGE IN CUSHING SYNDROME



Pivonello R et al, Lancet Diabetes Endocrinol 2016

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BMD AFTER CURE OF CUSHING'S SYNDROME

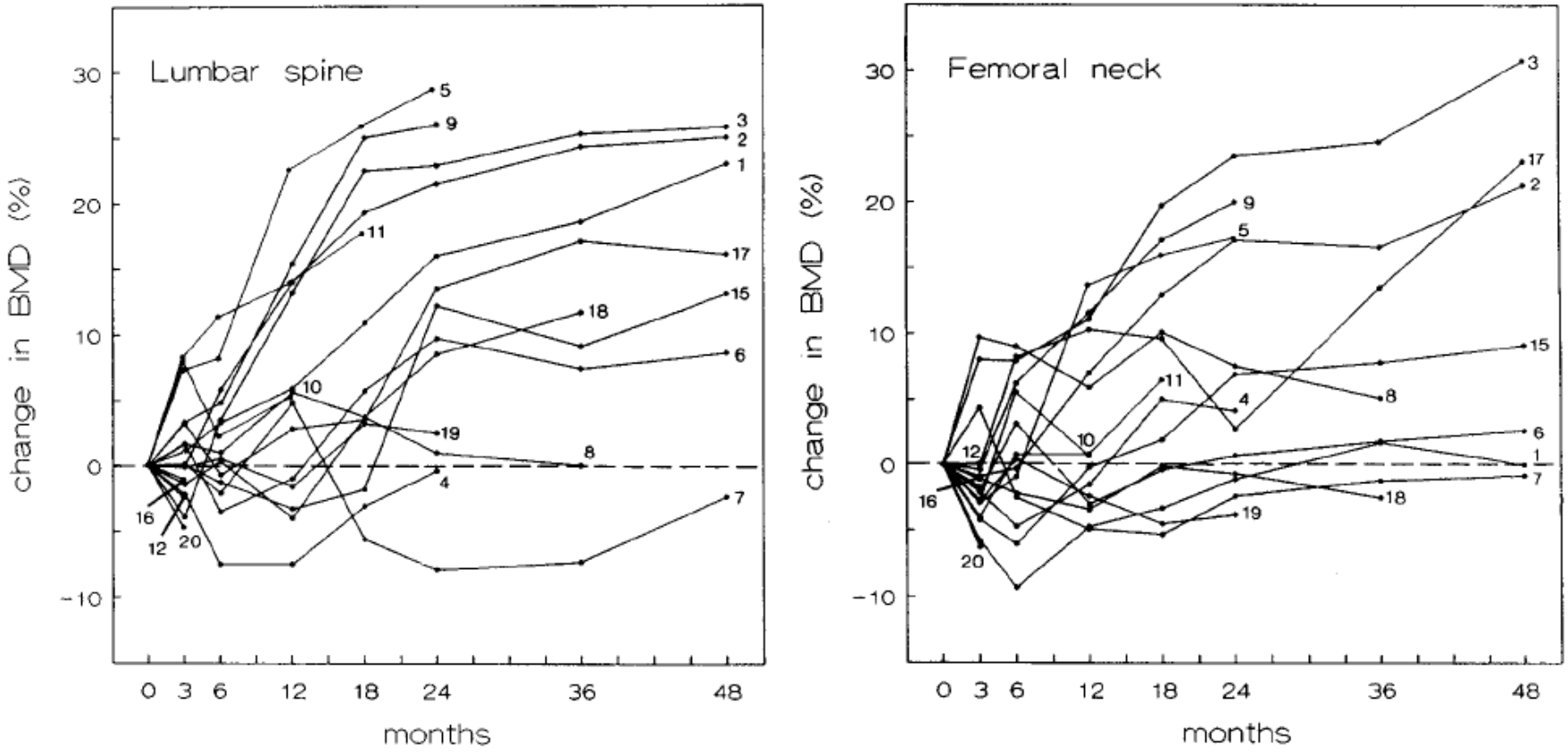
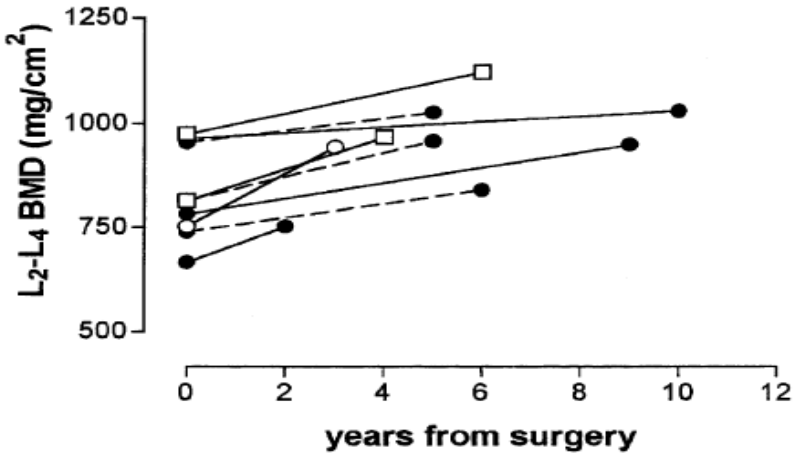
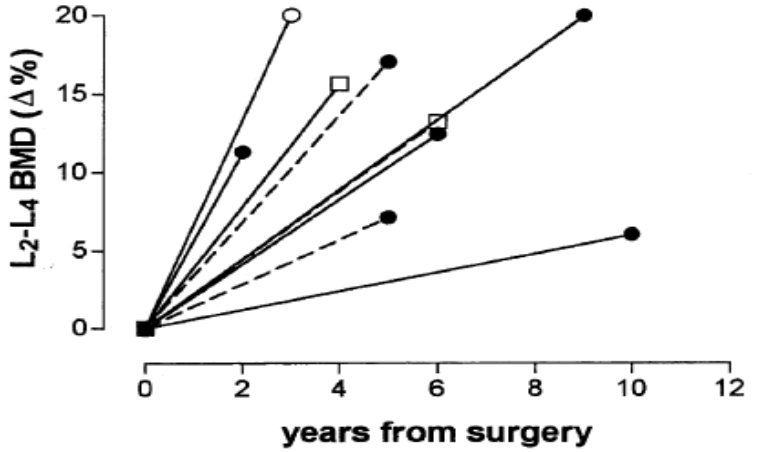


FIG. 1. Percentage change in BMD in the lumbar spine (L1-L4) and femoral neck after surgical cure of 18 patients with Cushing's syndrome. The individual values at seven time points after surgery were compared with the pretreatment value (t = 0 months; mean of two determinations). Note that the improvement of BMD in the lumbar spine in patients 7 and 8 is less than that in the other patients. Both patients used glucocorticoids in doses that were higher than the normal substitution dose, and patient 7 was treated for a malignant midline granuloma 9 months after bilateral adrenalectomy.

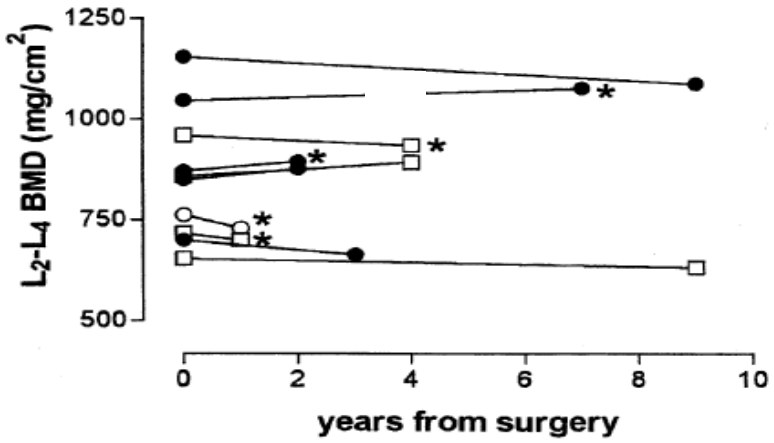
BMD IN CUSHING'S SYNDROME: MEDICAL TREATMENT

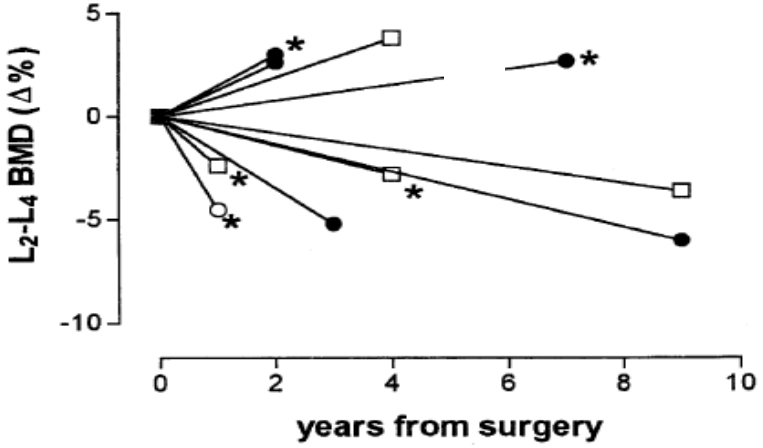
9 pts (1 male, 8 female) cured (6 adrenal adenomas, 3 Cushing's disease).





10 pts (1 male, 9 female) with active Cushing's disease, treated with ketoconazole

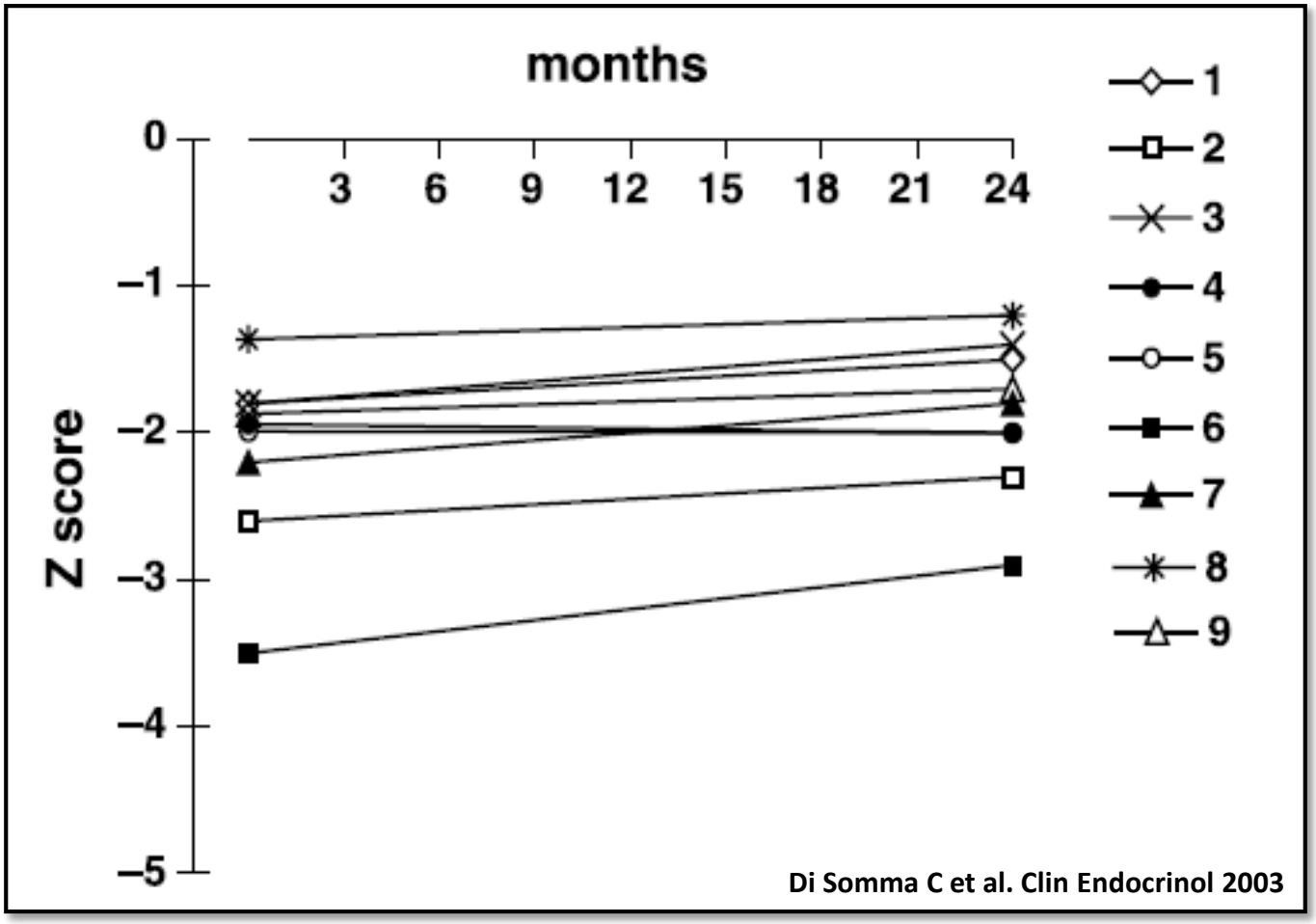




Luisetto G et al. Osteoporos Int 2001

BMD AFTER CURE OF CUSHING'S SYNDROME

9 adults with Cushing Disease (3 M, 6 F; age 32–50 years)



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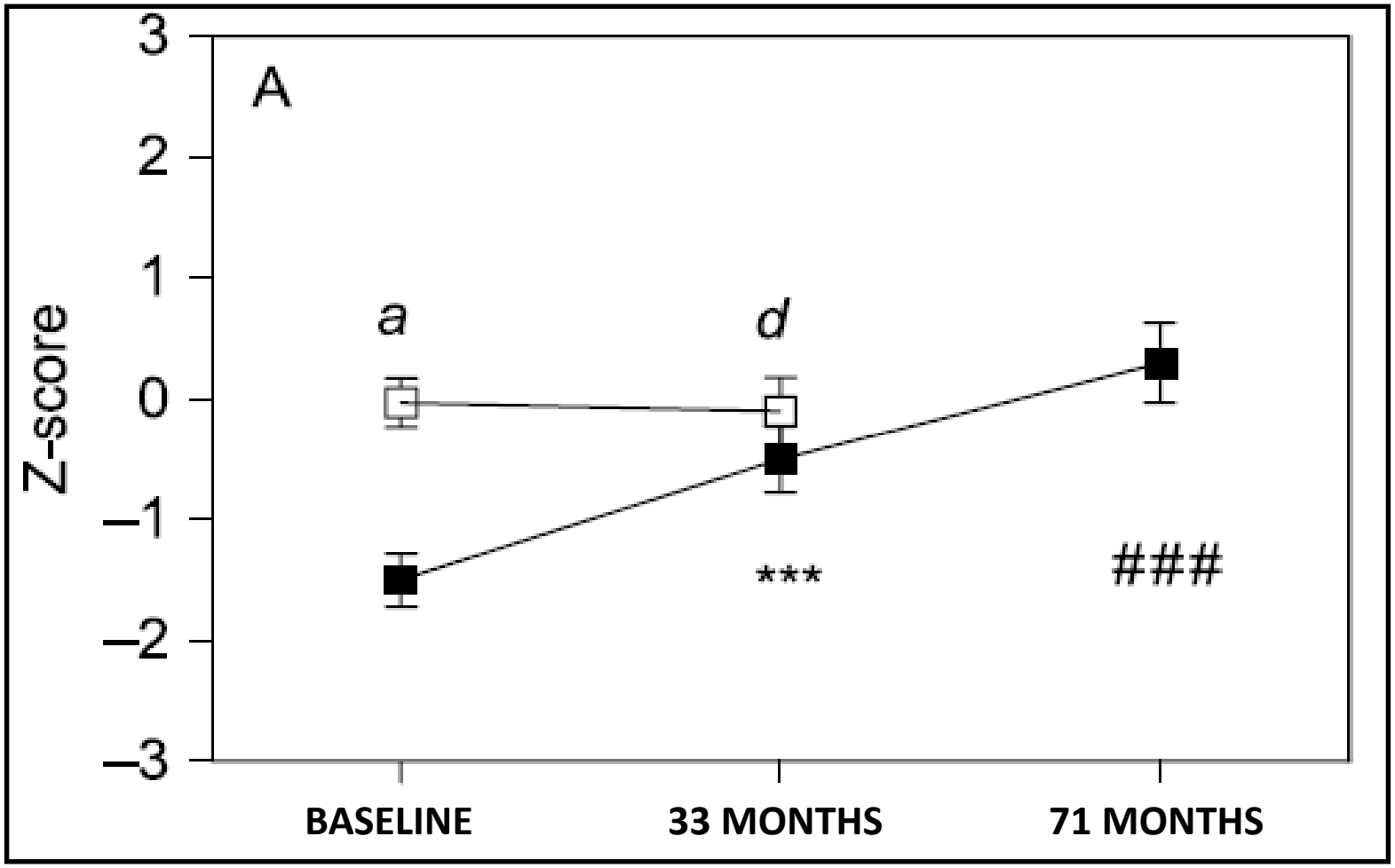
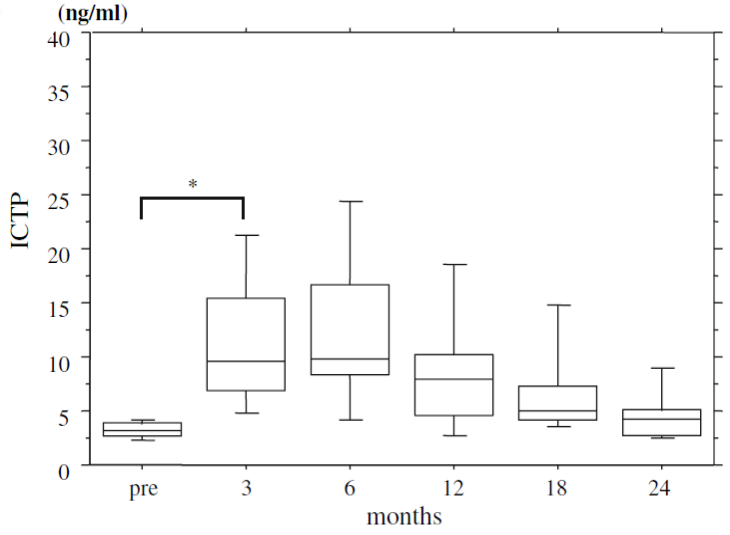
BMD AFTER CURE OF CUSHING'S SYNDROME

33 patients and 25 controls followed up for 33 (1FU) and 71 (2FU) months

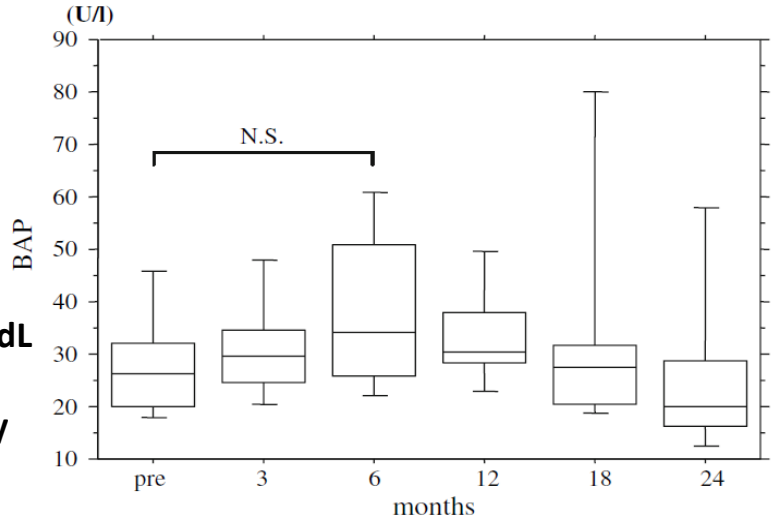


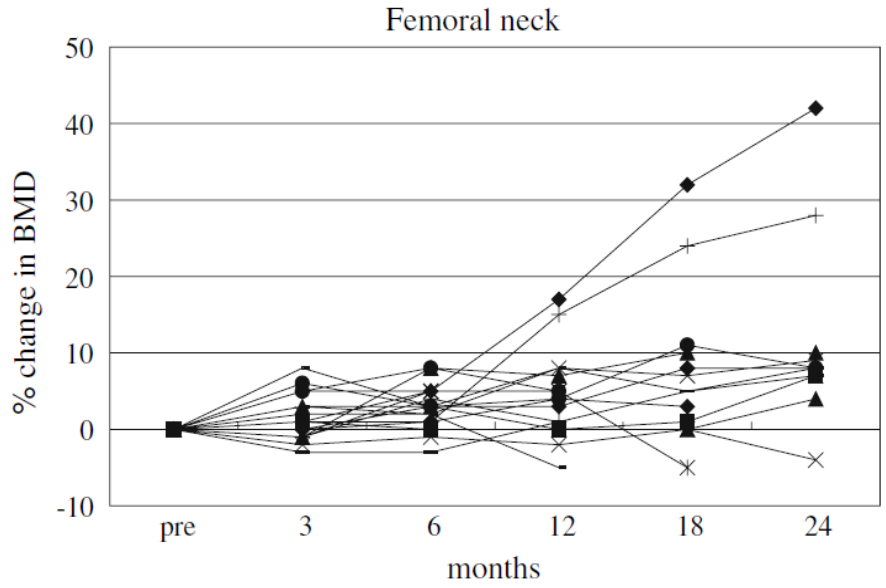
Kristo C et al. Eur J Endocrinol 2006

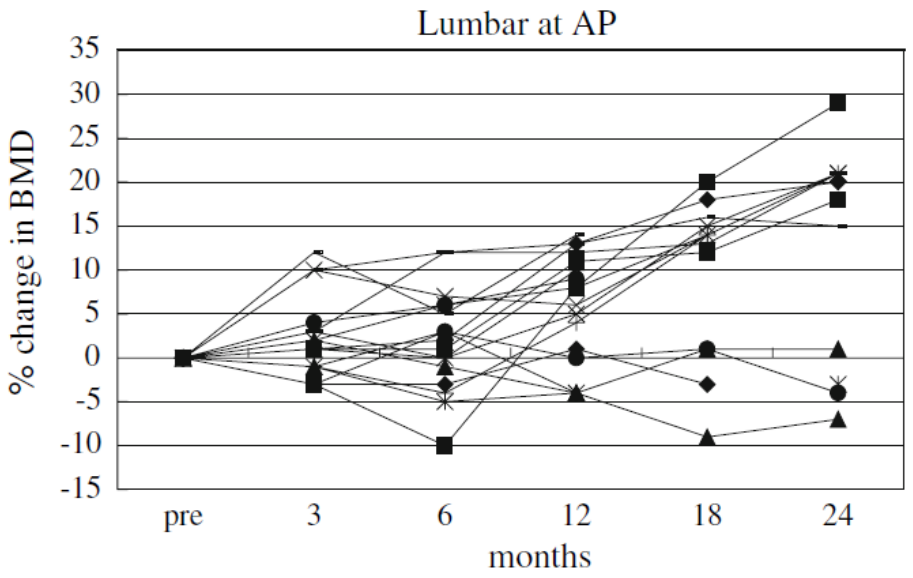
INCREASED BONE DENSITY AND TURNOVER AFTER CURE OF ADRENAL CUSHING SYNDROME



17 Patients (14F)
Age 42±11 yrs
Cortisol 22.7±8.4 µg/dL
FU 21.8±4.3 months
UFC 244 ± 184 µg/day







Kawamata A et al, World J Surg 2008

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CUSHING'S SYNDROME AND FRACTURES

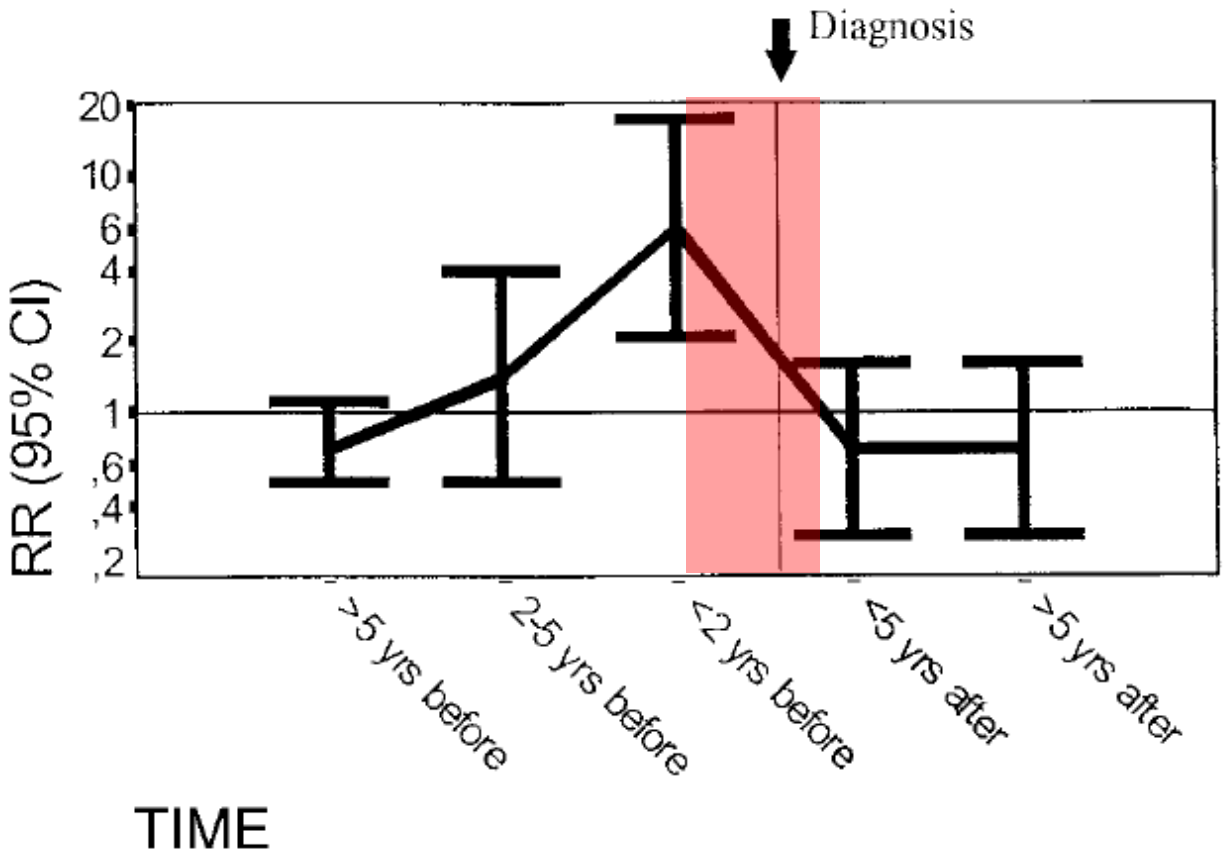

Figure 1 Fracture risk in patients compared with controls before and after the diagnosis (rate ratio (RR)) and 95% confidence interval (CI)). Note the log scale on the ordinate.

Vestergaard P et al, Eur J Endocrinol 2002

104 patients affected by Cushing Syndrome and 312 control subjects studied by a self administered questionnaire.

There was an increased fracture risk within the last 2 years prior to diagnosis (OR 6.0, 95%CI 2.1-17.2).

More than 2 years before and following diagnosis there were no increase in fracture risk.

No difference in fracture risk between patients with adrenal or pituitary disease

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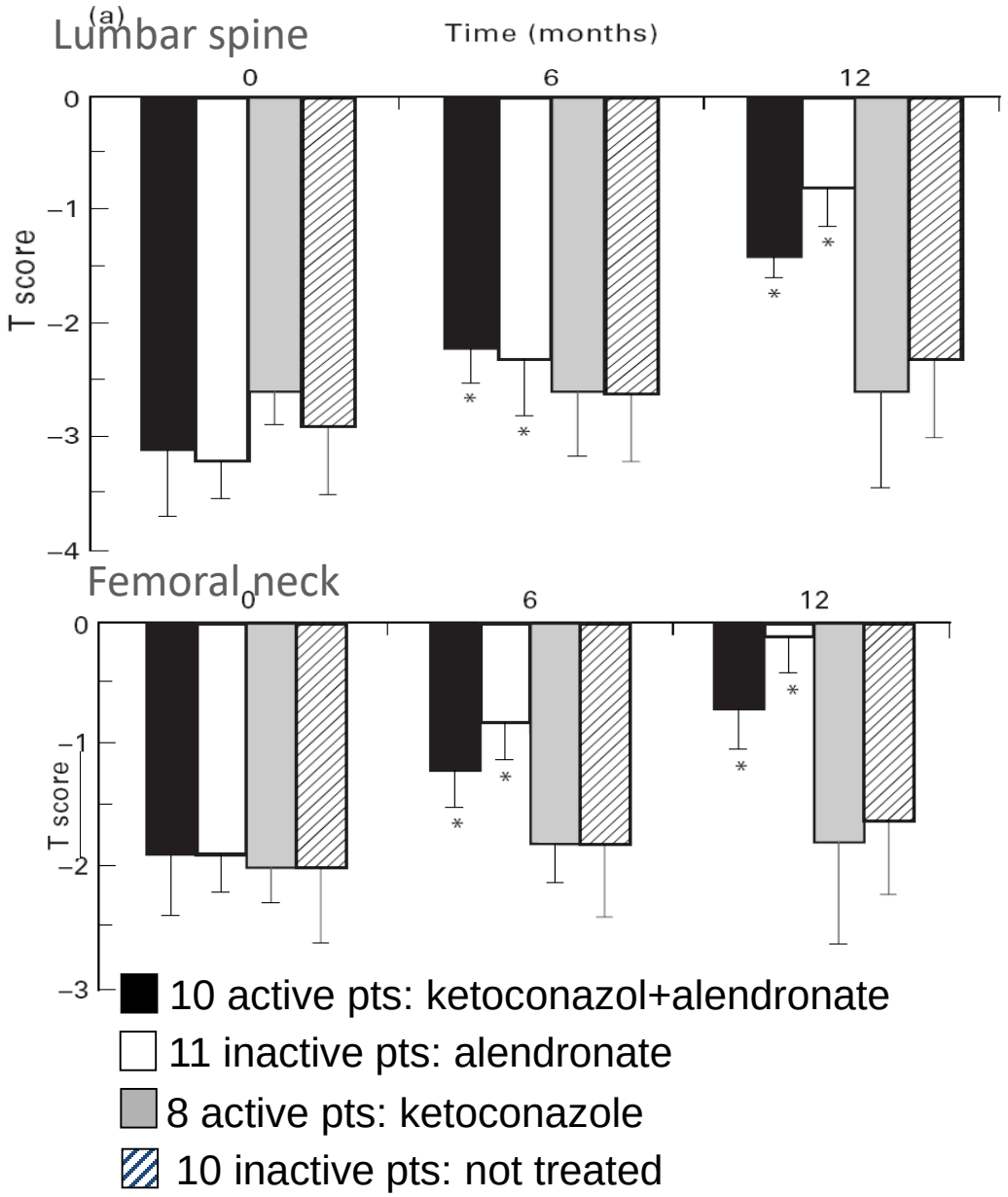
ALENDRONATE IN THE OSTEOPOROSIS OF CUSHING'S DISEASE



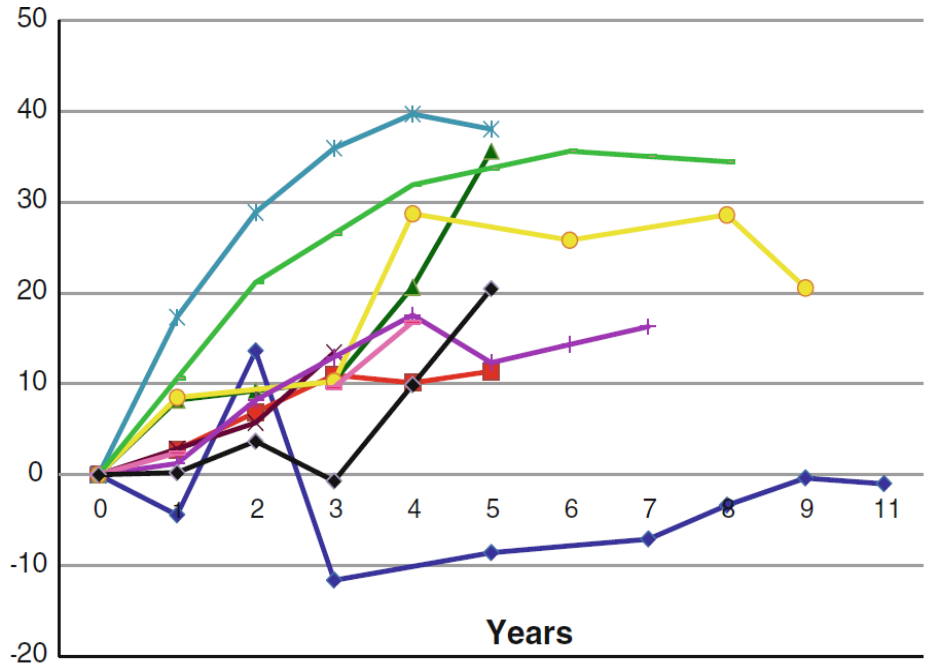
Di Somma C et al. Clin Endocrinol 1998

"…The results of the present study show that a 12 month treatment period with alendronate induced an improvement in bone mineral density greater than in untreated patients…"

PERCENTAGE BMD VARIATION AFTER CURE OF ENDOGENOUS CUSHING SYNDROME

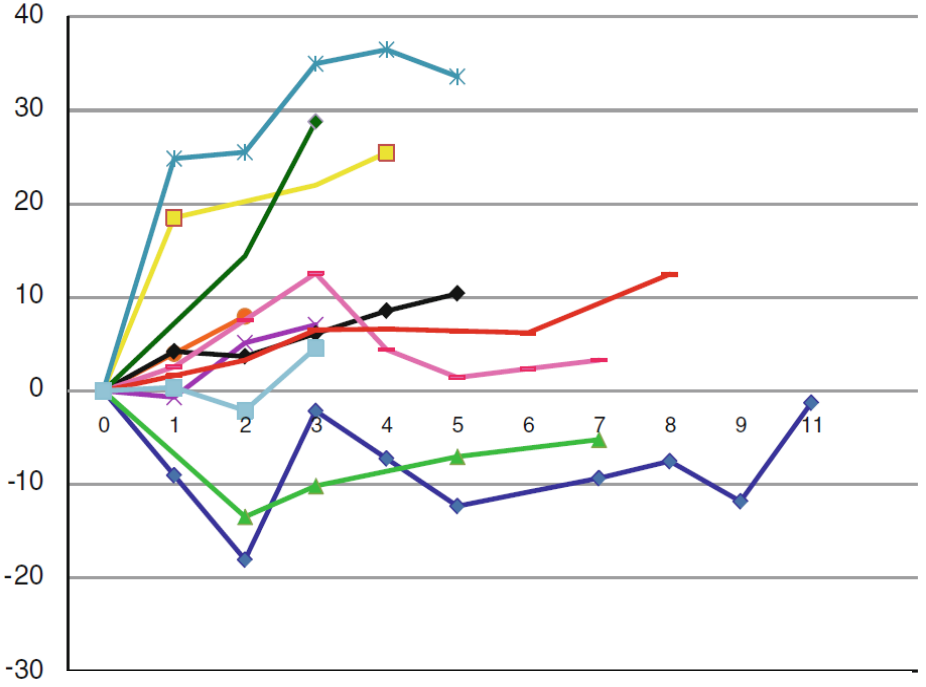
Randazzo MR et al, Pituitary 2012

Spine



The BMD increase at spine tended to be higher in patients who were not treated with bisphosphonates than in the patients treated, (40% vs. 6% P = 0.0559).

Femur



The BMD increase at femur was not different.

Patients with untreated GHD showed a trend of lower improvement of BMD at spine T score than patients without GHD

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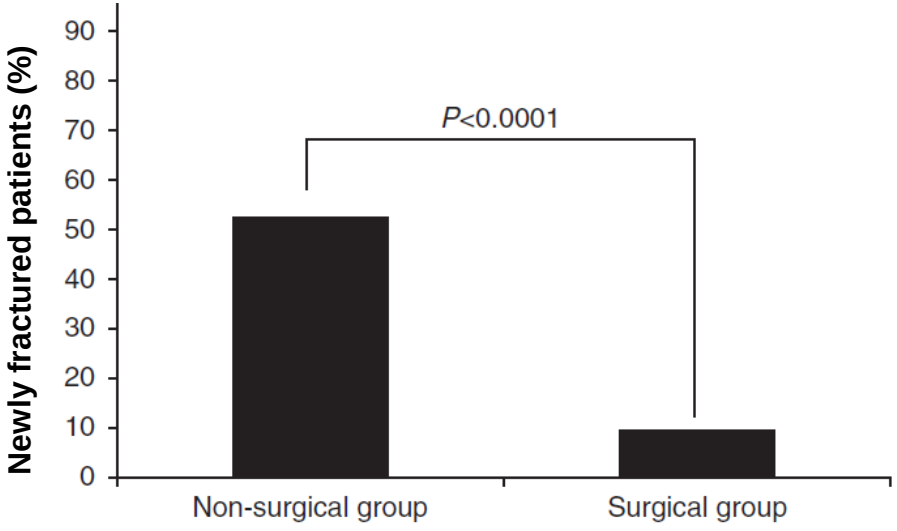
ADRENALECTOMY REDUCES THE RISK OF FRACTURES IN SH

Salcuni AS et al, Eur J Endocrinol 2016

Variables	No Surgery n=23	Surgery n=32
Age (years)	65.4±7.05 (51 to 75)	61.3±8.1 (38 to 75)
Gender (females)	10 (43.5)	22 (68.8)
BMI (kg/m^2)	26.1±4.2 (19.5 to 35.5)	26.5±3.9 (21.3 to 35.3)
Diameter of adenoma (cm)	2.8±0.9 (2.0 to 5.0)	3.4±1.2 (2 to 7.0)
25-Hydroxyvitamin D (ng/ml)	22.4±7.3 (12.0 to 37.1)	21.9±8.7 (12 to 44)
ACTH (pg/ml)	7.7±1.7 (5 to 9.8)	6.8±2.4 (1.6 to 12.0)
1 mg-DST (μg/dl)	3.4±0.7 (2.0 to 5.8)	4.4±2.3 (1.9 to 9.2)
UFC (μg/24 h)	63.7±38.9 (11.5 to 175.3)	75.1±33.0 (15.5 to 171.4)
LS BMD (*Z*-score)	0.23±1.4 (−1.8 to 2.7)	−0.86±1.27[§] (−2.9 to 1.9)
FN BMD (*Z*-score)	0.14±1.2 (−2.4 to 2.7)	−0.54+0.9[†] (−1.9 to 1.7)
Patients with VFx (%)	15 (65.2)	15 (46.9)
Absolute number of VFx	21	22



LACK OF SKELETAL RECOVERY AFTER CURE FROM CUSHING'S SYNDROME

- **Hypovitaminosis D**
- **Hypogonadism**
- **GH deficit**
- **Glucocorticoids overtreatment**

IN CUSHING'S SYNDROME THE MAIN PREDICTOR OF ABNORMAL BMD IS THE DURATION OF GC REPLACEMENT

Dependent variable	*Predictors*	*B*	*p*	*Constant*	R^2
BMC				1.82	0.57
	Duration of GC treatment	−0.002	<0.01		
	Age at CS diagnosis	−0.010	<0.05		
	BMI	0.017	<0.05		
L-BMD	Duration of GC treatment	−0.001	0.001	1.12	0.27

Duration of GC treatment is expressed in months.
GC, glucocorticoids; BMI, body mass index; B, unstandardized coefficient.

Barahona MJ et al, J Bone Mineral Res 2009

CONCLUSIONS

- **Myopathy is highly prevalent in Cushing's syndrome (42-83%) and affects the proximal part of lower limbs and can take months to years to resolve.**
- **Scarce data on the effect of the recovery from Cushing Syndrome on muscle.**
- **Surgical remission improved BMD in most studies, more rapidly at spine, but the complete recovery may require more than 5 years.**
- **Ketoconazole treatment does not seem to ameliorate the bone consequences.**
- **The duration of glucocorticoid replacement is negatively correlated with BMD in women with Cushing's syndrome in long-term surgical remission.**
- **Hypovitaminosis D, GC over-treatment, hypogonadism, GH deficit might affect the time to bone recovery.**

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- Cristina Eller Vainicher
- Serena Palmieri
- Valentina Morelli
- Elisa Cairoli
- Paolo Beck-Peccoz
- Anna Spada

List of the main symptoms and signs associated with Cushing's syndrome

Symptoms and signs	Prevalence (%)
	90–100
Central obesity	
Rounded face ("moon face")	
Facial plethora	
Decreased libido	
	70–90
Purple striae	
Menstrual disturbances	
Hirsutism	
Erectile dysfunction	
Hypertension	
	50–70
Muscle weakness	
Posterior neck fat deposit ("buffalo hump")	
Body bruising	
Glucose intolerance/diabetes	
Osteopenia/osteoporosis	
Emotional lability/depression	
	20–50
Headache	
Backache	
Limb edema	
Recurrent infections	
Hypokaliemic alkalosis	
Nephrolithiasis	
	0–20
Acne	
Alopecia	

Pivonello R et al, Endocrinol Clin Metab North Am 2008