ABC (Altogether to Beat Cushing's syndrome)
"Viaggio alla (ri)scoperta della sindrome di Cushing«
Napoli, 10-12 maggio 2017

LA GUARIGIONE DALLA SINDROME DI CUSHING:
EFFETTO SU COMPOSIZIONE CORPOREA E METABOLISMO

OBESITA' VISCERALE E COMPOSIZIONE CORPOREA

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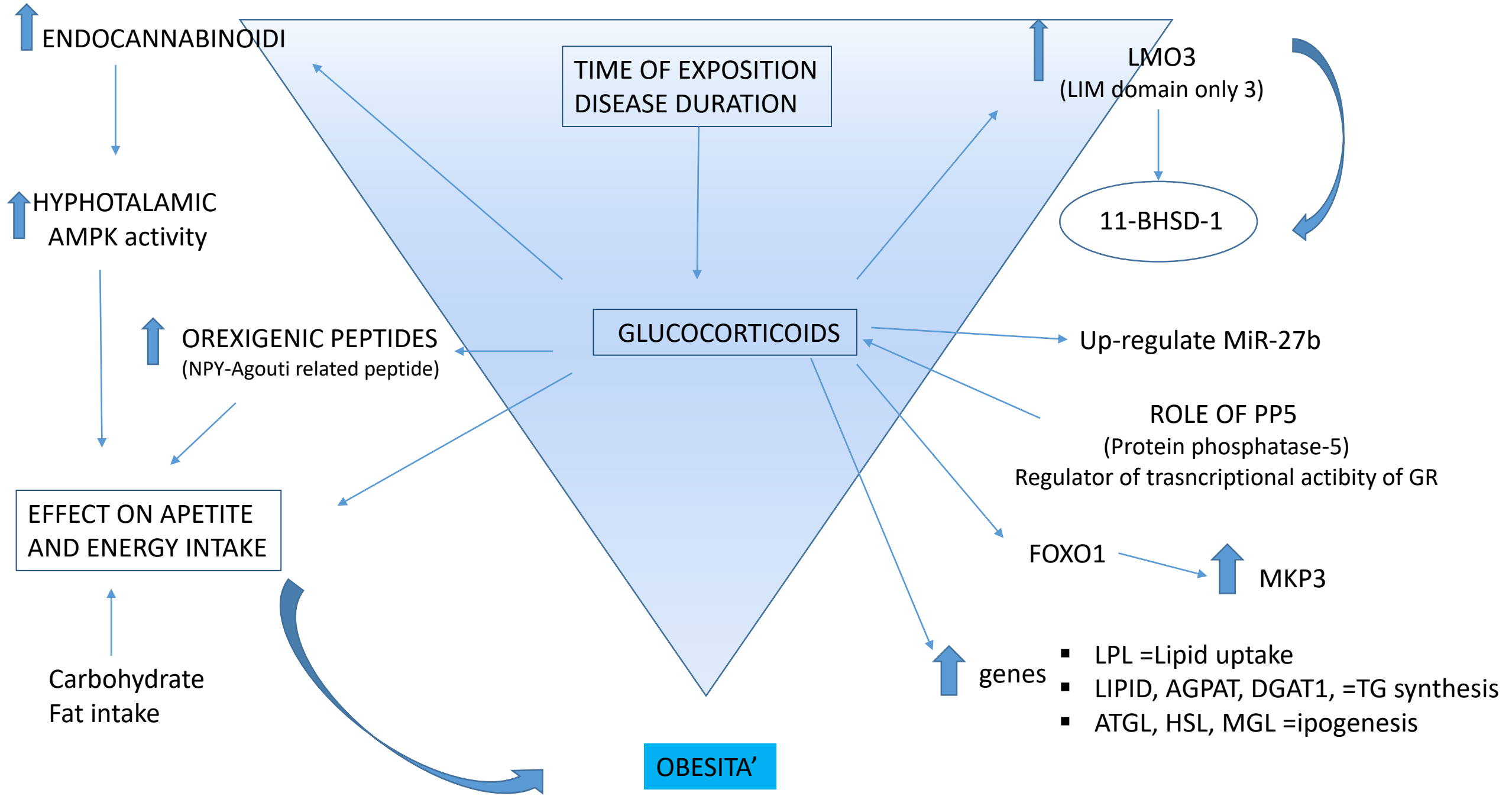
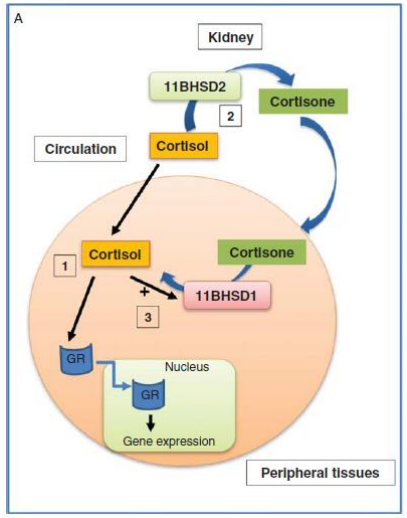
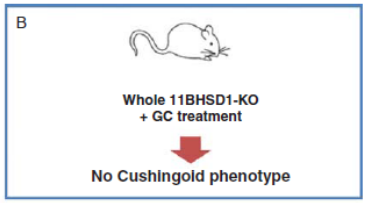
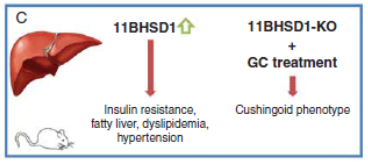
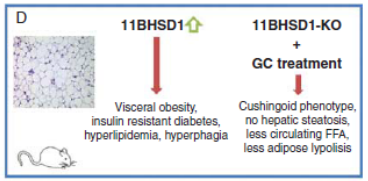

ENDOCANNABINOIDI
HYPHOTALAMIC
AMPK activity
OREXIGENIC PEPTIDES
(NPY-Agouti related peptide)
EFFECT ON APETITE
AND ENERGY INTAKE
Carbohydrate
Fat intake
TIME OF EXPOSITION
DISEASE DURATION
GLUCOCORTICOIDS
LMO3
(LIM domain only 3)
11-BHSD-1
Up-regulate MiR-27b
ROLE OF PP5
(Protein phosphatase-5)
Regulator of trasncriptional actibity of GR
FOXO1
MKP3
genes
LPL =Lipid uptake
LIPID, AGPAT, DGAT1, =TG synthesis
ATGL, HSL, MGL =ipogenesis
OBESITA'

Glucocorticoids effects on adipose tissue



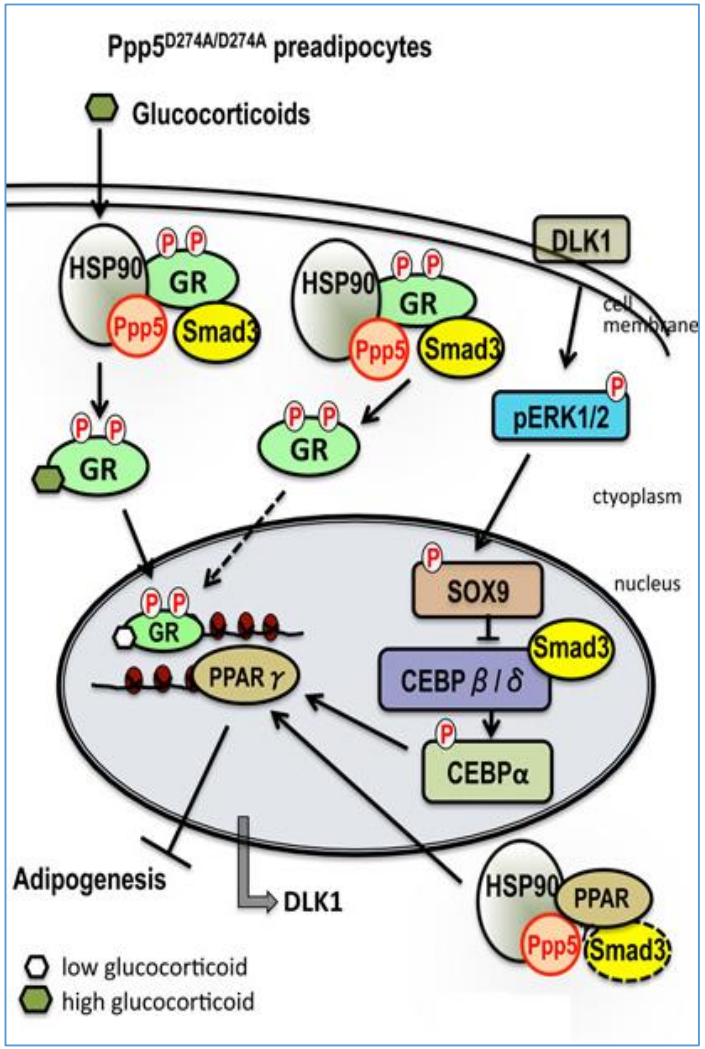






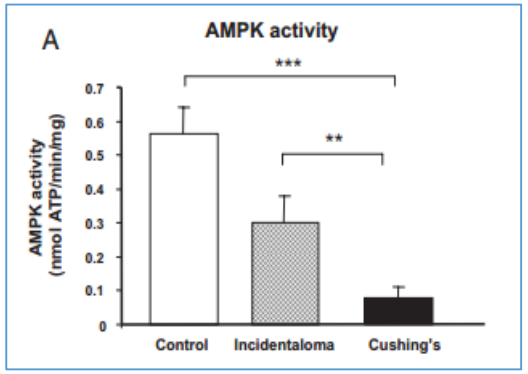
Morgan et al PNAS 2014
Ferraù- Korbonitz EJE 2015

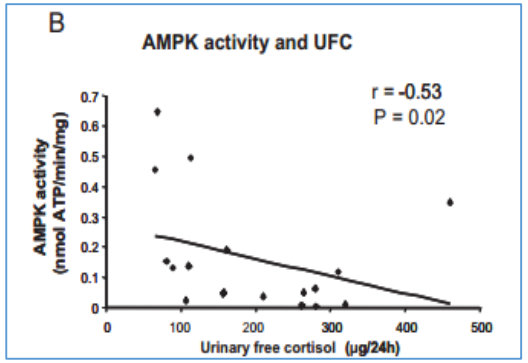
PP5 (protein phosphatasi 5)

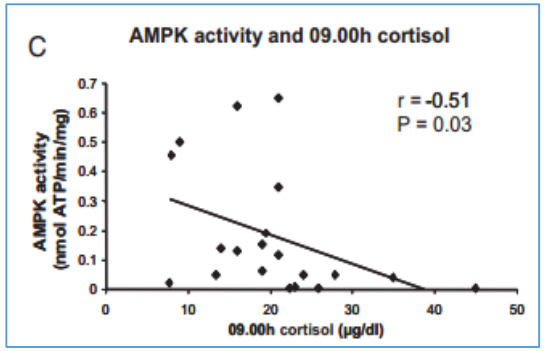


Jacob W et al. Biochem. J 2015

AMPK expression in VAT in CS





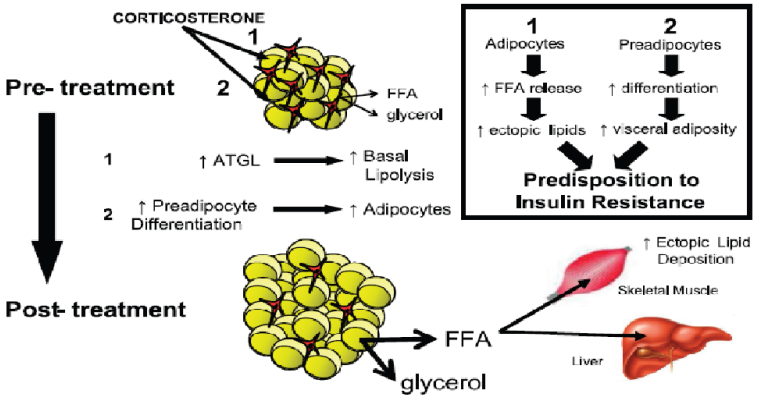


Kola et al JCEM 2008

Pleiotropic actions of glucocorticoids in adipose tissue

Glucocorticoid

↑ Adipogenesis



Adipocyte metabolism

- Glucose metabolism ↓
- Insulin sensitivity ↑↓
- Lipid metabolism
  - Lipolysis ↑↓
    ATGL, HSL, MGL
  - TG synthesis ↑
    FAS, ACC, DGAT, LPL

Adipokine production

- Produced in adipocytes
  - ↑ Leptin, SAA, RBP4
  - ↑↓ Adiponectin
- Produced in stromal cells
  - ↓ IL-6, TNF, CCL2, IL-8

CENTRAL OBESITY

Lee et al *Biochim Biopphys Acta 2015*
Campbel J et al *AJP-Cell Physiol* 2011

Persistence of Increased Cardiovascular Risk in Patients with Cushing's Disease after Five Years of Successful Cure

ANNAMARIA COLAO, ROSARIO PIVONELLO, STEFANO SPIEZIA, ANTONGIULIO FAGGIANO, DIEGO FERONE, MARIAGIOVANNA FILIPPELLA, PAOLO MARZULLO, GAETANA CERBONE, MARCELLO SICILIANI, AND GAETANO LOMBARDI

Parameters	Patients (n = 15)	Sex- and age-matched controls (n = 30)	*P*	BMI-matched controls (n = 30)	*P*
Body mass index (kg/m^2)	28.5 ± 1.2	23.5 ± 0.5	<0.001	28.2 ± 1.0	NS
Waist/hip ratio	0.88 ± 0.02	0.76 ± 0.02	<0.001	0.81 ± 0.02	<0.05
Heart rate (beats/min)	75 ± 2.8	71.2 ± 2.0	NS	70.0 ± 3.0	NS
Systolic blood pressure (mm Hg)	136.0 ± 4.6	117.7 ± 2.9	<0.005	127.5 ± 4.0	NS
Diastolic blood pressure (mm Hg)	91.3 ± 3.6	80.7 ± 2.9	<0.05	82.2 ± 2.6	<0.05
Fasting blood glucose levels (mg/dL)	104.9 ± 7.0	84.5 ± 1.8	<0.001	94.7 ± 3.0	NS
Serum triglycerides levels (mg/dL)	130.8 ± 17.8	107.6 ± 12.7	NS	120.5 ± 13.6	NS
Total blood cholesterol levels (mg/dL)	213.2 ± 10.8	175.5 ± 9.4	<0.05	189.5 ± 8.9	NS
LDL cholesterol levels (mg/dL)	139.1 ± 9.5	98.9 ± 9.0	<0.01	120.5 ± 8.0	NS
HDL cholesterol levels (mg/dL)	48.0 ± 2.0	61.8 ± 4.2	<0.05	54.5 ± 2.0	<0.05
Total/HDL cholesterol ratio	4.5 ± 0.2	3.0 ± 0.2	<0.001	3.5 ± 0.2	<0.05
Prothrombine time (%)	102.4 ± 2.1	105.0 ± 3.4	NS	103.5 ± 2.0	NS
Activated partial thromboplastine time (s)	28.7 ± 0.7	27.2 ± 1.2	NS	27.9 ± 1.0	NS
Plasma fibrinogen levels (mg/dL)	350.8 ± 32.7	262.0 ± 14.6	<0.01	280.4 ± 18.4	<0.05
Serum lipoprotein-a levels (mg/dL)	153.3 ± 5.0	119.0 ± 10.2	<0.05	147.5 ± 3.7	NS
Plasma ACTH levels (ng/L)	35.9 ± 6.1	42.3 ± 5.6	NS	33.4 ± 5.0	NS
Serum cortisol levels (μg/L)	144.8 ± 11.5	135 ± 10.9	NS	156.5 ± 10.4	NS
Urinary cortisol levels (μg/24 h)	99.1 ± 8.5	85.5 ± 7.9	NS	120.4 ± 9.5	NS
Fasting serum insulin levels (micro-U/mL)	25.1 ± 5.8	10.5 ± 3.1	<0.05	18.7 ± 4.2	NS

JCEM 1999

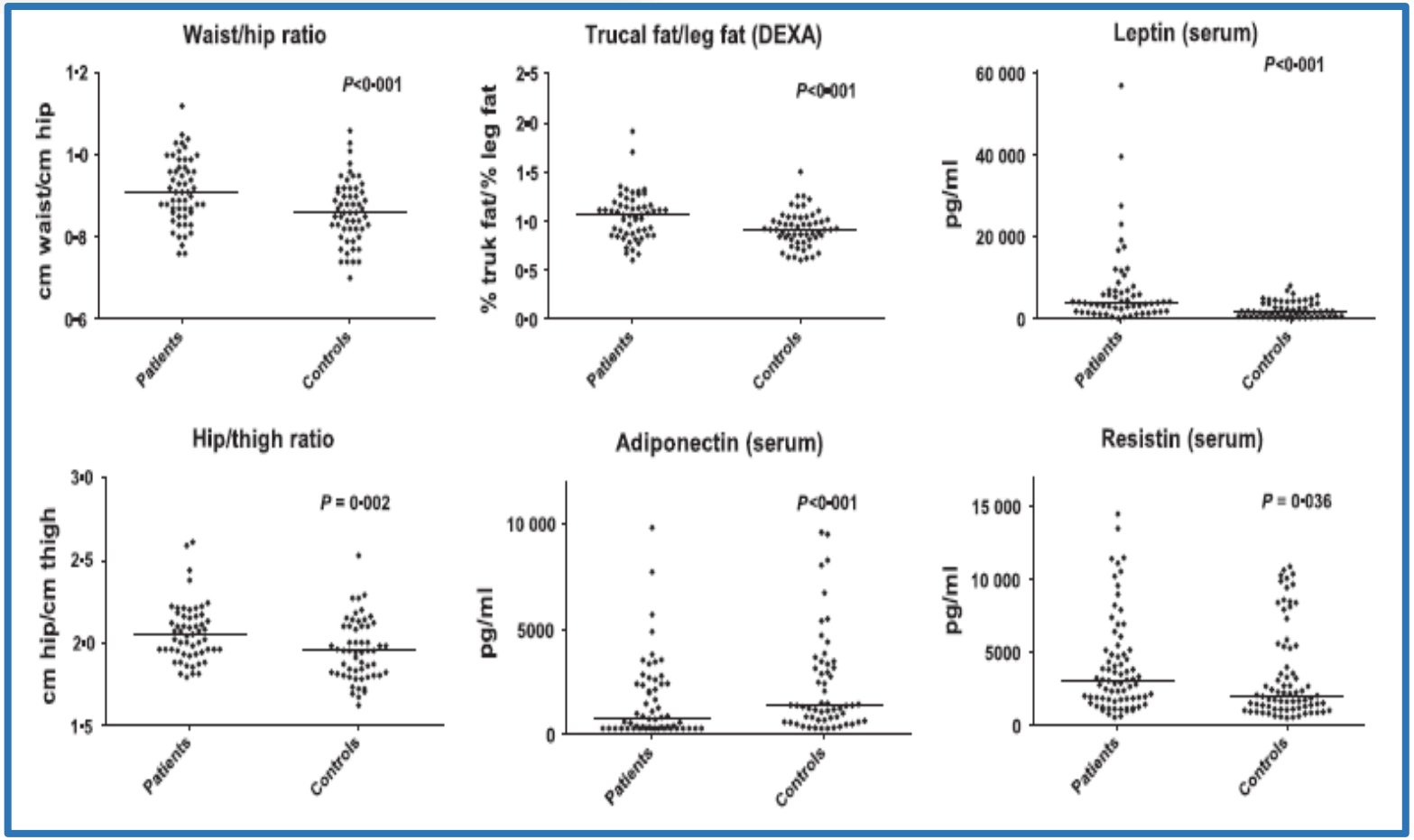
Persistent centripetal fat distribution and metabolic abnormalities in patients in long-term remission of Cushing's syndrome

Margreet Wagenmakers, Sean Roerink, Linda Gil, Theo Plantinga, Jan Smit, Romana Netea-Maier and Ad Hermus

- 58 CS in remission >= 5 yrs
- 58 age-, gender- and BMI-matched healthy controls

DXA scan

	Patients in remission of CS (n = 58)	Healthy control subjects (n = 58)	P-value
Gender (n): male/female	12/46	12/46	
Age (years ± SD)	50·8(12·3)	51·2(12·4)	0·863
BMI (kg/m^2 ± SD)	26·5(4·2)	26·3(4·1)	0·793
Smoking: yes/no	14/44	5/53	0·024*
Pack years ± SD	11·5(15·6)	6·9(13·9)	
Alcohol consumption: yes/no	10/48	13/45	0·485
Treatment modalities [n, (%)]			
Unilateral adrenalectomy	19(32·8)	–	–
Bilateral adrenalectomy	12(20·7)	–	–
Pituitary surgery	38(65·5)	–	–
Pituitary radiotherapy	13(22·4)	–	–
Hormonal deficiencies [n,(%)]			
Glucocorticoid deficiency	21(36·2)	–	–
Growth hormone deficiency	15(25·9)	–	–
Thyroid hormone deficiency	25(43·1)	–	–
Mineralocorticoid deficiency	11(19·0)	–	–
Testosterone deficiency in men	6/12 (50)	–	–
Oestrogen deficiency in women†	25/46 (54·3)	29/46 (63·0)	–
Comorbidities [n,(%)]			
Hypertension	18(31·0)	0 (0)	–
Diabetes mellitus	4(6·9)	0 (0)	–
Hypercholesterolaemia	12(20·7)	0 (0)	–
Cushing type [n,(%)]			
Pituitary	40(69·0)	–	–
Adrenal	18(31·0)	–	–



Clinical Endocrinology (2015)

Body Composition and Cardiovascular Risk Markers after Remission of Cushing's Disease: A Prospective Study Using Whole-Body MRI

Eliza B. Geer, Wei Shen, Erika Strohmayer, Kalmon D. Post, and Pamela U. Freda

14 CD patients (12 female); before and post-surgery;
mean 20 m post-surgery

Whole body MRI

WC (cm)		BMI (kg/m^2)	
Preoperative	Postoperative	Preoperative	Postoperative
111.1	106.0	38.0	34.8
91.4	85.7	30.9	28.0
85.1	74.9	25.7	21.7
106.6	96.0	36.2	31.1
96.5	73.7	25.1	18.3
92.4	102.4	30.2	30.6
120.0	123.0	43.7	40.0
100.5	85.0	29.1	24.8
89.0	92.5	27.9	25.8
104.5	83.7	31.2	26.9
111.7	123.0	38.3	38.5
106.5	99.3	25.2	24.9
113.0	97.8	31.6	28.8
113.0	94.9	36.1	31.0
103.0	95.6[c]	32.1	28.9[d]
10.6	15.1	5.6	6.0

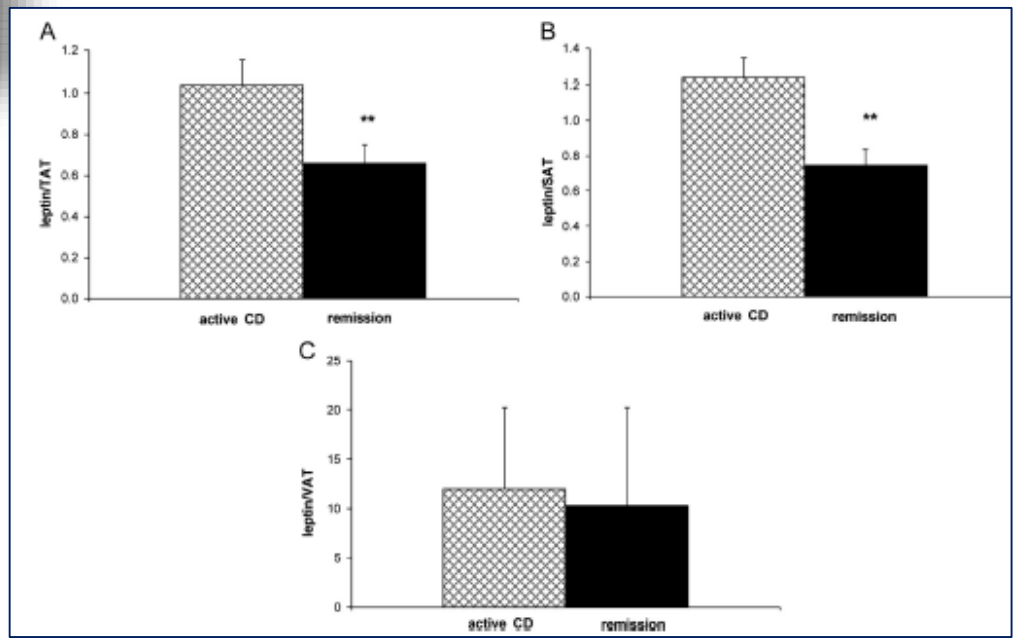
Measure (kg)	Active CD	Remission	Difference	Change (%)	Value decreased (no. of patients)	*P* value[a]
VAT	4.59 ± 2.68	3.21 ± 2.05	−1.38	−29.3	12	0.004
Pelvic BMAT[b]	0.26 ± 0.11	0.19 ± 0.09	−0.07	−20.5	11	0.012
TrSAT	19.54 ± 7.35	15.72 ± 7.92	−3.82	−21.9	12	0.0005
Limb SAT	13.82 ± 7.33	12.01 ± 7.29	−1.81	−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

Clin Endocrinol Metab 97: 1702–1711, 2012

Body Composition and Cardiovascular Risk Markers after Remission of Cushing's Disease: A Prospective Study Using Whole-Body MRI

Eliza B. Geer, Wei Shen, Erika Strohmayer, Kalmon D. Post, and Pamela U. Freda

Measure	Active CD	Remission	P[a]
HOMA-IR	3.1 ± 1.9	1.3 ± 0.7	0.0004
Leptin (ng/ml)	41.3 ± 20.3	23.0 ± 17.8	0.00002
CRP (mg/liter)[b]	5.2 (1.1–12.5)	1.8 (1.3–15.2)	0.69
HMWApN (μg/ml)[b]	6.0 (2.6–8.4)	6.1 (2.9–6.5)	0.43
TC (mg/dl)	202.5 ± 36.1	186.4 ± 32.5	0.03
TG (mg/dl)	121.2 ± 55.2	109.4 ± 65.3	0.55
LDL (mg.dl)	117.2 ± 31.6	107.0 ± 25.1	0.08
HDL (mg/dl)	61.2 ± 16.4	57.4 ± 13.3	0.20
TC/HDL	3.5 ± 1.2	3.4 ± 0.8	0.53
LDL/HDL	2.1 ± 0.9	2.0 ± 0.6	0.55

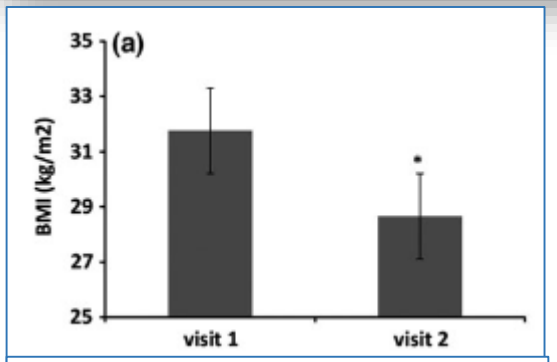


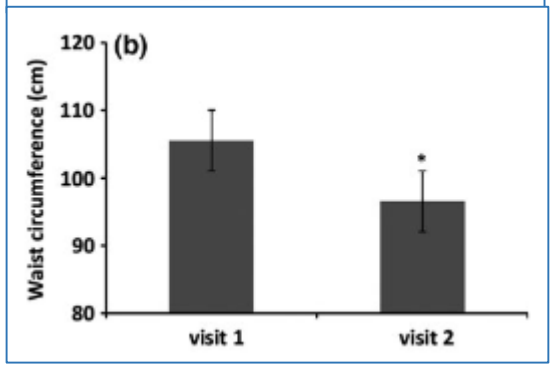
	HOMA-IR		CRP		Leptin		HMWApN	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
WC	NS	NS	NS	0.804 (0.002)	0.594 (0.025)	0.640 (0.014)	NS	NS
BMI	NS	0.621 (0.018)	0.720 (0.008)	0.806 (0.002)	0.696 (0.006)	0.801 (0.001)	NS	NS
Pelvic BMAT	−0.841 (0.0001)	−0.809 (0.001)	NS	NS	NS	NS	0.645 (0.032)	0.636 (0.048)
SAT	NS	0.585 (0.028)	0.811 (0.001)	0.658 (0.020)	0.850 (0.0001)	0.911 (0.0001)	NS	NS
VAT	NS	NS	NS	0.688 (0.013)	NS	NS	NS	NS
HOMA-IR			NS	0.621 (0.031)	NS	NS	−0.664 (0.026)	−0.842 (0.002)

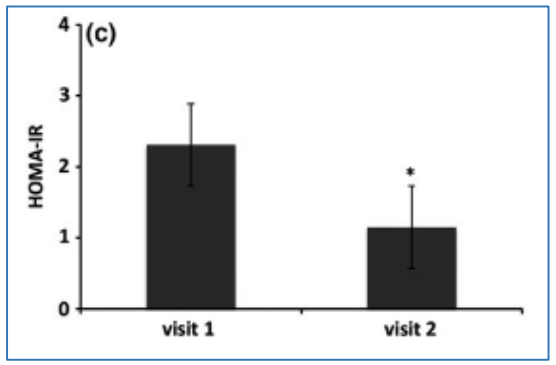
Clin Endocrinol Metab 2012

Proinflammatory cytokines remain elevated despite long-term remission in Cushing's disease: a prospective study

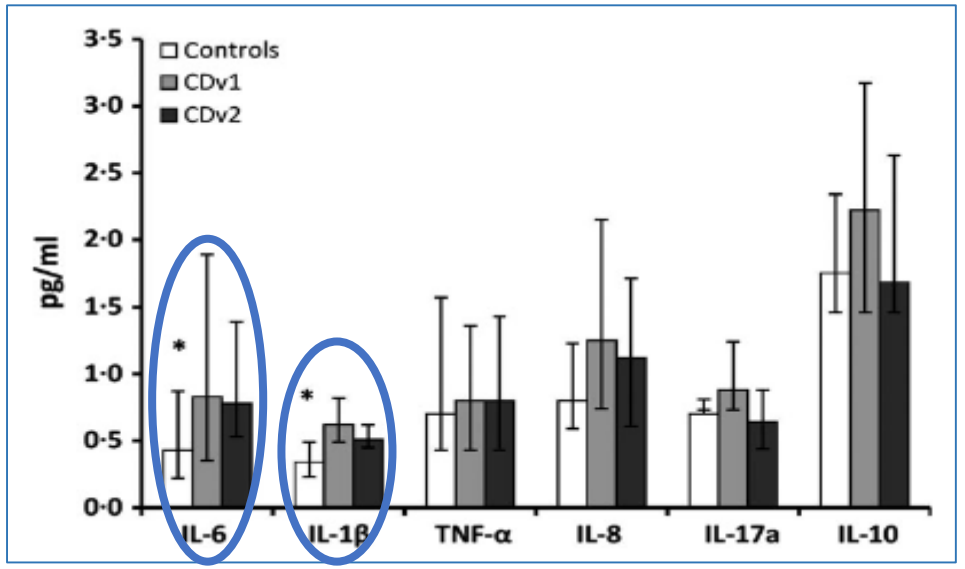
Nirali Shah*, Henry H. Ruiz*, Usman Zafar*, Kalmon D. Post†, Christoph Buettner* and Eliza B. Geer*,†







	Visit 1	Visit 2	*P*-value
TAT (kg)	35·62 (25·90–48·57)	28·39 (21·84–37·54)	<0·001
TrSAT (kg)	18·11 (12·79–25·92)	14·19 (10·92–19·96)	<0·001
VAT (kg)	4·22 (3·16–5·26)	2·73 (1·84–3·78)	<0·001
SAT (kg)	29·47 (22·16–41·86)	24·22 (18·56–33·31)	<0·001
SM (kg)	21·82 (19·11–24·42)	20·52 (18·35–22·23)	0·004
IMAT (kg)	1·18 (0·84–1·58)	0·90 (0·64–1·37)	0·04
HFF (%)*	6·64 (2·83–25·75)	3·95 (0·93–10·12)	0·03



- 31 CD (25 female) V1=baseline; V2=remissione
- 18 controls age, sex, BMI matched
- Media: 195 m (range 65–58 m)
- Whole-body MRI

Clinical Endocrinology 2017

Persistent Body Fat Mass and Inflammatory Marker Increases after Long-Term Cure of Cushing's Syndrome

37 CS women (27 Pituitary 10 adrenal) età media: 50± 14 aa; 14 Active CS: 85 matched healthy women

Estrogen-deficient

TABLE 3. Comparison in estrogen-deficient women between cured and active CS patients and normal matched controls: role of estrogens

	Cured CS	Active CS	Controls	*P*
n	17	8	42	
Total fat mass (%)	43 ± 6	39.2 ± 7	37.5 ± 7	<0.05[a]
Trunk fat mass (%)	46 ± 6	40.8 ± 9	37.4 ± 8	0.001[a]
Lean body mass (kg)	37 ± 7	39 ± 4	40 ± 5	NS
Adiponectin (ng/ml)	16 (7–31)	13 (8–19)	19 (5–56)	NS
sTNF-R1 (ng/ml)	2 (1.2–4.2)	1.5 (1–2)	1.2 (0.8–2.2)	<0.01[a,b]
sTNF-R2 (ng/ml)	3.5 (2–11)	3 (1–3)	3 (2–5)	NS
IL-6 (pg/ml)	0.5 (0.07–11)	0.38 (0.2–6.7)	0.29 (0.07–1.2)	<0.05[a]
Insulin (pmol/liter)	68 (14–134)	58 (14–212)	34 (14–241)	NS
HOMA-IR	2.2 (0.4–4)	1.8 (0.3–7)	1.1 (0.3–8)	NS
SBP (mm Hg)	140 (110–160)	130 (100–135)	130 (90–154)	<0.01[a,b]
DBP (mm Hg)	75 (60–100)	72.5 (70–75)	70 (59–94)	NS
Current age (yr)	60 ± 10	53 ± 10	60 ± 7.4	NS

Results are expressed as mean ± SD or median (range). HOMA-IR, HOMA of insulin resistance; NS, not significant; SBP, systolic BP; DBP, diastolic BP.

[a] $P < 0.05$ between cured CS and controls.

[b] $P < 0.05$ between cured CS and active CS.

X

Estrogen-sufficient

TABLE 2. Comparison in estrogen-sufficient women between cured and active CS patients and normal matched controls: role of estrogens

	Cured CS	Active CS	Controls	*P*
n	20	6	43	
Total fat mass (%)	36.8 ± 7	39.6 ± 5	33.9 ± 7	NS
Trunk fat mass (%)	36.2 ± 9	39.8 ± 5	31.5 ± 8	NS
Lean body mass (kg)	38 ± 6	40.6 ± 4	40 ± 5	NS
Adiponectin (ng/ml)	11.5 (5–32)	13 (9.8–26)	17.6 (4.5–49)	NS
sTNF-R1 (ng/ml)	1.4 (1–2.7)	1.8 (1.4–2)	1.18 (0.8–2.4)	0.001[a,b]
sTNF-R2 (ng/ml)	2.8 (1.6–6)	3.3 (2–7)	2.7 (2–5)	NS
IL-6 (pg/ml)	0.5 (0.1–1.8)	0.5 (0.15–0.8)	0.37 (0.17–1.4)	<0.05[a]
Insulin (pmol/liter)	43 (14–86)	78 (28–115)	35 (14–131)	NS
HOMA-IR	1.4 (0.4–2.5)	2.5 (0.8–3.7)	1.06 (0.4–4)	NS
SBP (mm Hg)	110 (100–140)	140 (130–145)	111 (100–140)	<0.01[b,c]
DBP (mm Hg)	65 (60–85)	80 (75–100)	70 (60–90)	<0.01[b,c]
Current age (yr)	41 ± 10	37 ± 9	40 ± 8.5	NS

Results are expressed as mean ± SD or median (range). HOMA-IR, HOMA of insulin resistance; NS, not significant; SBP, systolic BP; DBP, diastolic BP.

[a] $P < 0.05$ between cured CS and controls.

[b] $P < 0.05$ between active CS and controls.

[c] $P < 0.05$ between cured CS and active CS.

***Barahona et al JCEM* 2009**

GLUCOCORTICOID RECEPTOR POLYMORPHISMS: EFFECTS ON GC SENSITIVITY

The polymorphisms BclI and N363S of the GR gene (NR3C1) have been associated with:
- enhanced sensitivity to GC,
- increased abdominal obesity,
- an adverse lipid profile,
- hyperinsulinemia

(Van Rossum et al Recent Prog horm Res 2004; Huizenga et al JCEM 1998; Di Blasio et al Clin Endocrinol 2003; Van Rossum et al Clin Endocrinol 2003)

The ER22/23EK GR polymorphism has been associated with:
- GC resistance
- favorable metabolic profile and body composition

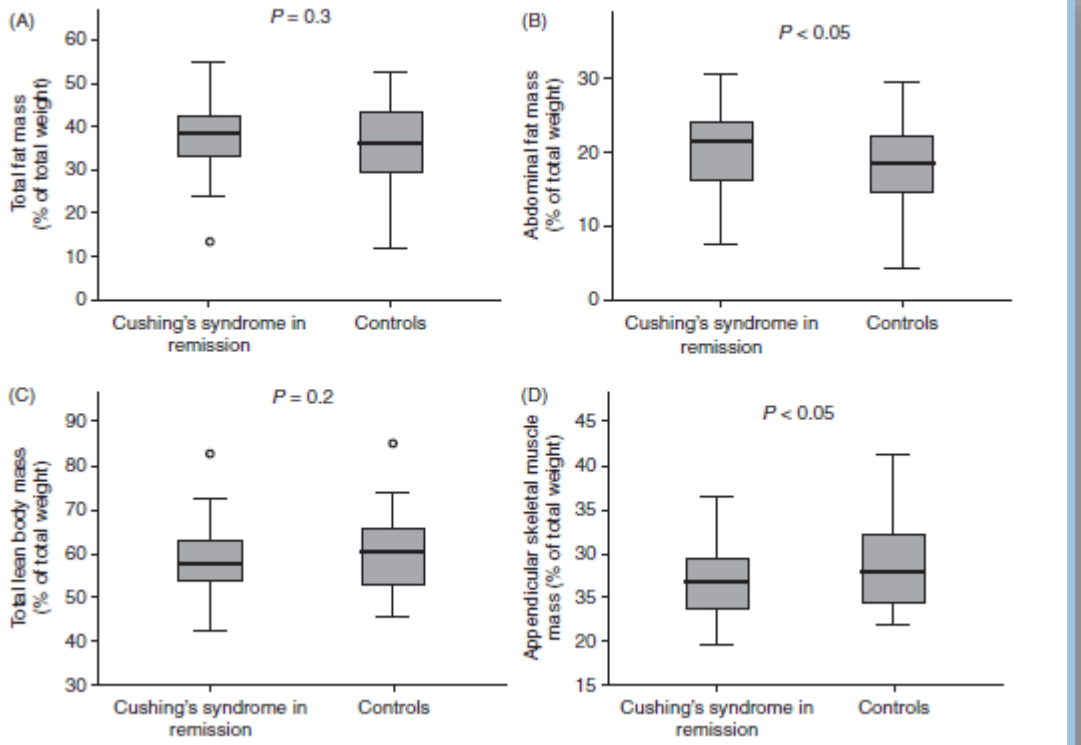
(Van Rossum et al Diabetes 2002; Van Rossum et al JCEM 2004)

The A3669G polymorphism of the GR gene (NR3C1) has been associated with:
- a protective role in patients with CS,
- attenuating the effects of GC excess on glucose metabolism.

(Trementino L et al EJE 2012)

Body composition and bone mineral density in women with Cushing's syndrome in remission and the association with common genetic variants influencing glucocorticoid sensitivity

50 CS women (38 CD, 12 AA) in remission;
mean age: 37±13 yrs at diagnosi, 53 ±14 at follow-up
Mean remission: 13 aa
50 age and gender matched controls



Polymorphism (rs1045642) in the **ABCB1 gene (**GC transmembrane transporter) associated with:

- **increased abdominal fat mass** (B 1.7, 95% CI 0.3 to 3.1, P=0.016)
- **decreased apendicular skeletal muscle mass (ASMM)** (B 1.3, 95% CI 2.5 to 0.02, P=0.019).

Ragnarsson et al EJE 2015

CONCLUSION

- Despite long-term cure, CS patients exhibit persistent abdominal fat mass accumulation despite overall weith loss, with the consequent unfavorable adipokine profile, leading to a state of low-grade inflammation.
- This seems to be independent of aetiology of CS, treatment strategies and presence of comorbidity. However, the estrogen deficiency seems to be an associated risk factor
- This situation determines a persistent and increased cardiovascular risk in these patients
- More studies are necessary to evaluate the influence of GC polymorphisms on cardiovascular and metabolic health that may influence the follow-up (i.e: carriers having a more stringent follow-up)
- Surgical or medical treatment of CS patients, seem to present different body composition outcomes: being better in the surgical group.